ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Triptans for Migraine Therapy

A Pharmacoeconomic Analysis

Doug Coyle, Karen Lee, Kelley-Anne Sabarre

January 31, 2014

Executive Briefing

- This report assesses the current evidence for the cost-effectiveness of triptans for treatment of migraines and the economic impact of alternative changes to the funding status of triptans.
- Evidence suggest that triptans are cost effective compared to ergots for the treatment of migraines.
- If triptans were available under Exceptional Access Program (EAP) at a generic price of 25% of branded cost, there would be a reduction in expenditure by Ontario Public Drug Programs (OPDP). Imposing quantity limits would further reduce cost but not to as great an extent.
- Changing the reimbursement status of all triptans to general benefit/limited use with or without quantity limits, and even with a generic price of 25% of average branded cost, would lead to a significant increase in expenditure by OPDP, and may lead to use in populations where the cost effectiveness of triptans has not been established.
- Thus, maintaining triptan coverage under EAP and reimbursing generic formulations would lead to cost savings; while it is expected that, in contrast, changing the reimbursement status to general benefit/limited use and reimbursing generic formulations with or without imposing quantity limits would lead to wider use of triptans at increased expenditure.

Executive Summary

Research Questions

RQ1. What is the current evidence for the cost-effectiveness of triptans (alone or in combination with other drugs) for acute treatment of migraines compared to: other triptans, acetaminophen, antiemetic's, acetylsalicylic acid (ASA) and ergots?

RQ2. What is the economic impact of alternative changes to the funding status of triptans (e.g. restricted vs. more open access)?

Methods

Systematic Review of Published Economic Evaluations

To address RQ1, we conducted a systematic review of the available literature on the cost-effectiveness of triptans (alone or in combination with other drugs) for acute treatment of migraines compared to: other triptans, acetaminophen, antiemetics, acetylsalicylic acid (ASA), and ergots. The focus of the systematic critical review was on the strength and quality of evidence addressing the cost-effectiveness of triptans. The generalizability of the studies to Ontario Public Drug Plan (OPDP) were based on whether a Canadian perspective was considered, inclusion of generic drug costs, inclusion of the costs associated with the treatment of migraine (not simply the drug acquisition costs), and reporting of the incremental cost-effectiveness ratio.

De novo Economic Evaluation

Given the nature of the research question and the consistent cost of triptans, there was no requirement for a traditional economic evaluation to assess the value for money for each of the candidate treatments.

Reimbursement Based Economic Assessment

To address RQ2, we developed an applied, policy-oriented economic model to facilitate consideration of alternative reimbursement strategies for triptans.

The first step involved forecasting expenditure for each triptan over the next 3 years. Analysis utilized OPDP data on current usage of triptans. Costs for the next three years were estimated using time series analyses. The second step involved identifying alternative approaches to reimbursement of triptans. Strategies were identified during the scoping assessment along with further consultation with OPDP. The final step involved forecasting the budget expenditure on triptans for each alternative reimbursement strategy.

Findings

Systematic Review of Published Economic Evaluations

A comprehensive search of the literature identified 21 studies: 5 studies assessing the cost effectiveness of a triptan with another class of acute migraine treatments and 18 studies comparing one or more

triptans in terms of cost effectiveness (some studies addressed both of the above). In general, the literature examining the cost effectiveness of triptans contained a number of common limitations. This significantly reduces their usefulness in aiding in decision making.

The study conducted by the National Clinical Guideline Centre (NCGC) is likely the most applicable to the research question concerning the cost effectiveness of triptans compared to other classes of therapies. The NCGC report found that for triptan-naïve patients, triptans were both more effective and more costly than acetaminophen, ergots, and nonsteroidal anti-inflammatory drugs (NSAIDs) and that for triptan-experienced patients, the addition of NSAIDs or acetaminophen to triptans was dominated by triptans alone. The incremental cost per quality-adjusted life year (QALY) gained for triptans ranged from £683 to £15,852 per QALY (£2011, or $1,081 to $25,101 per QALY in 2013 CDN$[1,2]).

With regards to cost effectiveness among triptans, the Finnish Medicines Agency sponsored study is likely the most applicable. This report found that sumatriptan 100 mg dominated all other triptans with the exception of eletriptan 40 mg. The incremental cost per QALY gained for eletriptan versus sumatriptan was €19,659 per QALY (€2012, or $30,793 per QALY in 2013 CDN$[1,2]).

Despite the poor quality of many of the published studies, the weight of evidence suggests that triptans are more cost effective for the acute treatment of migraines than ergots.

Reimbursement Based Economic Assessment

In 2012, expenditure by OPDP on triptans was $1.62 million, whilst expenditure on ergots was $0.26 million. Total number of users of triptans and ergots was 2,628, with 1,090 for triptans and 1,538 for ergots. The number of units per user was 100 for triptans and 166 for ergots. The most commonly prescribed triptan was sumatriptan (52% of total triptan units) which also contributed most of the budget impact (45% of total triptan and ergot expenditure). Ergots cost was an average of $1.03 per unit whilst triptans ranged from $11.48 for naratriptan to $15.36 for rizatriptan; the average cost per unit was based on both generic and brand use using the appropriate unit costs. The cost of administering EAP claims for triptans was estimated to be approximately $11,000 in 2012.

Without any change in reimbursement for triptans, it is forecasted that expenditure on triptans will rise over the next three years; $1.67 million in 2013 followed by $1.74 million in 2014 followed by $1.81 million in 2015. However, oral ergots (i.e., Cafergot), which constituted 97.7% of total OPDP expenditure on ergotamine products in 2012, were discontinued in December 2013. Consequently, without data on the shift from oral to non-oral ergot formulations it is not possible to forecast ergot expenditure. It should be noted that some of the patients using oral ergot products may be switched to other acute non-ergot migraine medications, such as triptans. Thus, estimates of triptan expenditure may be underestimates.

All EAP strategies which included generic costs equivalent to 25% of average branded cost would lead to a reduction in total expenditure ranging from 16%-84%. A strategy of ensuring generic drugs cost 25% of the branded cost and requiring replacement of brand name agents with their generic formulation, when available would lead to a reduction in expenditure of 69%. Imposing a 6 per month quantity limit in addition to the above would lead to a reduction in expenditure of 84%.

All strategies which included GB/LU, would lead to an increase in total costs ranging from $2,446,497to $5,519,241(134%-302%) or $2,300,232 to $3,603,504 (126%-197%) in 2015 based on data from other

provinces which have more liberal reimbursement of triptans (based on Alberta and Manitoba usage respectively).

Conclusions

Evidence suggests that triptans are cost effective compared to ergots for the treatments for migraines.

Without any change in reimbursement for triptans, it is expected that expenditure on triptans will rise over the next three year, whilst the expenditure on ergots is unclear with the discontinuation of the oral formulation.

If triptans were available under EAP at a generic price of 25% of average branded cost, there would be a significant reduction in expenditure by OPDP. In addition to maintain coverage under EAP with generic pricing at 25% of average branded cost, the imposition of quantity limits would lead to only a modest reduction in costs

Changing the reimbursement status of all triptans to general benefit/limited use with or without quantity limits, and even with a generic price of 25% of average branded cost, would lead to a significant increase in expenditure by OPDP. This is the result of the predicted expanded use, which more than fully offsets savings by using generic products. Further, changing reimbursement to GB/LU may lead to use in populations where the cost effectiveness of triptans has not been established.

The analysis suggests that maintaining triptan coverage under EAP and reimbursing generic formulations would lead to cost savings; in contrast, changing the status to general benefit/limited use, reimbursing generic formulations or imposing quantity limits would lead to increased expenditure.

Table of Contents

List of Tables

List of Figures

Abbreviations

AE	adverse events
ASA	acetylsalicylic acid
CADTH	Canadian Agency for Drugs and Technologies in Health
CBA	cost-benefit analysis
CCOHTA	Canadian Coordinating Office for Health Technology Assessment
CDN$	Canadian dollars
CEA	cost-effectiveness analysis
CIHI	Canadian Institute for Health Information
CNS	central nervous system
CUA	cost-utility analysis
DC	Doug Coyle
DHE	dihydroergotamine mesylate
EAP	Exceptional Access Program
GB	general benefit
ICER	incremental cost-effectiveness ratio
ICES	Institute for Clinical Evaluative Sciences
ICUR	incremental cost-utility ratio
KAS	Kelley-Anne Sabarre
LU	limited use
MSE	mean square error
MOHLTC	Ontario Ministry of Health and Long-Term Care
N/A	not applicable
NCGC	National Clinical Guideline Centre
NHS	National Health Service
NHSEED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NSAIDs	nonsteroidal anti-inflammatory drugs
ODB	Ontario Drug Benefit
OPDP	Ontario Public Drug Plan
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
QWB	Quality of Wellbeing Scale
QWB-SA	Quality of Wellbeing Scale - self-administered
SEK	Swedish krona
SM1	success measure 1
SM2	success measure 2
SNAE	sustained pain-free, no adverse events

USD$	American dollars

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 work was supported by the Institute for Clinical Evaluative Sciences (ICES), a non-profit research institute sponsored by the Ontario MOHLTC, and by the Canadian Institute for Health Information (CIHI). 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.

Introduction

This report assesses the current evidence for the cost-effectiveness of triptans for treatment of migraines and the economic impact of alternative changes to the funding status of triptans.

Research Questions

RQ1. What is the current evidence for the cost-effectiveness of triptans (alone or in combination with other drugs) for acute treatment of migraines compared to: other triptans, acetaminophen, antiemetics, ASA and ergots?

RQ2. What is the economic impact of alternative changes to the funding status of triptans (e.g. restricted vs. more open access)?

Methods

Systematic Review of Published Economic Evaluations

To address RQ1 we conducted a systematic review of the available literature on the cost-effectiveness of triptans (alone or in combination with other drugs) for acute treatment of migraines compared to: other triptans, acetaminophen, antiemetics, ASA, and ergots. The focus of the systematic critical review was on the strength and quality of evidence addressing the cost-effectiveness of triptans. The generalizability of the reports to OPDP is dependent on a number of methodological factors. Key issues in this review were whether the study adopted a Canadian perspective, whether generic costs were included, where costs associated with the treatment of migraine and not simply the drug acquisition costs were included, and whether incremental cost-effectiveness ratio were reported.

Search Strategy

A search of the medical literature from 1946 to present (2013 November 11) in Ovid Medline (indexed, in-process and other non-indexed) and Embase Classic & Embase 1947 to 2013 November 08 was conducted in order to capture all relevant literature. Key words relating to triptans for the treatment of migraines were combined with a standardized search strategy for identifying economic analyses adopted by National Health Service Economic Evaluation Database (NHS EED). The complete search strategy can be found in Appendix A1: Search Strategies and Results.

In addition, the Tufts CEA registry and NHSEED were also searched for relevant articles. Grey literature was identified through the Canadian Agency for Drugs and Technologies in Health (CADTH) and National Institute for Health and Care Excellence (NICE) websites. Moreover, the reference lists of relevant studies were hand searched for additional relevant studies.

Search Findings

920 citations were identified from the original search.

One reviewer (KAS) independently reviewed the literature searches in order to identify potential articles for inclusion within the critical appraisal. Any uncertainties were resolved through consensus with a second reviewer (DC).

Of the 920 citations that were identified, a total of 72 economic citations were identified for potential inclusion; 819 citations were excluded. The reasons for exclusion were the following: not an economic analysis, not migraine, or not a relevant intervention. An additional 32 citations were excluded; reasons for exclusion were as follows: non-English, not available or not full text. Results of the search can be found in Appendix A2: Results of Search.

The 72 potential studies identified during the literature review were reviewed by one reviewer (KAS). Of these, 21 publications, which addressed the objective of the review, were selected for inclusion. Those studies that were not included within the review along with the reasons for exclusion are detailed in Appendix A3: Excluded Studies.

De novo Economic Evaluation

Given the nature of the research question and the similar cost of triptans, it was determined that there was no requirement for a traditional economic evaluation to assess the value for money for each of the candidate treatments. Evidence on differential clinical effectiveness will be sufficient to consider selective reimbursement strategies within the reimbursement based economic assessment.

Reimbursement Based Economic Assessment

Applied, Policy Oriented Economic Model

An applied, policy-oriented economic model focusing on financial impact was created to facilitate consideration of alternative reimbursement strategies for triptans. The analysis utilized OPDP data on usage of triptans (almotriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) and ergots (ergot and ergot alkaloid) from 2000-2012. Oral ergots were discontinued in 2013. Thus, without adequate data on the shift from oral ergots to non-oral ergot formulations, it was not possible to forecast ergot expenditure. The model was developed within Microsoft Excel.

Expenditures for the next three years, 2013-2015, were predicted using time series analysis. Four models were used to forecast expenditure.

1. A linear model whereby expenditure was assumed to increase by the same amount each year and also increase with each new triptan covered under OPDP.
2. An exponential model where an exponential relationship between expenditure and time and number of triptans covered was assumed.
3. A power model whereby a non-linear relationship between time and expenditure was allowed – this model also incorporated the number of triptans covered.
4. A constant growth model whereby a constant percentage increase in expenditure was assumed with the addition of a triptan to coverage also leading to a percentage increase.

Of the four models, the most suitable model for forecasting was selected based on the following procedure. The linear, exponential and constant growth models were compared in terms of mean square error (MSE) and the model with the lowest error chosen. If the linear model was chosen, the significance of the power term within the power model was then assessed and if an insignificant impact

on MSE was observed, the linear model was still preferred.

Alternative approaches to reimbursement of triptans were then identified. Budget expenditure on triptans for each alternative reimbursement strategy was forecasted using the most suitable model. Strategies considered included changes to the reimbursement mechanism (EAP versusGB/LU), reduction in generic drug costs and the imposition of quantity limits.

The following assumptions were made:

- For EAP1, prescribed generic formulations were assumed to cost 25% of the current brand cost.
- For EAP2, EAP1 except for all products where a generic equivalent was available, cost was assumed to be 25% of the branded cost
- For EAP3, EAP2 plus for all formulations without a generic equivalent, units were allocated to other formulations of the same product where a generic equivalent is available.
- For GB/LU1, all products with a generic equivalent must be priced at 25% of the brand cost and replacement of brand name agents with their generic formulation, when available, is required.
    - The increase in prescription volume was estimated using utilization data for Alberta and Manitoba (provinces with less restrictive access to triptans with much higher usage) relative to Ontario. The relative rate of triptan use (volume) in Alberta/Manitoba versus Ontario was applied to the forecasted cost for Ontario.
- For GB/LU2, a similar approach to that adopted for estimating EAP3 was adopted.
- For quantity limits under EAP, only usage up to the quantity limits based on Ontario data were considered. Thus, we weighted the estimated total expenditures by the proportion of usage below the quantity limits for Ontario in 2012.
- For quantity limits under GB/LU, only usage up to the quantity limits based on Alberta and Manitoba data were considered. Thus, we weighted the estimated total expenditures by the proportion of usage below the quantity limits for Alberta/Manitoba in 2012.

A table of all of 20 reimbursement strategies can be found in Appendix B (Table 1 Reimbursement Strategies).

Findings

Systematic Review of Published Economic Evaluations

Included Studies

Of the 21 reports selected for inclusion, almost half were American,[3-11] three were Canadian,[12-14] and six were European (UK, Spain, Finland, and Sweden) studies,[15-20] and two involved multiple countries (European; European and North American).[21,22] More than half of the included studies were financed by manufacturers[3-6,8-11,14,17,19-21] and five were sponsored by health technology assessment organization or the department of health.[7,12,13,15,16]

Almost half of the reports were informal analyses (CEAs that considered effectiveness measures which

may not be clinical meaningful or difficult to interpret such as costs per successful treatment) which did not include incremental costs per relevant outcomes.[3-6,8,17,20,22,23] Ten reported incremental cost-effectiveness ratio (ICER),[7,9,10,12-14,16,18,19,21] while six reported incremental cost-utility ratio (ICUR).[11-16] The most common comparator was other triptans, followed by ergots, then ASA plus antiemetic, acetaminophen alone and triptan in combination with other comparators NSAIDs or acetaminophen].

A total of three studies used a patient population of 18-65 years of age,[7,16,19] while one used a patient population of 12 years of age and older,[15] another assumed that patients were 40 years of age,[18] while another study specified a patient population ranging from less than 18 year of age to over 45 years of age.[20] A total of 15 studies did not specify the age of the patient population modelled,[3-6,8-14,17,20-23]

All studies used either a decision tree or decision analytic model with the exception of one trial based model.[7] Almost half of the reports[4-6,8-11,14,18,19,23] used effectiveness data derived from the same published meta-analysis,[24] which has previously been criticized in terms of its appropriateness (ref). Two reports used effectiveness data derived from a network meta-analysis/mixed treatment comparison.[15,16]

Only three reports included costs associated with the management of adverse events.[7,11,19] Most studies considered sensitivity analysis; nine reports included deterministic sensitivity analysis,[4-8,14,16,19] and six included both deterministic and probabilistic sensitivity analysis.[5,9,12,13,15,18,25]

Given the timing of studies, only two reports included generic prices for triptan,[16,22] while three studies discounted drug acquisition costs to account for future generic pricing. [5,8,19]

A table summarizing included studies is provided in Appendix A5: Characteristics of Reviewed Studies.

The quality of each study was assessed in terms of: the source of efficacy data; the costs associated with the treatment of migraine which include cost of adverse events (although the systematic review suggests that clinical evidence supports no difference in adverse event rates between triptans and compared to other migraine therapies)and not simply drug acquisition costs; the consideration of utility values, more specifically, the use of preference-based measures; and the adoption of sensitivity analysis.

Overall Conclusions

Overall, the studies identified in this review are of poor quality and all have considerable limitations to its applicability to the current Canadian setting. Many studies were informal analysis that considered costs per successful treatment rather than incremental costs per outcomes; used effectiveness data from sources of meta-analysis of "questionable methods and applicability;"[26] excluded costs associated with adverse events; included branded prices as opposed to generic prices; and used utility values from non-preference-based measures.

Of the three Canadian studies, results suggest that triptans are more cost effective than ergots and ASA plus metoclopramide, and in some instances dominate comparators. One manufacturer sponsored study found that the manufacturer's triptan was the most cost effective triptan. This was a consistent finding across all manufacturer sponsored studies.

Although the economic analyses of these Canadian studies reflect various comparators (triptans, ergots,

and ASA plus antiemetic), these studies were published in 1995-2002 which were based on older cost information and prior to the availability of generics. Moreover, the costs associated with the management of adverse events were not considered and non-preference-based measures were used to estimate quality of life. Therefore, applicability of Canadian studies to any decision regarding the cost effectiveness of triptans should be done with caution.

Of the non-Canadian studies, six were cost-effectiveness analysis (CEA), one was a cost-effectiveness/cost-utility analysis (CEA/CUA), and another two were cost-utility analysis (CUA). Results of the nine informal analyses do not provide useful information; therefore, only comments regarding the results of CEA/CUA are discussed. Results consistently found that the drug of the manufacturer who sponsored the analysis was the most cost effective triptan. In addition, analysis found that triptans are more cost effective than ergots.

The studies conducted by NCGC and funded by the Finnish Medicines Agency maybe the most applicable to the question at hand.[16,26] Both studies compared triptans to a variety of alternative treatments and were independent from manufacturer sponsorship. The population modelled in the analysis by NCGC was patients aged 12 and over, while patients aged 18-65 were modelled in the analysis funded by the Finnish Medicines Agency.

The results of the NCGC report suggest that for naïve patients, triptans were more cost effective than acetaminophen, ergots, and NSAIDs and that for experienced patients, the addition of NSAIDs or acetaminophen to triptans dominated triptans alone.[26] This independent economic analysis considered non-triptan medications as well as non-triptan and triptan combinations. Moreover, effectiveness data were derived from network meta-analysis; as well, this analysis considered quality of life. However, its applicability is limited since adverse events were not included within the model and non-preference-based measures were used to estimate quality of life.[15]

The results from the Finnish Medicines Agency sponsored report imply that sumatriptan 100 mg dominated all other triptans with the exception of eletriptan 40 mg.[16] This independent economic analysis considered a variety of triptans. Effectiveness data were derived from mixed treatment comparison and this analysis considered quality of life. However, its applicability is limited since the costs associated with the management of adverse events were not considered and non-preference-based measures were used to estimate quality of life.[15]

Results from manufacturer sponsored economic analyses suggest that rizatriptan, eletriptan and almotriptan are the most cost effective triptan; this is similar to a systematic review of the cost effectiveness of triptan conducted by CADTH.[26] There are concerns over the potential bias due to sponsorship; therefore, it is difficult to accept these results at face value. Overall, most CEA compared the cost effectiveness of triptans, while CUA compared the cost effectiveness of triptan and non-triptan medications. Applicability of non-Canadian studies to any decision regarding the cost effectiveness of triptans is limited given that they are not from the Canadian perspective; most do not consider generic prices or comparisons to no therapy or non-triptan medications.

While there were subgroups of interest were identified by the research team (e.g., use in patients <65 and >65 years), there was insufficient evidence in published economic evaluations to address these issues.

A full systematic review report can be found in Appendix A - A Systematic Review of Economic Evidence.

Reimbursement Based Economic Assessment

Choice of Time Series Model

Based on the criteria for choosing the appropriate model, the linear model was chosen for all analyses for both the forecasting of triptan and ergot expenditure (see Appendix B1: Model Details for full model details).

Forecasting Expenditure

Triptan expenditure has increased at a steady rate from $0.57 million in 2000 to $1.62 million in 2012 (figures adjusted to 2012 average costs). All four time series models forecasted increased expenditure over the next three years. The linear model forecasted that by 2015 the expenditure on triptans would increase to $1.81 million assuming no new triptans were covered by OPDP.

Ergot expenditure declined from $0.42 million in 2000 to $0.26 million in 2006 and has remained relatively constant since with expenditures of $0.26 million in 2012 (figures adjusted to 2012 average costs). Due to the discontinuation of oral ergots in 2013, it is not possible to forecast expenditure in ergots.

Alternative Approaches to Reimbursement Considered

Alternative reimbursement strategies varied according to the process of reimbursement – current EAP status, EAP with generic costs equivalent to 25% of branded costs, EAP with replacement of brand name agents with their generic formulation when available, EAP with no coverage of brand products, GB/LU for all triptans and GB/LU for generic products only – and the imposition of quantity limits – no limit, no more than 6 per month, no more than 12 per month and no more than 18 per month. For all GB/LU strategies it was assumed that generic products would cost 25% of the branded equivalent and that replacement of brand name agents with their generic formulation, when available, would be required.

A total of 20 reimbursement strategies were considered (full details provided in Table 1 Reimbursement Strategies).

Impact of Alternative Approaches to Reimbursement

42.4% of prescriptions under EAP are for brand name products. It is expected that triptan expenditure in 2015 will be $1,812,914. Requiring that under EAP generic triptans should be 25% of brand cost (Option EAP1) is forecasted to reduce expenditure on triptans by 16% (a reduction of $0.30 million in 2015). Combining reduced generic costs with the requirement of replacement of brand name agents with their generic formulation, when available, (Option EAP2) will reduce expenditure by 69% (a reduction of $1.25 million in 2015). A policy of covering under EAP only the triptans for which a generic equivalent is available (Option EAP3) in combination with reduced generic costs with the requirement of replacement of brand name agents with their generic formulation will have little incremental budget impact over the previous option (a reduction of $1.26 million in 2015).

Based on current prescribing in Alberta where triptans are available similar to general benefit/limited use for eligible patients aged 18-64years, coverage of triptans through general benefit/limited use is forecasted to lead to an increase in the expenditure of triptans in Ontario by 302% (an increase of $5.52 million in 2015). Restricting coverage under GB/LU to only generic products will lead to an increase of 293% (an increase of $5.35 million in 2015). Similarly, based on current prescribing in Manitoba where triptans are available with a passive quantity limit of 12, coverage of triptans through general benefit/limited use is forecasted to lead to an increase in the expenditure of triptans in Ontario by 197% (an increase of $3.60million in 2015). Restricting coverage under GB/LU to only generic products will lead to an increase of 190% (an increase of $3.47 million in 2015).

Imposition of quantity limits when triptans are available through EAP will lead to small absolute decreases in total triptan expenditures. For example, for strategy EAP2 the incremental reduction in triptan expenditure through imposing a quantity limit of 6 per month compared to no quantity limits would be approximately $285,000 (a reduction of $1.54 million compared to a reduction of $1.25 million).

However, for strategies involving access to triptans through GB/LU based on Alberta usage, the impact of quantity limits is much greater. For strategy GB/LU2, the incremental reduction in triptan expenditure through imposing a quantity limit of 6 per month compared (strategy GB/LU4) to no quantity limits (strategy GB/LU2) would be approximately $2.90 million. For strategy GB/LU2, the incremental reduction in triptan expenditure through imposing a quantity limit of 12 per month (strategy GB/LU6) compared to no quantity limits would be approximately $1.44 million. However, overall expenditure on triptans would still be significantly greater than if they remained on EAP (an increase of $2.45 million under GB/LU4, $3.90 million under GB/LU6 and $5.35 million under GB/LU2).

Similarly, for strategies involving access to triptans through GB/LU based on Manitoba usage, the impact of quantity limits is much greater. For strategy GB/LU2, the incremental reduction in triptan expenditure through imposing a quantity limit of 6 per month compared (strategy GB/LU4) to no quantity limits (strategy GB/LU2) would be approximately $1.17 million. For strategy GB/LU2, the incremental reduction in triptan expenditure through imposing a quantity limit of 12 per month (strategy GB/LU6) compared to no quantity limits (strategy GB/LU2) would be approximately $0.31 million. However, overall expenditure on triptans would still be significantly greater than if they remained on EAP (an increase of $2.30 million under GB/LU4, $3.17 million under GB/LU6 and $3.47 million under GB/LU2).

A full budget impact analysis report can be found in Appendix B - Budget Impact Analysis.

Overall Conclusions

In 2012, expenditure by OPDP on triptans was $1.62 million, whilst expenditure on ergots was $0.26 million. Without any change in reimbursement for triptans, it is expected that expenditure on triptans will rise over the next three years.

Ensuring that under EAP, generic products are priced at 25% of brand products will lead to a reduction in

total costs. Quantity limits will have only a small impact on total expenditures if triptans remained under EAP.

If triptans were moved to GB/LU costs will increase substantially even with the imposition of quantity limits.

Conclusions

Evidence suggest that triptans are cost effective compared to ergots for the treatments for migraines.

Without any change in reimbursement for triptans, it is expected that expenditure on triptans will rise over the next three year.

If triptans were available at a generic price of 25% of average branded cost, regardless of a quantity limit reimbursement status, there would be a reduction in expenditure by OPDP.

Changing the reimbursement status of all triptans to general benefit/limited use with or without quantity limits, and even with a generic price of 25% of average branded cost, would lead to a significant increase in expenditure by OPDP.

References

1. Bank of Canada. 10-year currency converter. 2014. Bank of Canada. 9-1-0014.

2. Bank of Canada. Inflation Calculator. 2014. Bank of Canada. 9-1-2014.

3. Adelman JU, Belsey J. Meta-analysis of oral triptan therapy for migraine: number needed to treat and relative cost to achieve relief within 2 hours. J Manag Care Pharm.2003;9(1):45-52.

4. Kelman L, Von Seggern RL. Using patient-centered endpoints to determine the cost-effectiveness of triptans for acute migraine therapy. Am J Ther.2006;13(5):411-7.

5. Mullins CD, Weis KA, Perfetto EM, Subedi PR, Healey PJ. Triptans for migraine therapy: a comparison based on number needed to treat and doses needed to treat. J Manag Care Pharm.2005;11(5):394-402.

6. Mullins CD, Subedi PR, Healey PJ, Sanchez RJ. Economic analysis of triptan therapy for acute migraine: A medicaid perspective. Pharmacotherapy.2007;27(8):1092-101.

7. Payne K, Kozma CM, Lawrence BJ. Comparing dihydroergotamine mesylate and sumatriptan in the management of acute migraine: A retrospective cost-efficacy analysis. Pharmacoeconomics.1996;10(1):59-71.

8. Perfetto EM, Weis KA, Mullins CD, Subedi P, Healey S. An economic evaluation of triptan products for migraine. Value Health.2005;8(6):647-55.

9. Williams P, Reeder CE. Cost-Effectiveness of Almotriptan and Rizatriptan in the Treatment of Acute Migraine. Clin Ther.2003;25(11):2903-19.

10. Williams P, Reeder CE. A comparison of the cost-effectiveness of almotriptan and sumatriptan in the treatment of acute migraine using a composite efficacy/tolerability end point. J Manag Care Pharm.2004;10(3):259-65.

11. Zhang L, Hay JW. Cost-effectiveness analysis of rizatriptan and sumatriptan versus Cafergot in the acute treatment of migraine. CNS Drugs.2005;19(7):635-42.

12. Evans KW. Economic evaluation of oral sumatriptan compared with oral caffeine/ergotamine for migraine. Pharmacoeconomics.1997;12(5):565-77.

13. Ilersich L. An economic analysis of sumatriptan for acute migraine [Internet]. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 1997 Jul. [cited 2013 Nov 11]. Available from: http://cadth.ca/media/pdf/sumatrip_ov_e.pdf

14. Thompson M, Gawel M, Desjardins B, Ferko N, Grima D. An economic evaluation of rizatriptan in the treatment of migraine. PharmacoEconomic.2005;23(8):837-50.

15. National Clinical Guideline Centre. CG150 Headaches: full guideline [Internet]. London:

National Clinical Guideline Centre; 2012 Sep. [cited 2013 Nov 11]. Available from: http://guidance.nice.org.uk/CG150/Guidance

16. Asseburg C, Peura P, Oksanen T, Turunen J, Purmonen T, Martikainen J. Cost-effectiveness of oral triptans for acute migraine: Mixed treatment comparison. Int J Technol Assess Health Care.2012;28(4):382-9.

17. Belsey JD. The clinical and financial impact of oral triptans - An updated meta-analysis. J Med Econ.2002;5(79-89):79-89.

18. Ramsberg J, Henriksson M. The cost-effectiveness of oral triptan therapy in Sweden. Cephalalgia.2007 Sep;27(1):54-62.

19. Slof J, Badia X, Magaz S, Lainez MJ, Galvan J, Heras J. Cost-efficacy of oral triptans in the treatment of acute migraine. J Med Econ.2005;8:27-43.

20. Wells N, Hettiarachchi J, Drummond M, Carter D, Parpia T, Pang F. A cost-effectiveness analysis of eletriptan 40 and 80 mg versus sumatriptan 50 and 100 mg in the acute treatment of migraine. Value Health.2003;6(4):438-47.

21. Belsey JD. Cost effectiveness of oral triptan therapy: A trans-national comparison based on a meta-analysis of randomised controlled trials. Curr Med Res Opin.2004;20(5):659-69.

22. Hens M, Villaverde-Hueso A, Alonso V, Abaitua I, Posada de la PM. Comparative cost-effectiveness analysis of oral triptan therapy for migraine in four European countries. Eur J Health Econ.2013;10.

23. Reeder CE, Steadman S, Goldfarb SD. Economic comparison of oral triptans for management of acute migraine: implications for managed care. Am J Manag Care.2002;8(3 Suppl):S80-S84.

24. Ferrari MD. Erratum: Triptans (serotonin, 5-ht1b/1d agonists) in migraine. Detailed results and methods of a meta-analysis of 53 trials (Cephalagia (2002) 22 (633-658)). Cephalalgia.2003;23(1):71.

25. Hawkins K, Wang S, Rupnow MFT. Indirect cost burden of migraine in the United States. J Occup Environ Med.2007;49(4):368-74.

26. Canadian Agency for Drugs and Technologies in Health. Triptans for Acute Migraine: Comparative Clinical Effectiveness and Cost-effectiveness [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2007 Mar. [cited 2013 Nov 11]. Available from: http://cadth.ca/en/products/health-technology-assessment/publication/690

27. Fox-Rushby JA, Cairns J. Economic evaluation. New York: Open University Press; 2005.

28. Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies: Canada [Internet]. 3. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006. [cited 2013 Jun 12]. Available from:

http://www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf

29. Garattini L, Koleva D, Casadei G. Modeling in pharmacoeconomic studies: funding sources and outcomes. Int J Technol Assess Health Care.2010 Jul;26(3):330-3.

30. A randomized, double-blind comparison of sumatriptan and Cafergot in the acute treatment of migraine. The Multinational Oral Sumatriptan and Cafergot Comparative Study Group. Eur Neurol.1991;31(5):314-22.

31. Sumatriptan, serotonin, migraine, and money. Lancet.1991;339(8786):151-2.

32. Adelman JU, Adelman LC, Freeman MC, Von Seggern RL, Drake J. Cost Considerations of Acute Migraine Treatment. Headache.2004;44(3):271-85.

33. Becker WJ. Are the triptans for migraine therapy worth the cost? Can J Neurol Sci.2000;27(2):111-5.

34. Cady RC. Reduction of labor costs associated with treating migraine in the workplace. Arch Intern Med.1999;159(2):197.

35. Curtiss FR. Best value for money in triptans. J Manag Care Pharm.2005;11(5):419-21.

36. Feczko JM. Cost of sumatriptan. Lancet.1992;340(8813):243.

37. Goldberg LD. The cost of migraine and its treatment. Am J Manag Care.2005;11(Suppl 2):S62-S67.

38. Guidotti M, Ravasio R. Clinical and economic comparison of frovatriptan versus other oral triptans in the treatment of acute migraine in the real-world setting. Clin Drug Invest.2009;29(11):693-702.

39. Hoffman L, Mayzell G, Pedan A, Farrell M, Gilbert T. Evaluation of a monthly coverage maximum (drug-specific quantity limit) on the 5-HT1 agonists (triptans) and dihydroergotamine nasal spray. J Manag Care Pharm.2003;9(4):335-45.

40. Johnson K. Migraine therapy: Balancing efficacy and safety with quality of life and cost. Formulary.2002;37(12):634-44.

41. Kozma CM, Reeder CE. Comparison of the economic, clinical, and humanistic attributes of dihydroergotamine and sumatriptan. Clin Ther.1995;17(2):315-9.

42. Lofland JH, Nash DB. Oral serotonin receptor agonists: A review of their cost effectiveness in migraine. Pharmacoeconomics.2005;23(3):259-74.

43. Rapoport AM, Adelman JU. Cost of migraine management: A pharmacoeconomic overview. Am J Manag Care.1998;4(4):531-45.

44. Rothrock JF. A costly attack of migraine. Headache.2008;48(6):951.

45. Savani N, Martin A, Browning D. Switching patients with migraine from sumatriptan to other triptans increases primary care costs. Int J Clin Pract.2004;58(8):758-63.

46. Siva PA, Mohonty S, Satyanarayana B. A cost effective and large-scale synthesis of Zolmitriptan: An anti-migraine drug. Der Pharma Chemica.2012;4(1):347-51.

47. Von Seggern RL, Adelman JU. Cost considerations in headache treatment part 2: Acute migraine treatment. Headache.1996;36(8):493-502.

48. Lampl C, Buzath A, Yazdi K, Sandor PS. Ergot and triptan overuse in Austria - An evaluation of clinical data and cost. Cephalalgia.2002;22(10):807-11.

49. Mannix LK, Adelman JU, Goldfarb SD, Von S, Kozma CM. Almotriptan versus sumatriptan in migraine treatment: direct medical costs of managing adverse chest symptoms. Am J Manag Care.2002;8(3 Suppl):S94-101.

50. Wang JT, Barr CE, Goldfarb SD. Impact of chest pain on cost of migraine treatment with almotriptan and sumatriptan. Headache.2002;42(Suppl 1):S38-S43.

51. Wang JT, Barr CE, Torigoe Y, Wang E, Rowland CR, Goldfarb SD. Cost savings in migraine associated with less chest pain on new triptan therapy. Am J Manag Care.2002;8(3 Suppl):S102-S107.

52. Caro G, Getsios D, Caro JJ, Raggio G, Burrows M, Black L. Sumatriptan: Economic evidence for its use in the treatment of migraine, the Canadian comparative economic analysis. Cephalalgia.2001;21(1):12-9.

53. Caro JJ, Getsios D, Raggio G, Caro G, Black L. Treatment of migraine in Canada with naratriptan: A cost-effectiveness analysis. Headache.2001;41(5):456-64.

54. Cohen JA, Beall D, Beck A, Rawlings J, Miller DW, Clements B, et al. Sumatriptan treatment for migraine in a health maintenance organization: Economic, humanistic, and clinical outcomes. Clin Ther.1999;21(1):190-204.

55. Gerth WC, Sarma S, Hu XH, Silberstein SD. Productivity Cost Benefit to Employers of Treating Migraine with Rizatriptan: A Specific Worksite Analysis and Model. J Occup Environ Med.2004;46(1):48-54.

56. Joish VN, Armstrong EP. Use of decision analysis in modeling the cost-effectiveness of oral vs SC sumatriptan. Formulary.2000;35(6):532-9.

57. Legg RF, Sclar DA, Nemec NL, Tarnai J, Mackowiak JI. Cost-effectiveness of sumatriptan in a managed care population. Am J Manag Care.1997;3(1):117-22.

58. Legg RF, Sclar DA, Nemec NL, Tarnai J, Mackowiak JI. Cost benefit of sumatriptan to an

employer. J Occup Environ Med.1997;39(7):652-7.

59. Litaker DG, Solomon GD, Genzen JR. Impact of sumatriptan on clinic utilization and costs of care in migraineurs. Headache.1996;36(9):538-41.

60. Lofland JH, Locklear JC, Frick KD. Different approaches to valuing the lost productivity of patients with migraine. Pharmacoeconomics.2001;19(9):917-25.

61. Lofland JH, Kim SS, Batenhorst AS, Johnson NE, Chatterton ML, Cady RK, et al. Cost-effectiveness and cost-benefit of sumatriptan in patients with migraine. Mayo Clin Proc.2001;76(11):1093-101.

62. Williams P, Dowson AJ, Rapoport AM, Sawyer J. The cost effectiveness of stratified care in the management of migraine. Pharmacoeconomics.2001;19(8):819-29.

63. Caro G, Getsios D, Caro JJ, Raggio G, Burrows M, Black L. Sumatriptan: economic evidence for its use in the treatment of migraine, the Canadian comparative economic analysis. Cephalalgia.2001;21(1):12-9.

64. Caro JJ, Getsios D, Raggio G, Caro G, Black L. Treatment of migraine in Canada with naratriptan: a cost-effectiveness analysis. Headache.2001;41(5):456-64.

65. Legg RF, Sclar DA, Nemec NL, Tarnai J, Mackowiak J, I. Cost-effectiveness of sumatriptan in a managed care population. Am J Manag Care.1997;3(1):117-22.

66. Legg RF, Sclar DA, Nemec NL, Tarnai J, Mackowiak J, I. Cost benefit of sumatriptan to an employer. J Occup Environ Med.1997;39(7):652-7.

67. Lofland JH, Kim SS, Batenhorst AS, Johnson NE, Chatterton ML, Cady RK, et al. Cost-effectiveness and cost-benefit of sumatriptan in patients with migraine. Mayo Clin Proc.2001;76(11):1093-101.

68. Slof J. Cost-effectiveness analysis of early versus non-early intervention in acute migraine based on evidence from the 'Act when Mild' study. Appl Health Econ Health Policy.2012;10(3):201-15.

69. Adelman JU, Belsey J. Meta-analysis of oral triptan therapy for migraine: number needed to treat and relative cost to achieve relief within 2 hours. J Manag Care Pharm.2003;9(1):45-52.

70. Asseburg C, Peura P, Oksanen T, Turunen J, Purmonen T, Martikainen J. Cost-effectiveness of oral triptans for acute migraine: mixed treatment comparison. Int J Technol Assess Health Care.2012 Oct;28(4):382-9.

71. Evans KW, Boan JA, Evans JL, Shuaib A. Economic evaluation of oral sumatriptan compared with oral caffeine/ergotamine for migraine. Pharmacoeconomics.1997;12(5):565-77.

72. Ilersich L. An economic analysis of sumatriptan for acute migraine. 1997.

73. Mullins CD, Weis KA, Perfetto EM, Subedi PR, Healey PJ. Triptans for migraine therapy: a

comparison based on number needed to treat and doses needed to treat. J Manag Care Pharm.2005;11(5):394-402.

74. Ramsberg J, Henriksson M. The cost-effectiveness of oral triptan therapy in Sweden. Cephalalgia.2007;27(1):54-62.

75. Thompson M, Gawel M, Desjardins B, Ferko N, Grima D. An economic evaluation of rizatriptan in the treatment of migraine. Pharmacoeconomics 23[8], 837-850. 2005.

76. Williams P, Reeder CE. Cost-effectiveness of almotriptan and rizatriptan in the treatment of acute migraine. Clin Ther.2003;25(11):2903-19.

77. Williams P, Reeder CE. A comparison of the cost-effectiveness of almotriptan and sumatriptan in the treatment of acute migraine using a composite efficacy/tolerability end point. J Manag Care Pharm.2004;10(3):259-65.

78. Zhang L, Hay JW. Cost-effectiveness analysis of rizatriptan and sumatriptan versus Cafergot in the acute treatment of migraine. CNS Drugs.2005;19(7):635-42.

79. Zhang L, Hay JW. Cost-effectiveness analysis of rizatriptan and sumatriptan versus Cafergot in the acute treatment of migraine. CNS Drugs.2005;19(7):635-42.

80. Statistics Canada. Canadian Community Survey (CCHS), C2012 Annual Component surveys. [Microdata] . 2013. Ottawa, Ontario.

81. Chu MK, Buse DC, Bigal ME, Serrano D, Lipton RB. Factors associated with triptan use in episodic migraine: results from the American Migraine Prevalence and Prevention Study. Headache.2012 Feb;52(2):213-23

Appendices

Appendix A - A Systematic Review of Economic Evidence

Research Question

What is the current evidence for the cost-effectiveness of triptans (alone or in combination with other drugs) for acute treatment of migraines compared to: other triptans, acetaminophen, antiemetic's, ASA and ergots?

Review of the Published Literature

Search Strategy and Search Findings

Search Strategy

A search of the medical literature from 1946 to present (2013 November 11) in Ovid Medline (indexed, in-process and other non-indexed) and Embase Classic & Embase 1947 to 2013 November 08 was conducted in order to capture all relevant literature. Key words relating to triptans for the treatment of migraines were combined with a standardized search strategy for identifying economic analyses adopted by NHS EED. The complete search strategy can be found in Appendix A1: Search Strategies and Results.

In addition, the Tufts CEA registry and NHSEED were also searched for relevant articles. Grey literature was identified through CADTH and NICE websites. Moreover, the reference lists of relevant studies were hand searched for additional relevant studies.

Search Findings

920 citations were identified from the original search.

One reviewer (KAS) independently reviewed the literature searches in order to identify potential articles for inclusion within the critical appraisal. Any uncertainties were resolved through consensus with another reviewer (DC).

Of the 920 citations that were identified, a total of 72 economic citations were identified for potential inclusion within the report; 819 citations were excluded. The reasons for exclusion were the following: not an economic analysis, not migraine, or not relevant intervention. An additional 32 citations were excluded; reasons for exclusion were as follows: non-English, not available or not full text. Results of the search can be found in Appendix A2: Results of Search.

The 72 potential studies identified during the literature review were reviewed by one reviewer (KAS). Of these, 21 publications which addressed the objective of the review were selected for inclusion. Those studies that were not included within the review along with the reasons for exclusion are detailed in Appendix A3: Excluded Studies.

Included Studies

The comprehensive list of included studies can be found in Appendix A4: List of Included Studies.

Summary and Critical Appraisal of Included Studies: Migraine

Included Studies

Of the 21 reports selected for inclusion, almost half were American,[3-11] three were Canadian,[12-14] and six were European (UK, Spain, Finland, and Sweden) studies,[15-20] and two involved multiple countries (European; European and North American).[21,22] More than half of the included studies were financed by manufacturers[3-6,8-11,14,17,19-21] and five were sponsored by health technology assessment organization or the department of health.[7,12,13,15,16]

Almost half of the reports were informal analyses which considered costs per successful treatment rather than incremental costs per outcomes,[3-6,8,17,20,22,23] ten considered ICER,[7,9,10,12-14,16,18,19,21] while six considered ICUR.[11-16]The most common comparator was triptan, followed by ergots, then ASA plus antiemetic, acetaminophen alone and triptan in combination with other comparators (NSAIDs or acetaminophen).

A total of three studies used a patient population of 18-65 years of age,[7,16,19] while one used a patient population of 12 years of age and older,[15] another assumed that patients were 40 years of age,[18] while another study specified a patient population ranging from less than 18 year of age to over 45 years of age.[20] A total of 15 studies did not specify the age of the patient population modelled,[3-6,8-14,17,20-23]

All studies were either a decision tree and decision analytic model with the exception of one trial based model.[7] Almost half of the reports[4-6,8-11,14,18,19,23] used effectiveness data derived from a published meta-analysis,[24] only two reports used effectiveness data derived from a network meta-analysis/mixed treatment comparison.[15,16]

Only three reports included costs associated with the management of adverse events.[7,11,19] Most studies considered sensitivity analysis; nine reports included deterministic sensitivity analysis,[4-8,14,16,19] and six included both deterministic and probabilistic sensitivity analysis.[5,9,12,13,15,18,25]

Only two reports considered generic prices for triptan,[16,22] while three studies discounted drug acquisition costs to account for generic pricing. [5,8,19]

A table summarizing included studies is provided in Appendix A5: Characteristics of Reviewed Studies.

The quality of each study was assessed in terms of: the source of efficacy data; the costs associated with the treatment of migraine which include cost of adverse events and not simply drug acquisition costs; the consideration of utility values, more specifically, the use of preference-based measures; and the adoption of sensitivity analysis.

Common Issues

Five common issues can be found throughout this review: informal analyses, use of a meta-analysis of questionable methods and applicability, exclusion of adverse event costs(although the systematic review suggests that clinical evidence supports no difference in adverse event rates between triptans and compared to other migraine therapies), use of branded prices, and use of non-preference-based measures for quality of life estimates.

First, many reports were informal analyses which considered costs per successful treatment rather than incremental costs per outcome. Typically, these informal analyses report results as average cost effectiveness ratios. Since economic evaluations are comparative analyses, incremental cost effectiveness ratios as opposed to average costs effectiveness ratios should be presented, preferably using multidimensional outcomes such as QALYs or outcomes that are patient relevant such as impact on quality of life.[27]

Second, almost half the studies used effectiveness data derived from a single published meta-analysis.[24] According to a systematic review of the cost effectiveness of triptan conducted by CADTH,[26] this meta-analysis had many limitations which, therefore, led to the conclusion that the meta-analysis had "questionable methods and applicability."[26] Limitations highlighted in the systematic review were: overestimates of efficacy data; heterogeneity of included clinical trials; conflicting results with individual trials.

Third, the majority of studies excluded costs associated with the management of adverse events. Neglecting costs associated with the management of adverse events limits the usefulness of these studies to the question at hand.

Fourth, almost all studies used branded prices for triptans as manufacturer sponsored studies tend to be connected at the point of seeking formulary reimbursement. Currently in Canada, most triptans are now available in generic form. Therefore, the results of studies using branded prices have limited applicability unless reanalysis using generic prices is feasible.

Lastly, all studies which included a cost-utility analysis used utility values derived from the Quality of Wellbeing Scale (QWB) which is a non-preference-based measure. Preference-based measures are encouraged in economic analyses[28], therefore these studies which included utility values from non-preference-based measures have limited applicability.

A further consideration is that the majority of studies are industry sponsored and are therefore susceptible to the biases and limitations that have been found in manufacture sponsored evaluations.[29]

Canadian Studies

Thompson et al. (2005)

A 2005 study by Thompson and colleagues funded by Merck Frosst Canada was a cost-effectiveness/cost-utility analysis of rizatriptan compared with usual care, sumatriptan 50 mg, sumatriptan 100 mg, naratriptan 2.5 mg, and zolmitriptan 2.5 mg in men and women who experience moderate-severe migraines and for whom other acute therapies such as NSAIDs, single analgesics are insufficient or contraindicated.[14]

The study was conducted using a decision tree with a time frame of 24 hours. Effectiveness data for triptans was derived from a published meta-analysis.[24] The efficacy measure included pain-free response at 2 hours and sustained pain free for 2-24 hours. Adverse events were not modeled. Utility values were

derived from QWB. Costs were based on published and unpublished Canadian sources. The costs of triptans were based on the Ontario Drug Benefit (ODB) Formulary plus a 10% mark-up.

Strengths of this analysis include that it is from a Canadian perspective and reflect the course of disease, as well, rescue medication and health care service and costs were considered. Limitations of the analysis include that the costs of managing adverse events were not considered; some studies have included hospitalization costs as result of cardiovascular events, central nervous system (CNS) events, chest events.[7,11,19] Moreover, effectiveness data were derived from a meta-analysis of "questionable methods and applicability."[26] Finally, utility values were derived from non-preference-based measures.

In both government and societal perspectives, rizatriptan was the least costly among triptans. Rizatriptan dominated all other triptans. In one-way deterministic analyses, rizatriptan remained dominant compared to all other triptans; however, parameters tested in the analyses were not presented.

Applicability of this study may be limited given that this study examines only the cost effectiveness of triptans and effectiveness data were derived from a meta-analysis of "questionable methods and applicability."[26]

Evans (1997)

A 1997 study by Evans sponsored by Canadian Coordinating Office for Health Technology Assessment (CCOHTA) was a cost- effectiveness/cost-utility/cost-benefit analysis of one oral sumatriptan 100 mg in comparison with two oral caffeine 100 mg/ergotamine 1 mg in patients with migraine. The study population considered was not detailed.[12]

The study was conducted using a decision tree with a time frame of 48 hours (CEA), and 1 year [CUA, cost-benefit analysis (CBA)]. Effectiveness data were derived from a meta-analysis using informal comparison. The primary efficacy measure was conversion of moderate or severe headache to mild or no headache at 2 hours. Adverse events were not modeled. Utility values were derived from QWB. Costs were based on Canadian data from random and non-random telephone surveys, Statistics Canada, and Canadian Institute for Health Information. In the base case, the cost of sumatriptan and caffeine/ergotamine was based on the lowest branded price from a random telephone survey of 20 Canadian community pharmacies.

Strengths of this analysis include that it is from a Canadian perspective incorporating Canadian costs. Health service use and costs are considered.

Limitations of this analysis include that the cost of sumatriptan and caffeine/ergotamine derived from non-generic treatments; these branded prices were not reported. Additionally, the model assumed both treatments were given only once to abort migraine attack and once more if there was a recurrence within 48 hours of relief; this poses a bias since for oral caffeine/ergotamine two tablets are given at the onset of migraine, followed by one each half hour until the attack is aborted. Effectiveness data were

derived using indirect comparison. Adverse events were not included in the model. Utility values were derived from non-preference-based measures. Probabilistic analysis results are not particularly useful, as the underlying uncertainty over whether sumatriptan is cost effectiveness was not demonstrated using conventional formats.

Caffeine/ergotamine was the least costly strategy, however, resulted in a lower expected utility than sumatriptan. The incremental cost effectiveness ratios for sumatriptan versus caffeine/ergotamine from a societal perspective were -$25 per attack aborted, -$7,507 per QALY, and $42 per patient per year and from a provincial health department perspective were $98 per attack aborted and $29,366 per QALY. In sensitivity analyses, with respect to the societal perspective, the results are sensitive to relative effects and drug costs. With respect to provincial health department perspective, the results were insensitive to changes. In the subgroup analysis, sumatriptan was slightly superior in treating severe migraine attacks as opposed to moderate migraine attacks.

Overall, this study is of poor quality. Although, the study is from a Canadian perspective that compared triptan to non-triptan medication and considered healthcare service use and costs, it does not use data from reliable sources. Therefore, the applicability of this study to any decision regarding the cost effectiveness of oral sumatriptan compared with oral caffeine/ergotamine should be done with caution.

Ilersich (1997)

In 1997, CCOHTA funded a study by Ilersich.[13] This study was a cost- effectiveness/cost-utility/cost-benefit analysis of oral sumatriptan 100 mg, 1 Cafergot tablet, acetylsalicylic acid 975 mg plus metoclopramide 10 mg, subcutaneous sumatriptan 6 mg, subcutaneous dihydroergotamine 1 mg, and intranasal butorphanol 1 mg in patients with migraine.

This study was conducting using a decision tree with a time frame of 48 hours. A meta-analysis conducted by the author was used to estimate the relative effectiveness of the treatments for input into the model. The efficacy measure included conversion from severe/moderate pain to mild or none pain. Recurrence and other events such as emergency room visit and hospitalization were considered. Adverse events were not modeled. Utility values were derived from QWB. Costs were based on published and unpublished Canadian and international sources. The costs of treatments were based on a survey of community pharmacy retail prices.

Strengths of this analysis include that it is from a Canadian perspective incorporating a variety of comparators and effectiveness data were derived from a meta-analysis conducted by the authors. Additionally, health care service and costs were included into the model. Limitations of this analysis include that drug acquisition costs were based on non-generic price, which is not representative of the current situation; adverse events were not modeled; and utility values were derived from non-preference-based measures.

In terms of drug acquisition costs, ASA plus metoclopramide was the least costly at $0.13. From a government perspective, the incremental cost utility ratio for oral sumatriptan versus

ASA/metoclopramide was $47,200 per QALY. The incremental cost utility ratio for oral sumatriptan versus subcutaneous dihydroergotamine was $62,600 per QALY. From a societal perspective, oral sumatriptan dominated oral ergotamine/caffeine. The incremental cost utility ratio for oral sumatriptan versus subcutaneous dihydroergotamine was $24,500 per QALY, and the net benefit was -$159. The authors report the results being insensitive to parameter changes in deterministic and probabilistic analysis; however, data were not shown.

Although this study is from a Canadian perspective and compared triptan to other triptans and non-triptan medication, use of non-generic price, disregard for adverse events and values derived from non-preference-based measures limits its applicability. Therefore, the applicability of this study to any decision regarding the cost effectiveness of triptans should be done with caution.

Non-Canadian Studies

Hens et al. (2013)

A recent economic analysis conducted by Hens et al. compared the average cost per unit of effectiveness of oral almotriptan 12.5 mg, sumatriptan (brand name and generic) 50 mg, and zolmitriptan 2.5 mg among four European Countries (France, Italy, UK, and Spain).[22] The study considered adult patients diagnosed with migraine according to the International Headache Classification, who were unresponsive to analgesics or anti-inflammatory drugs.

Two decision trees were constructed – Scenario A which used lower effectiveness probabilities and Scenario B which considered higher effectiveness probabilities. Efficacy data used in two published economic analyses[3,18] were used as the relative effectiveness of the treatments for input into the model. Costs included within the model were published market drug prices of pharmacies for a single dose of treatment from national drug directories.

Generic sumatriptan was the least costly treatment. The average cost per unit of effectiveness of generic sumatriptan ranged from €14.50-€36.67 (Scenario A), €9.16-€23.16 (Scenario B); with UK having the least average cost per unit of effectiveness. Sensitivity analysis was not considered.

The study has several weaknesses. The study is an informal analysis; reporting an average cost per unit of effectiveness of each treatment, rather than the incremental cost per outcome. Only drug cost acquisition costs were considered. Sensitivity analysis and costs associated with managing adverse events or health care service use and costs were not considered.

Applicability of this study is limited given that it is not from the Canadian perspective and the study is an informal analysis which included only drug cost acquisition costs within the analysis.

Asseburg et al. (2012)

A recent study by Asseburg and colleagues funded by the Finnish Medicines Agency was a cost-effectiveness/cost-utility analysis of oral triptans (sumatriptan 100 mg in comparison with almotriptan 12.5 mg, eletriptan 40 mg, frovatriptan 2.5 mg, naratriptan 2.5 mg, rizatriptan 10 mg, sumatriptan 50

mg, zolmitriptan 2.5 mg, zolmitriptan 5 mg) for the treatment of acute migraine.[16]

A decision-tree model used to evaluate oral triptan therapies in Sweden[18] was adapted to the Finnish setting, and extended to incorporate additional treatment arms and to evaluate the quality of life associated with additional treatments. A systematic review using mixed treatment comparison was used to estimate the relative effectiveness of the treatment for input into the model. Efficacy measures included 2 hour response, 2 hour pain-free, and recurrence, with the primary end point being sustained pain-free, no adverse events (SNAE). Sustained pain free 24 hours and recue medication were not considered. Costs included within the model were drug acquisition costs and productivity losses; costs associated with the management of adverse events, and health care service use and costs were not considered. Utility values were derived from the Quality of Wellbeing Scale self-administered (QWB-SA) cited in Thompson et al;[14] in deterministic analysis, utility values from EQ-5D were considered.

Sumatriptan 100 mg was the least costly treatment at €20.86 per attack. Sumatriptan 100 mg dominated all treatments with the exception of eletriptan 40 mg. The incremental cost effectiveness ratios for eletriptan 40 mg versus sumatriptan 100 mg were €43.65 per SNAE and €19,659 per QALY. In one way sensitive analyses, results were insensitive to drug acquisition costs and utility values.

Although the study is independent and efficacy data is derived from a systematic review using mixed treatment comparison, applicability of this study may be limited given it is not from the Canadian perspective and health care service use and costs as well as costs of managing adverse events were not considered.

National Clinical Guideline Centre, 2012

A recent health technology assessment conducted on behalf of the NICE in the UK compared the cost effectiveness of NSAIDs, acetaminophen, ergots, triptans, triptan in combination with NSAIDs and triptan in combination with acetaminophen in patients aged 12 or over, diagnosed with migraine.[15]

A decision tree was constructed beginning at migraine onset. A network meta-analysis was used to estimate the relative effectiveness of the treatments for input into the model. Sustained pain free at 24 hours was considered the primary outcome. Health care service use and costs as well as costs of managing adverse events were not considered. Utility gains were derived from QWB.

Acetaminophen, ergots, and NSAIDs were less costly, but less effective compared to triptans. The incremental cost utility ratio for triptans versus acetaminophen was £15,852 per QALY, versus NSAIDs was £12,635 and versus ergots was £683. Thus, it could be interpreted that triptans were the most cost effective alternative for treatment of naïve patients. The incremental cost per QALY gained for triptans + acetaminophen versus acetaminophen was £5,913 per QALY; and for triptans + NSAIDs versus NSAIDs was £4,780 per QALY. In one-way deterministic analyses, results were sensitive to triptan costs. In scenario based deterministic analysis, results were sensitive to the assumption of sustained headache response at 24 hours as the primary clinical outcome. In probabilistic analysis, triptan in combination with NSAIDs and triptan in combination with acetaminophen had the highest probability of being cost effective.

Applicability of this study may be limited given it is not from the Canadian perspective; the patient population includes children aged 12 and over; and health care service use and costs as well as costs of

managing adverse events were not considered. However, this study is independent and included a comparison of non-triptan medications as well as a combination of triptan and non-triptan medications, suggesting that conclusion from this study may apply to Canada.

Mullins et al. (2007)

Mullins and associates compared the cost effectiveness of oral triptans (almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) from a US Medicaid perspective.[6] Effectiveness data were derived from a published meta-analysis.[24] Efficacy measures included: headache relief at 2 hours, pain-free at 2 hours, recurrence of headache pain, and sustained pain-free. Costs included within the model were non-generic prices of treatments from seven American states.

In five of seven states, eletriptan 20 mg had the lowest cost to treat 100 patients and in two of seven states, eletriptan 40 mg had the lowest cost to treat 100 patients. In terms of cost per successfully treated patient, eletriptan 40 mg had the lowest in all seven states. In one-way deterministic analysis, results were sensitive to dosing assumption; as eletriptan 40 mg had the lowest cost to treat 100 patients in all seven states.

The study has weaknesses. This study is an informal analysis that considered only drug acquisition costs. As well, effectiveness data were derived from a meta-analysis of "questionable methods and applicability."[26]

Applicability of this study is limited given it is not from the Canadian perspective and this study is an informal analysis which included only drug acquisition costs of non-generic treatments within the analysis.

Kelman et al. (2006)

Kelman and colleagues compared the cost effectiveness of oral triptans (almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) from a US payer perspective.[4]

Effectiveness data were derived from a published meta-analysis.[24] Efficacy measures included sustained pain-free defined as pain free at 2 hours post-dosing with no recurrence and no rescue medication for 2-24 hours. Costs included within the model were drugs acquisition costs.

Almotriptan 12.5 mg and rizatriptan 10 mg were most cost effective in terms of achieving 100 sustained pain-free patients ($7,120, $7,427 respectively). Almotriptan 12.5 mg and rizatriptan 10 mg were most cost effective in terms of attaining 100 sustained pain-free patients with no-adverse events patients ($8,298, $12,545 respectively).

The study has key limitations. This study is an informal analysis that considered only drug acquisition costs and effectiveness data were derived from a meta-analysis of "questionable methods and applicability."[26]

Applicability of this study is limited given it is not from the Canadian perspective and this study is an

informal analysis which included only drug acquisition costs of non-generic treatments within the analysis.

Mullins et al. (2005)

Mullins and associates compared the cost effectiveness of oral triptans (almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) from a US healthcare payer perspective.[5] Effectiveness data were derived from a published meta-analysis.[24] Efficacy measures included: 2-hour response therapeutic gain, 2-hour pain-free therapeutic gain, 24-hour sustained pain-free, and recurrence. Costs included within the model were drugs acquisition costs which were based on average wholesale price, less 15% to account for generic pricing.

Eletriptan 40 mg had the lowest cost to successfully treat 100 patients ($5,630), while naratriptan 2.5 mg had the highest cost to successfully treat 100 patients ($11,136). In one-way deterministic analysis, results were insensitive to dosing assumption.

The study has three main weaknesses. The study is an informal analysis. Effectiveness data were derived from a meta-analysis of "questionable methods and applicability."[26] Only drug acquisition costs were considered.

Applicability of this study is limited given it is not from the Canadian perspective and this study is an informal analysis which included only drug acquisition costs within the analysis.

Perfetto et al. (2005)

Perfetto and colleagues compared the cost effectiveness of oral triptans (almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) from a US payer perspective.[8] Effectiveness data were derived from a published meta-analysis.[24] Effectiveness measures included response at 2 hours, pain free at 2 hours, sustained pain-free rate, recurrence rate in the 24 hour-period. Costs included within the model were average wholesale price discounted by 15% for a branded triptan.

Eletriptan had the lowest cost to treat 100 patient attack ($1,560) and lowest cost per successfully treated patient ($56.39). Results were not presented as ICER.

The study has several weaknesses. The study is an informal analysis. Only drug acquisition costs were considered. Effectiveness data are derived from a meta-analysis of "questionable methods and applicability."[26]

Applicability of this study is limited given it is not from the Canadian perspective and this study is an informal analysis which included only drug acquisition costs within the analysis.

Ramsberg & Henriksson (2005)

Ramsberg and Henriksson compared the cost-effectiveness of oral triptans (eletriptan, rizatriptan, zolmitriptan, almotriptan, and sumatriptan) from a Swedish societal perspective.[18] Effectiveness data

were derived from a published meta-analysis.[24] Efficacy measures were pain-free at 2 hours and recurrence with the primary measure being SNAE. Costs included within the model were drug acquisition costs and productivity losses.

Eletriptan and rizatriptan dominated all other triptans. The incremental cost effectiveness ratio for rizatriptan versus eletriptan was €99.80 per SNAE. In one-way deterministic analysis, results were insensitive to treatment effects. In scenario based deterministic analysis, results were sensitive to no placebo adjustment using SNAE as outcome; no placebo adjustment using pain free at 2 hours as outcome; and no placebo adjustment using pain free at 2 hours , no adverse events as outcome. In probabilistic analysis, eletriptan and rizatriptan had the highest probability of being cost effective.

This study has one key weakness, effectiveness data were derived from a meta-analysis of "questionable methods and applicability."[26] Although the detailed sensitivity analysis suggests that conclusions from the study may apply to Canada, this analysis does not include a comparison to no therapy or other non-triptan medications.

Applicability of this study is limited given it is not from the Canadian perspective and the analysis does not include a comparison to no therapy or other non-triptan medications.

Slof et al. (2005)

Slof and colleagues compared the cost effectiveness of sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, and almotriptan from a Spanish payer perspective.[19]

Effectiveness data were derived from a published meta-analysis.[24] Efficacy measures included sustained pain-free defined as pain free at 2 hours post-dosing with no recurrence and no rescue medication for 2-24 hours. Costs included drugs acquisition costs as well as costs associated with chest related and CNS related adverse events. Drugs acquisition costs were discounted at 40% co-payment.

Naratriptan 2.5 mg was the least costly treatment, with total costs of €3.64. Naratriptan 2.5 mg, sumatriptan 50 mg, and almotriptan 12.5 mg dominated all other triptans. The incremental cost effectiveness ratio sumatriptan versus naratriptan was €23.09 per sustained pain-free patient. The incremental cost effectiveness ratio for almotriptan versus sumatriptan was €10.45 per sustained pain-free patient. In scenario based deterministic analysis, results were sensitive to low adverse events costs; zolmitriptan 2.5 mg and rizatriptan 10 mg were no longer dominated by naratriptan 2.5 mg, sumatriptan 50 mg, and almotriptan 12.5 mg.

Although this study considered the costs of managing adverse events, this study has a key weakness. Effectiveness data were derived from a meta-analysis of "questionable methods and applicability."[26]

Applicability of this study is limited given it is not from the Canadian perspective. Despite the consideration for cost of managing adverse events, this study is not independent; it is sponsored by Almirall Prodesfarma –the manufacturer of Almogran®, the brand name of almotriptan.

Zhang & Hay (2005)

Zhang & Hay compared the cost effectiveness of rizatriptan, Cafergot, and sumatriptan from a societal perspective.[11] For rizatriptan and sumatriptan, effectiveness data were derived from a published meta-analysis[24] and from the Multinational oral Sumatriptan and Cafergot Comparative Study using indirect comparison[30]. Direct costs included: physician visit cost, drug acquisition cost, cost of hospital drug and medical supplies; indirect costs included: patient travel and waiting time. Costs of managing adverse events were derived from hospitalization costs as a result of cardiovascular events.

Rizatriptan and sumatriptan dominated Cafergot; while rizatriptan dominated sumatriptan. In deterministic analysis, results were sensitive to treatment effect.

The study has weaknesses. Effectiveness data were derived from meta-analysis of questionable methods and applicability. Utilities were derived from QWB which is not a preference-based measure.

Although this analysis considers the cost effectiveness of triptan compared to ergot and another triptan, health care service use and costs as well as costs associated with the management of adverse events are considered, applicability of this study is limited given it is not from the Canadian perspective and non-generic costs are considered.

Belsey (2004)

Belsey compared the cost effectiveness of oral triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) among six international countries (USA, UK, Canada, Germany, Italy, and the Netherlands).[21] A meta-analysis using informal comparison was used to estimate the relative effectiveness of the treatment for input into the model. Efficacy measures included pain-free at 2 hours. Costs included within the model were drug acquisition costs.

For five of six countries, rizatriptan 10 mg and eletriptan 40 mg dominated sumatriptan 100 mg; all other triptans were less costly and less effective than sumatriptan 100 mg. In Canada, rizatriptan 10 mg dominated sumatriptan 100 mg; all other triptans were less costly and less effective than sumatriptan.

The study has key weaknesses. The estimates of relative effectiveness of the treatment derived from informal comparison and only drug acquisition costs are considered in the analysis.

Applicability of this study is limited given it is not from the Canadian perspective and only drug acquisition costs are included within the analysis.

Williams & Reeder (2004)

Williams and Reeder compared the cost-effectiveness of oral almotriptan and oral sumatriptan from a US healthcare payer perspective.[10] Effectiveness data were derived from a published meta-analysis.[24] Efficacy measures were sustained freedom from pain with the composite endpoint being SNAE. Costs included physician visit, emergency department visit, hospitalization, and drug acquisition costs.

Almotriptan was the most costly treatment relative to sumatriptan 50 mg and 100 mg. The incremental cost effectiveness ratio of almotriptan versus sumatriptan 50 mg was $11.60 per SNAE and versus sumatriptan 100 mg was $15.92.

Although costs associated with resource utilization are considered in the model, this study has one key

weakness, effectiveness data were derived from a meta-analysis of "questionable methods and applicability."[26] Probabilistic analysis results are not particularly useful, as the underlying uncertainty over whether almotriptan is cost effectiveness was not demonstrated using conventional formats.

Applicability of this study is limited given it is not from a Canadian perspective and generic prices as well costs associated with the management of adverse events are not considered.

Adelman & Besley (2003)

Adelman and Besley compared the cost effectiveness of oral triptans (almotriptan, zolmitriptan, frovatriptan, sumatriptan, rizatriptan and naratriptan) from a US population health perspective.[3] Effectiveness data were derived from a meta-analysis using indirect comparison. Efficacy measure included pain free at 2 hours after initial dosing. Only drug acquisition costs were included within the model.

In terms of mean cost to achieve pain-free status in one patient at 2 hours after initial dosing, rizatriptan 10 mg and almotriptan 12.5 mg were most cost effective and frovatriptan 2.5 mg was the least cost effective ($48.34, $48.57, $162.49 respectively). Sensitivity analysis was not considered.

This study has three key limitations. The study is an informal analysis. Effectiveness data were derived using indirect comparison. Only drug acquisition costs were considered in the model.

Applicability of this study is limited given it is not from the Canadian perspective and this study is an informal analysis which included only drug acquisition costs of non-generic treatments within the analysis.

Wells et al. (2003)

Wells and colleagues compared the cost effectiveness of eletriptans and sumatriptans from a UK healthcare system perspective.[20] Effectiveness data were derived from a single randomized, double-blind, double-dummy, placebo controlled phase III clinical trial. Efficacy measures included response at 1 hour, pain-free headache status at 2 hours, recurrence, and 24-hour sustained pain-free with pain-free headache status at 2 hours, no recurrence within 24 hours of the first dosing, and no requirement for recue medication being success measure 1 (SM1) & positive headache response at 1 hour, achievement of pain-free status by 2 hours being success measure 2 (SM2). Costs included within the model were drug acquisition costs and rescue medication.

In terms of SM1 and SM2, eletriptans have lowest cost per successfully treated attack. In terms of SM1, the cost per successfully treated attack of eletriptan 40 mg and 80 mg were £17.55, and £31.76 respectively. In terms of SM2, the cost per successfully treated attack of eletriptan 40 mg and 80 mg were £29.61, and £48.13 respectively.

The study has key limitations. The study is an informal analysis and effectiveness data were derived from a single placebo controlled trial.

Applicability of this study is limited given it is not from the Canadian perspective and effectiveness data included within the analysis were derived from a single study.

Williams & Reeder (2003)

Williams and Reeder compared the cost-effectiveness of almotriptan and rizatriptan from a US healthcare payer perspective.[9] Effectiveness data were derived from a published meta-analysis.[24] Efficacy measures were sustained freedom from pain with the composite endpoint being SNAE. Costs included within the model were physician visit, emergency department visit, hospitalization, and drug acquisition costs.

Almotriptan was the most costly treatment relative to rizatriptan. The incremental cost effectiveness ratio for almotriptan versus rizatriptan was $6.94 SNAE.

Although costs associated with resource utilization are considered in the model, this study has one key weakness, effectiveness data were derived from a meta-analysis of "questionable methods and applicability."[26] Probabilistic analysis results were not particularly useful, as the underlying uncertainty over whether almotriptan is cost effectiveness was not demonstrated using conventional formats.

Applicability of the study is limited given it is not from a Canadian perspective and non-generic prices are considered.

Belsey (2002)

Belsey compared the cost effectiveness of sumatriptan, rizatriptan, zolmitriptan, naratriptan, almotriptan, and eletriptan from a UK payer perspective.[17] Effectiveness data were derived from a meta-analysis conducted by the authors. Efficacy measures included pain-free at 2 hours. Costs included within the model were drug acquisition costs.

Rizatriptan 10 mg had the lowest average cost per pain-free patient at two hours (£14.15), while sumatriptan 100 mg had the highest average cost per pain-free patient at two hours (£37.61).

The study has two key weaknesses. The study is an informal analysis and only drug acquisition costs are considered in the analysis.

Applicability of this study is limited given it is not from the Canadian perspective and this study is an informal analysis which included only drug acquisition costs of non-generic treatments within the analysis.

Reeder et al. (2002)

Reeder and colleagues compared the cost effectiveness of oral triptans (almotriptan, rizatriptan, sumatriptan, zolmitriptan, and naratriptan) from a US payer perspective.[23] Effectiveness data were derived from a published meta-analysis.[24] Effectiveness measures included sustained pain-free defined as pain free at 2 hours post-dose, no headache recurrence up to 24 hours after initial dose, no use of rescue medications within the same 24-hour time frame. Costs included within the model were the cost of a single tablet; the source of costing was not stated.

Almotriptan was the most cost effective in terms of cost to attain 100 sustained pain-free patients and cost to attain 100 sustained pain free patients without adverse events.

The study has several limitations. This study is an informal analysis and interpretability of the results is limited since results are presented in a histogram and not as ICER. Effectiveness data were derived from a meta-analysis of "questionable methods and applicability."[26] Only drug costs were considered.

Applicability of this study is limited given it is not from the Canadian perspective and this study is an informal analysis which included only drug acquisition costs of non-generic treatments within the analysis.

Payne et al. (1996)

A 1999 study by Payne and colleagues funded by the UK Department of Health compared the cost effectiveness of 6 mg of subcutaneous sumatriptan with 1mg of subcutaneous dihydroergotamine mesylate (DHE) from a societal perspective.[7]

Results from a randomized controlled trial were used in the trial-based model. Outcomes were based on 11 efficacy outcomes from the randomized controlled trial. Direct costs included: drug acquisition costs, physician consultation time, pharmacist dispensing time, drug administration training time, patient travel and waiting time, and control of nausea and vomiting. Indirect costs included: costs of lost labour. Adverse events costs were considered; based on costs of controlling nausea and vomiting.

The incremental cost-efficacy ratios for sumatriptan versus DHE ranged from $4,131 to $6,697 per patient successfully treated. In scenario based deterministic analysis, results were sensitive to cost of lost labour: if cost of lost labour was $10,900, incremental cost ratios would be equivalent.

The key limitation of this study is that efficacy data is based on one randomized controlled trial.

Applicability of this study is limited given it is not from the Canadian perspective and results are from a trial-based model.

Overall Conclusions

Overall, the studies identified in this review are of poor quality and all have considerable limitations to its applicability to the current Canadian setting. Many studies were informal analysis that considered costs per successful treatment rather than incremental costs per outcomes; used effectiveness data from sources of meta-analysis of "questionable methods and applicability";[26] excluded costs associated with adverse events; included branded prices as opposed to generic prices; and used utility values from non-preference-based measures.

Of the three Canadian studies, results suggest that triptans are more cost effective than ergots and ASA plus metoclopramide, and in some instances dominate comparators. One manufacturer sponsored study found that the manufacturer's triptan was the most cost effective triptan.

Although the economic analyses of these Canadian studies reflect various comparators (triptans, ergots, and ASA plus antiemetic), dated and non-generic prices do not reflect the current situation. Moreover, the costs associated with the management of adverse events were not considered and non-preference-based measures were used to estimate quality of life. Therefore, applicability of Canadian studies to any

decision regarding the cost effectiveness of triptans should be done with caution.

Of the non-Canadian studies, six were CEA, one was a CEA/CUA, and another two were CUA. Results of the nine informal analyses do not provide useful information; therefore, only comments regarding the results of CEA/CUA are discussed. Results suggest that rizatriptan, eletriptan, and almotriptan are most cost effective triptans, and triptans as more cost effective than ergots; and in some cases dominate comparators.

The studies conducted by NCGC and funded by the Finnish Medicines Agency maybe the most applicable to the question at hand.[16,26] Both studies compared triptans to a variety of alternative treatments and were independent from manufacturer sponsorship. The population modelled in the analysis by NCGC was patients aged 12 and over, while patients aged 18-65 were modelled in the analysis funded by the Finnish Medicines Agency.

The results of the NCGC report suggest that for naïve patients, triptans were more cost effective than acetaminophen, ergots, and NSAIDs and that for experienced patients, the addition of NSAIDs or acetaminophen to triptans was dominated by triptans alone.[26] This independent economic analysis considered non-triptan medications as well as non-triptan and triptan combinations. Moreover, effectiveness data were derived from network meta-analysis; as well, this analysis considered quality of life. However, its applicability is limited since adverse events were included within the model and non-preference-based measures were used to estimate quality of life.[15]

The results from the Finnish Medicines Agency sponsored report imply that sumatriptan 100 mg dominated all other triptans with the exception of eletriptan 40 mg.[16] This independent economic analysis considered a variety of triptans. Effectiveness data were derived from mixed treatment comparison and this analysis considered quality of life. However, its applicability is limited since the costs associated with the management of adverse events were not considered and non-preference-based measures were used to estimate quality of life.[15]

Results from manufacturer sponsored economic analyses suggest that rizatriptan, eletriptan and almotriptan are the most cost effective triptan; this is similar to a systematic review of the cost effectiveness of triptan conducted by CADTH [26]. There are concerns over the potential bias due to sponsorship; therefore, it is difficult to accept these results at face value. Overall, most CEA compared the cost effectiveness of triptans, while CUA compared the cost effectiveness of triptan and non-triptan medications. Applicability of non-Canadian studies to any decision regarding the cost effectiveness of triptans is limited given that they are not from the Canadian perspective; most do not consider generic prices or comparisons to no therapy or non-triptan medications.

Overall Summary

In brief, 21 economic analyses were identified, most of which were non-Canadian studies. Despite consistent concerns over the quality and relevance of the available studies, the weight of evidence suggests that triptans are more cost effective than ergots. We discovered that in one study that triptan was more cost effective that ASA in combination with antiemetic.[13] We found that for naïve patients, triptans were more cost effective than acetaminophen, ergots, and NSAIDs and that for experienced patients, the addition of NSAIDs or acetaminophen to triptans was dominated by triptans alone.[15]

Most studies were informal analyses, which do not provide useful information. Of the CEA/CUA, only

two used effectiveness data from network meta-analysis/mixed treatment comparison. All CUA used utility values derived from non-preference-based measures. Only three analyses considered costs associated with the management of adverse events.

Conclusions

Economic evidence for the cost-effectiveness of triptans (alone or in combination with other drugs) for acute treatment of migraines compared to: other triptans, acetaminophen, antiemetic's, ASA and ergots suggest that there is limited independent analysis comparing triptans. Evidence suggests that triptans are more cost effective than ergots but there is very little evidence regarding the comparison of triptans alone or in combination with other non-triptan medications.

Overall, the studies identified in this review are of poor quality and although few studies address the question at hand, all have considerable limitations to its applicability to the Canadian setting. While Canadian studies consider comparisons of triptans and non-triptan medications, only three were identified, all three were dated and do not consider generic prices or costs of managing adverse events. Applicability of non-Canadian studies which compared triptans to other triptans and non-triptan medication studies are limited given that most do not consider generic prices or costs of managing adverse events. As well, the quality of non-Canadian economic analyses is poor since almost half are informal analyses that do not provide useful information. Moreover, most economic analyses are a comparison of triptans rather than triptans to non-triptan medications. In general, there is poor quality of utility and effectiveness estimates used within the models.

In brief, this review highlights the paucity and the poor quality of current economic evidence for the cost effectiveness of triptans alone or in combination with other drugs for acute treatment of migraines compared to other triptans or non-triptan medications.

Appendix A - Appendices

Appendix A1: Search Strategies and Results

The following are the search strategies and results used in Medline (Ovid) and Embase.

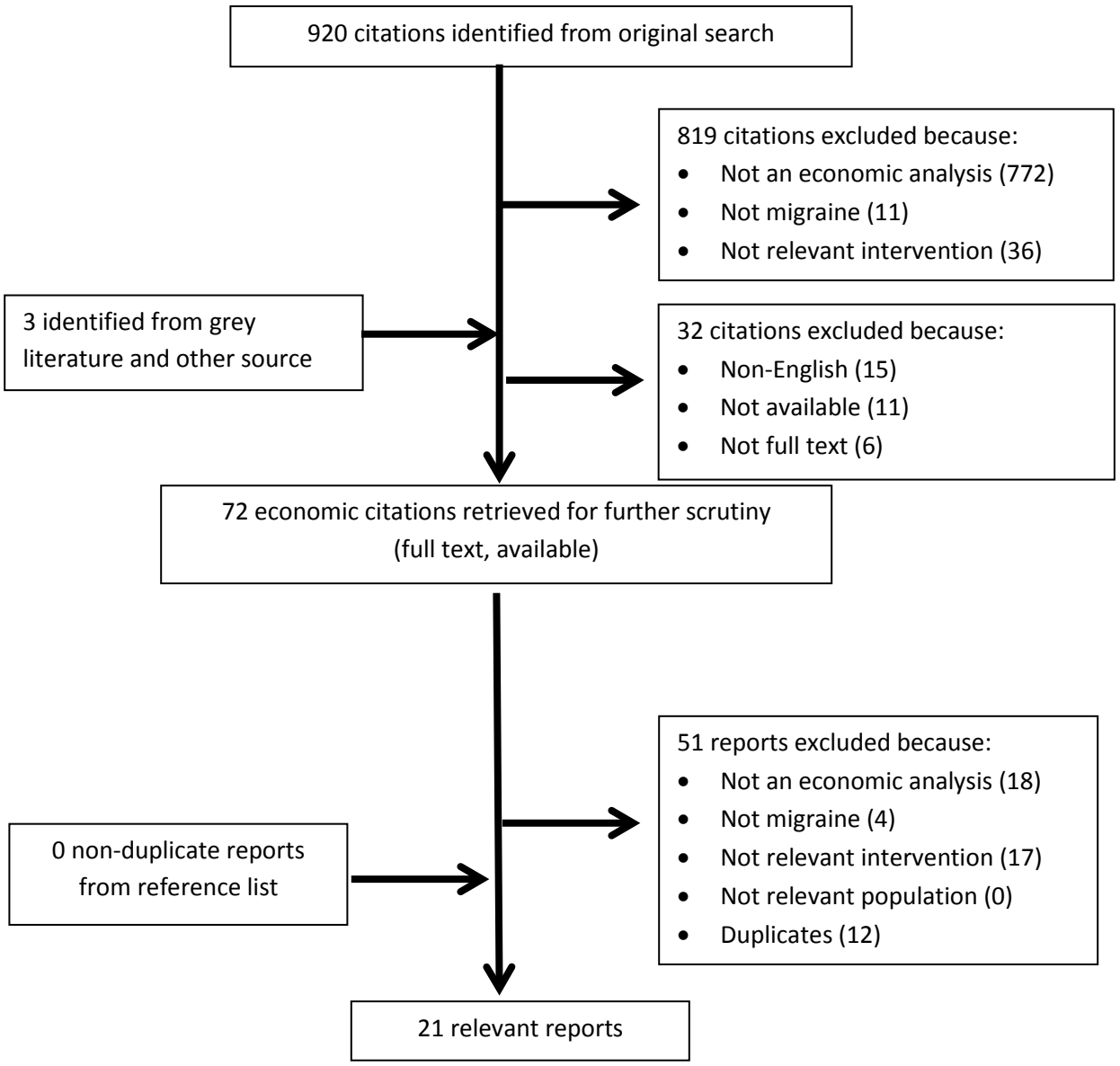
Medline (Ovid) In Process and Other Non-Index Citations 1946 to present (2013 November 11); Embase Classic & Embase 1947 to 2013 November 08)

1. exp Migraine Disorders/
2. (migrain* or migran*).tw.
3. (anti-migrain* or antimigrain* or anti-migran* or antimigran*).tw.
4. sick headache*.tw.
5. 1 or 2 or 3 or 4
6. exp Tryptamines/
7. (tryptamin* or tryptomin* or triptan* or indolylethylamine* or NSC 73938 or NSC73938).tw.
8. ("BRN 0125513" or CCRIS 8959 or EINECS 200-510-5 or Indol-3-ethylamine or UNII-422ZU9N5TV).tw.
9. Tryptamines.rn.
10. (almotriptan* or Almogran or Almotrex or Amignul or Axert or PNU 180638E or PNU-180638E or UNII-PJP312605E).tw.
11. almotriptan.rn.
12. (eletriptan* or Relpax or Relert or Relepax or "UK 116044" or "UK 116,044" or "UK-116044" or "UK-116,044" or UNII-22QOO9B8KI).tw.
13. eletriptan.rn.
14. (frovatriptan* or Allegro or Frova or Frovelan or Migard or Miguard or SB 209509 or VML-251 or VML251).tw.
15. frovatriptan.rn.
16. (naratriptan* or Amerge or Colatan or Naragran or Naramig or UNII-QX3KXL1ZA2).tw.
17. naratriptan.rn.
18. (rizatriptan* or Risatriptan* or "L 705,126" or "L 705126" or "L-705,126" or "L-705126" or Maxalt or "MK 0462" or MK 462 or MK-0462 or MK-462 or rizalief or rizalt or rizaliv or UNII-51086HBW8G).tw.
19. rizatriptan.rn.
20. (sumatriptan* or Arcoiran or Alsuma or BRN 6930870 or Diletan or Dolmigral or GR 43175 or GR 43175X or GR-43175 or HSDB 7742 or Imigran* or Imiject or Imitrex or micranil or Migril or Novelian or Sumigrene or Suminat or Sumatran or Sumatriptanum or Sumax or UNII-8R78F6L9VO or Zecuity).tw.
21. sumatriptan.rn.
22. (Zolmitriptan* or AscoTop or Flezol or Rapimelt or UNII-2FS66TH3YW or Zolmitriptan or Zomig or Zomig-ZMT or Zomigon or Zomigoro).tw.
23. Zolmitriptan.rn.
24. (Treximet or Trexima).tw.
25. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 5 and 25
27. Economics/

28. exp "Costs and Cost Analysis"/
29. "Value of Life"/
30. exp Economics, Hospital/
31. Economics, Medical/
32. Economics, Nursing/
33. Economics, Pharmaceutical/
34. 27 or 28 or 29 or 30 or 31 or 32 or 33
35. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
36. (expenditure$ not energy).ti,ab.
37. (value adj1 money).ti,ab.
38. budget$.ti,ab.
39. 35 or 36 or 37 or 38
40. 34 or 39
41. 26 and 40
42. exp migraine/
43. (migrain* or migran*).tw.
44. (anti-migrain* or antimigrain* or anti-migran* or antimigran*).tw.
45. sick headache*.tw.
46. 42 or 43 or 44 or 45
47. tryptamine derivative/
48. triptan derivative/
49. (tryptamin* or tryptomin* or triptan* or indolylethylamine* or NSC 73938 or NSC73938).tw,tn.
50. ("BRN 0125513" or CCRIS 8959 or EINECS 200-510-5 or Indol-3-ethylamine or UNII-422ZU9N5TV).tw,tn.
51. 61-54-1.rn.
52. almotriptan/
53. (almotriptan* or Almogran or Almotrex or Amignul or Axert or PNU 180638E or PNU-180638E or UNII-PJP312605E).tw,tn.
54. 154323-57-6.rn.
55. eletriptan/
56. (eletriptan* or Relpax or Relert or Relepax or "UK 116044" or "UK 116,044" or "UK-116044" or "UK-116,044" or UNII-22QOO9B8KI).tw,tn.
57. 143322-58-1.rn.
58. frovatriptan/
59. (frovatriptan* or Allegro or Frova or Frovelan or Migard or Miguard or SB 209509 or VML-251 or VML251).tw,tn.
60. 158747-02-5.rn.
61. naratriptan/
62. (naratriptan* or Amerge or Colatan or Naragran or Naramig or UNII-QX3KXL1ZA2).tw,tn.
63. 121679-13-8.rn.
64. rizatriptan/
65. (rizatriptan* or Risatriptan* or "L 705,126" or "L 705126" or "L-705,126" or "L-705126" or Maxalt or "MK 0462" or MK 462 or MK-0462 or MK-462 or rizalief or rizalt or rizaliv or UNII-51086HBW8G).tw,tn.
66. 144034-80-0.rn.

67. sumatriptan/
68. (sumatriptan* or Arcoiran or Alsuma or BRN 6930870 or Diletan or Dolmigral or GR 43175 or GR 43175X or GR-43175 or HSDB 7742 or Imigran* or Imiject or Imitrex or micranil or Migril or Novelian or Sumigrene or Suminat or Sumatran or Sumatriptanum or Sumax or UNII-8R78F6L9VO or Zecuity).tw,tn.
69. 103628-46-2.rn.
70. zolmitriptan/
71. (Zolmitriptan* or AscoTop or Flezol or Rapimelt or UNII-2FS66TH3YW or Zolmitriptan or Zomig or Zomig-ZMT or Zomigon or Zomigoro).tw,tn.
72. 139264-17-8.rn.
73. naproxen plus sumatriptan succinate/
74. (Treximet or Trexima).tw,tn.
75. 811794-26-0.rn.
76. 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75
77. 46 and 76
78. health economics/
79. exp economic evaluation/
80. exp "health care cost"/
81. exp pharmacoeconomics/
82. 78 or 79 or 80 or 81
83. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
84. (expenditure$ not energy).ti,ab.
85. (value adj2 money).ti,ab.
86. budget$.ti,ab.
87. 83 or 84 or 85 or 86
88. 82 or 87
89. 77 and 88
90. 41 or 89
91. remove duplicates from 90

Appendix A2: Results of Search



Appendix A3: Excluded Studies

The following table lists the studies excluded from the review in addition to the rationale for their exclusion.

Reference #	Study Reference	Reason for exclusion
[31]	Sumatriptan, serotonin, migraine, and money. Lancet.1991;339(8786):151-2.	Not an economic analysis
[26]	Canadian Agency for Drugs and Technologies in Health. Triptans for Acute Migraine: Comparative Clinical Effectiveness and Cost-effectiveness [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2007 Mar. [cited 2013 Nov 11]. Available from: http://cadth.ca/en/products/health-technology-assessment/publication/690	Not an economic analysis
[32]	Adelman JU, Adelman LC, Freeman MC, Von Seggern RL, Drake J. Cost Considerations of Acute Migraine Treatment. Headache.2004;44(3):271-85.	Not an economic analysis
[33]	Becker WJ. Are the triptans for migraine therapy worth the cost? Can J Neurol Sci.2000;27(2):111-5.	Not an economic analysis
[34]	Cady RC. Reduction of labor costs associated with treating migraine in the workplace. Arch Intern Med.1999;159(2):197.	Not an economic analysis
[35]	Curtiss FR. Best value for money in triptans. J Manag Care Pharm.2005;11(5):419-21.	Not an economic analysis
[36]	Feczko JM. Cost of sumatriptan. Lancet.1992;340(8813):243.	Not an economic analysis
[37]	Goldberg LD. The cost of migraine and its treatment. Am J Manag Care.2005;11(Suppl 2):S62-S67.	Not an economic analysis
[38]	Guidotti M, Ravasio R. Clinical and economic comparison of frovatriptan versus other oral triptans in the treatment of acute migraine in the real-world setting. Clin Drug Invest.2009;29(11):693-702.	Not an economic analysis
[25]	Hawkins K, Wang S, Rupnow MFT. Indirect cost burden of migraine in the United States. J Occup Environ Med.2007;49(4):368-74.	Not an economic analysis

39	Hoffman L, Mayzell G, Pedan A, Farrell M, Gilbert T. Evaluation of a monthly coverage maximum (drug-specific quantity limit) on the 5-HT1 agonists (triptans) and dihydroergotamine nasal spray. J Manag Care Pharm.2003;9(4):335-45.	Not an economic analysis
40	Johnson K. Migraine therapy: Balancing efficacy and safety with quality of life and cost. Formulary.2002;37(12):634-44.	Not an economic analysis
41	Kozma CM, Reeder CE. Comparison of the economic, clinical, and humanistic attributes of dihydroergotamine and sumatriptan. Clin Ther.1995;17(2):315-9.	Not an economic analysis
42	Lofland JH, Nash DB. Oral serotonin receptor agonists: A review of their cost effectiveness in migraine. Pharmacoeconomics.2005;23(3):259-74.	Not an economic analysis
43	Rapoport AM, Adelman JU. Cost of migraine management: A pharmacoeconomic overview. Am J Manag Care.1998;4(4):531-45.	Not an economic analysis
44	Rothrock JF. A costly attack of migraine. Headache.2008;48(6):951.	Not an economic analysis
45	Savani N, Martin A, Browning D. Switching patients with migraine from sumatriptan to other triptans increases primary care costs. Int J Clin Pract.2004;58(8):758-63.	Not an economic analysis
46	Siva PA, Mohonty S, Satyanarayana B. A cost effective and large-scale synthesis of Zolmitriptan: An anti-migraine drug. Der Pharma Chemica.2012;4(1):347-51.	Not an economic analysis
47	Von Seggern RL, Adelman JU. Cost considerations in headache treatment part 2: Acute migraine treatment. Headache.1996;36(8):493-502.	Not an economic analysis
48	Lampl C, Buzath A, Yazdi K, Sandor PS. Ergot and triptan overuse in Austria - An evaluation of clinical data and cost. Cephalalgia.2002;22(10):807-11.	Not migraine
49	Mannix LK, Adelman JU, Goldfarb SD, Von S, Kozma CM. Almotriptan versus sumatriptan in migraine treatment: direct medical costs of managing adverse chest symptoms. Am J Manag Care.2002;8(3 Suppl):S94-101.	Not migraine
50	Wang JT, Barr CE, Goldfarb SD. Impact of chest pain on cost of migraine treatment with almotriptan and sumatriptan. Headache.2002;42(Suppl 1):S38-S43.	Not migraine

51	Wang JT, Barr CE, Torigoe Y, Wang E, Rowland CR, Goldfarb SD. Cost savings in migraine associated with less chest pain on new triptan therapy. Am J Manag Care.2002;8(3 Suppl):S102-S107.	Not migraine
52	Caro G, Getsios D, Caro JJ, Raggio G, Burrows M, Black L. Sumatriptan: Economic evidence for its use in the treatment of migraine, the Canadian comparative economic analysis. Cephalalgia.2001;21(1):12-9.	Not relevant intervention
53	Caro JJ, Getsios D, Raggio G, Caro G, Black L. Treatment of migraine in Canada with naratriptan: A cost-effectiveness analysis. Headache.2001;41(5):456-64.	Not relevant intervention
54	Cohen JA, Beall D, Beck A, Rawlings J, Miller DW, Clements B, et al. Sumatriptan treatment for migraine in a health maintenance organization: Economic, humanistic, and clinical outcomes. Clin Ther.1999;21(1):190-204.	Not relevant intervention
55	Gerth WC, Sarma S, Hu XH, Silberstein SD. Productivity Cost Benefit to Employers of Treating Migraine with Rizatriptan: A Specific Worksite Analysis and Model. J Occup Environ Med.2004;46(1):48-54.	Not relevant intervention
56	Joish VN, Armstrong EP. Use of decision analysis in modeling the cost-effectiveness of oral vs SC sumatriptan. Formulary.2000;35(6):532-9.	Not relevant intervention
57	Legg RF, Sclar DA, Nemec NL, Tarnai J, Mackowiak JI. Cost-effectiveness of sumatriptan in a managed care population. Am J Manag Care.1997;3(1):117-22.	Not relevant intervention
58	Legg RF, Sclar DA, Nemec NL, Tarnai J, Mackowiak JI. Cost benefit of sumatriptan to an employer. J Occup Environ Med.1997;39(7):652-7.	Not relevant intervention
59	Litaker DG, Solomon GD, Genzen JR. Impact of sumatriptan on clinic utilization and costs of care in migraineurs. Headache.1996;36(9):538-41.	Not relevant intervention
60	Lofland JH, Locklear JC, Frick KD. Different approaches to valuing the lost productivity of patients with migraine. Pharmacoeconomics.2001;19(9):917-25.	Not relevant intervention
61	Lofland JH, Kim SS, Batenhorst AS, Johnson NE, Chatterton ML, Cady RK, et al. Cost-effectiveness and cost-benefit of sumatriptan in patients with migraine. Mayo Clin Proc.2001;76(11):1093-101.	Not relevant intervention
62	Williams P, Dowson AJ, Rapoport AM, Sawyer J. The cost effectiveness of stratified care in the management of migraine. Pharmacoeconomics.2001;19(8):819-29.	Not relevant intervention
63	Caro G, Getsios D, Caro JJ, Raggio G, Burrows M, Black L. Sumatriptan: economic evidence for its use in the treatment of migraine, the Canadian comparative economic analysis. 2001.	Not relevant intervention
64	Caro JJ, Getsios D, Raggio G, Caro G, Black L. Treatment of migraine in Canada with naratriptan: a cost-effectiveness analysis. 2001.	Not relevant intervention

65	Legg RF, Sclar DA, Nemec NL, Tarnai J, Mackowiak J, I. Cost-effectiveness of sumatriptan in a managed care population. 1997.	Not relevant intervention
66	Legg RF, Sclar DA, Nemec NL, Tarnai J, Mackowiak J, I. Cost benefit of sumatriptan to an employer. 1997.	Not relevant intervention
67	Lofland JH, Kim SS, Batenhorst AS, Johnson NE, Chatterton ML, Cady RK, et al. Cost-effectiveness and cost-benefit of sumatriptan in patients with migraine. 2001.	Not relevant intervention
68	Slof J. Cost-effectiveness analysis of early versus non-early intervention in acute migraine based on evidence from the 'Act when Mild' study. 2012.	Not relevant intervention
69	Adelman JU, Belsey J. Meta-analysis of oral triptan therapy for migraine: number needed to treat and relative cost to achieve relief within 2 hours. 2003.	Duplicate
70	Asseburg C, Peura P, Oksanen T, Turunen J, Purmonen T, Martikainen J. Cost-effectiveness of oral triptans for acute migraine: mixed treatment comparison. Int J Technol Assess Health Care.2012 Oct;28(4):382-9.	Duplicate
71	Evans KW, Boan JA, Evans JL, Shuaib A. Economic evaluation of oral sumatriptan compared with oral caffeine/ergotamine for migraine. 1997.	Duplicate
72	Ilersich L. An economic analysis of sumatriptan for acute migraine. 1997.	Duplicate
73	Mullins CD, Weis KA, Perfetto EM, Subedi PR, Healey PJ. Triptans for migraine therapy: a comparison based on number needed to treat and doses needed to treat. 2005.	Duplicate
74	Ramsberg J, Henriksson M. The cost-effectiveness of oral triptan therapy in Sweden. 2007.	Duplicate
75	Thompson M, Gawel M, Desjardins B, Ferko N, Grima D. An economic evaluation of rizatriptan in the treatment of migraine. Pharmacoeconomics 23[8], 837-850. 2005.	Duplicate
76	Williams P, Reeder CE. Cost-effectiveness of almotriptan and rizatriptan in the treatment of acute migraine. 2003.	Duplicate
77	Williams P, Reeder CE. A comparison of the cost-effectiveness of almotriptan and sumatriptan in the treatment of acute migraine using a composite efficacy/tolerability end point. 2004.	Duplicate
78	Zhang L, Hay JW. Cost-effectiveness analysis of rizatriptan and sumatriptan versus Cafergot in the acute treatment of migraine. 2005.	Duplicate
79	Zhang L, Hay JW. Cost-effectiveness analysis of rizatriptan and sumatriptan versus Cafergot in the acute treatment of migraine. CNS Drugs.2005;19(7):635-42.	Duplicate

Appendix A4: List of Included Studies

The following table lists the studies included within the review.

Reference #	Study Reference
13	Ilersich L. An economic analysis of sumatriptan for acute migraine [Internet]. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 1997 Jul. [cited 2013 Nov 11]. Available from: http://cadth.ca/media/pdf/sumatrip_ov_e.pdf
15	National Clinical Guideline Centre. CG150 Headaches: full guideline [Internet]. London: National Clinical Guideline Centre; 2012 Sep. [cited 2013 Nov 11]. Available from: http://guidance.nice.org.uk/CG150/Guidance
3	Adelman JU, Belsey J. Meta-analysis of oral triptan therapy for migraine: number needed to treat and relative cost to achieve relief within 2 hours. J Manag Care Pharm.2003;9(1):45-52.
16	Asseburg C, Peura P, Oksanen T, Turunen J, Purmonen T, Martikainen J. Cost-effectiveness of oral triptans for acute migraine: Mixed treatment comparison. Int J Technol Assess Health Care.2012;28(4):382-9.
17	Belsey JD. The clinical and financial impact of oral triptans - An updated meta-analysis. J Med Econ.2002;5(79-89):79-89.
21	Belsey JD. Cost effectiveness of oral triptan therapy: A trans-national comparison based on a meta-analysis of randomised controlled trials. Curr Med Res Opin.2004;20(5):659-69.
12	Evans KW. Economic evaluation of oral sumatriptan compared with oral caffeine/ergotamine for migraine. Pharmacoeconomics.1997;12(5):565-77.
22	Hens M, Villaverde-Hueso A, Alonso V, Abaitua I, Posada de la PM. Comparative cost-effectiveness analysis of oral triptan therapy for migraine in four European countries. 2013.
4	Kelman L, Von Seggern RL. Using patient-centered endpoints to determine the cost-effectiveness of triptans for acute migraine therapy. Am J Ther.2006;13(5):411-7.
5	Mullins CD, Weis KA, Perfetto EM, Subedi PR, Healey PJ. Triptans for migraine therapy: a comparison based on number needed to treat and doses needed to treat. J Manag Care Pharm.2005;11(5):394-402.
6	Mullins CD, Subedi PR, Healey PJ, Sanchez RJ. Economic analysis of triptan therapy for acute migraine: A medicaid perspective. Pharmacotherapy.2007;27(8):1092-101.
7	Payne K, Kozma CM, Lawrence BJ. Comparing dihydroergotamine mesylate and sumatriptan in the management of acute migraine: A retrospective cost-efficacy analysis. Pharmacoeconomics.1996;10(1):59-71.
8	Perfetto EM, Weis KA, Mullins CD, Subedi P, Healey S. An economic evaluation of triptan products for migraine. Value Health.2005;8(6):647-55.
18	Ramsberg J, Henriksson M. The cost-effectiveness of oral triptan therapy in Sweden. Cephalalgia.2007 Sep;27(1):54-62.

23	Reeder CE, Steadman S, Goldfarb SD. Economic comparison of oral triptans for management of acute migraine: implications for managed care. Am J Manag Care.2002;8(3 Suppl):S80-S84.
19	Slof J, Badia X, Magaz S, Lainez MJ, Galvan J, Heras J. Cost-efficacy of oral triptans in the treatment of acute migraine. 2005.
14	Thompson M, Gawel M, Desjardins B, Ferko N, Grima D. An economic evaluation of rizatriptan in the treatment of migraine. 2005.
20	Wells N, Hettiarachchi J, Drummond M, Carter D, Parpia T, Pang F. A cost-effectiveness analysis of eletriptan 40 and 80 mg versus sumatriptan 50 and 100 mg in the acute treatment of migraine. Value Health.2003;6(4):438-47.
9	Williams P, Reeder CE. Cost-Effectiveness of Almotriptan and Rizatriptan in the Treatment of Acute Migraine. Clin Ther.2003;25(11):2903-19.
10	Williams P, Reeder CE. A comparison of the cost-effectiveness of almotriptan and sumatriptan in the treatment of acute migraine using a composite efficacy/tolerability end point. J Manag Care Pharm.2004;10(3):259-65.
11	Zhang L, Hay JW. Cost-effectiveness analysis of rizatriptan and sumatriptan versus Cafergot in the acute treatment of migraine. CNS Drugs.2005;19(7):635-42.

Appendix A5: Characteristics of Reviewed Studies

Study	Thompson et al. 2005	Evans 1997
Sponsorship	Merck Frosst Canada	Canadian Coordinating Office of Health Technology Assessment
Country	Canada	Canada
Perspective	Ontario Ministry of Health and Long Term Care Societal	Societal Provincial health department (CEA/CUA only)
Study Type	CEA/CUA	CEA/CUA CBA
Comparators	Rizatriptan 10 mg Usual Care (aggregate of medications prescribed for migraine) Sumatriptan 50 mg Sumatriptan 100 mg Naratriptan 2.5 mg Zolmitriptan 2.5 mg	Sumatriptan 100 mg Cafergot (caffeine 100mg/ergotamine 1mg)
Populations	Men and women who experience moderate-severe migraines and for whom other acute therapies such as NSAIDs single analgesics are insufficient or contraindicated	Patients with migraine (details not specified)
Time horizon	24 hours	48 hours (CEA) 1 year (CUA, CBA)
Type of model	Decision tree	Decision Tree
Efficacy inputs	Pain-free response at 2 hours Sustained pain-free response for 2-24 hours	Conversion of a moderate or severe headache to mild or no headache at 2 hours (primary efficacy outcome) Recurrence within 48 hours
Adverse events	No costs associated with AE	No costs associated with AE
Utilities	QWB	QWB
Discounting	N/A	N/A
Outcomes	Incremental cost per additional attack Incremental cost per QALY	Incremental cost per attack aborted Incremental cost per QALY Incremental cost per patient per year

Results	MOH&LTC perspective versus usual care $49.82 per attack aborted versus usual care $31,845 per QALY versus other triptans other triptans are dominated by rizatriptan (rizatriptan is dominant) Societal perspective versus usual care rizatriptan dominated usual care versus other triptans are dominated by rizatriptan (rizatriptan dominated)	Societal Perspective -$25 per attack aborted -$7,507 per QALY $42 per patient per year Provincial Health Department Perspective $98 per attack aborted $29,366 per QALY
Types of sensitivity analysis	Deterministic analysis (one-way) Variables not provided for other triptans	Deterministic analysis (one-way) Societal Perspective: Drug acquisition costs Health service use and costs Utility values Treatment effect Wage Attack frequency Provincial Health Department Perspective: Drug acquisition costs Health service use and costs Utilities Treatment effect Deterministic analysis(threshold for CBA) Treatment effect Probabilistic Analysis (Monte Carlo analysis) Unclear Subgroup Analysis Severity of Attack
Sensitivity analysis results	MOH&LTC perspective Results insensitive to change Societal perspective Results insensitive to change	Deterministic Analysis (one-way) From a societal perspective results sensitive to relative effects and drug acquisition costs From a provincial health department perspective results insensitive to drug acquisition costs health service use and costs utility values treatment effect Probabilistic Analysis (Monte Carlo analysis) Results of PSA are unclear Subgroup Analysis In terms of subgroup analysis sumatriptan is slightly superior for treating severe attacks as opposed to moderate attacks

Points to consider	Costs in CDN$ (2002) Prices from the ODB Formulary plus additional 10% mark-up Efficacy data from published meta-analysis (for triptans) and naturalistic study (for usual care) No costs associated with the management of adverse events Utility values derived from QWB Variables not provided for other triptans in deterministic analysis Comparison to usual care and other triptan medications No comparison to no therapy or other non-triptan medications	Cost in CDN$ (1995) Generic price are not considered; prices are derived from the lowest price of 20 Canadian community pharmacies Efficacy data from informal comparison No costs associated with the management of adverse events Utility values derived from QWB Distributions used in PSA are not specified and results are not presented in conventional formats No comparison to no therapy or other non-triptan medications

Appendix A5: Characteristics of Reviewed Studies Continued

Study	Ilersich 1997	Hens et al. 2013
Sponsorship	Canadian Coordinating Office of Health Technology Assessment	No sponsorship
Country	Canada	Europe (France Italy Spain UK)
Perspective	Government Societal	Health-care payer
Study Type	CEA/CUA CBA	Informal analysis
Comparators	Sumatriptan 100 mg (oral) Cafergot 1 tablet (ergotamine/caffeine) Acetylsalicylic acid 975 mg plus Metoclopramide 10 mg Sumatriptan 6 mg (subcutaneous) Dihydroergotamine 1 mg (subcutaneous) Butorphanol 1 mg (intranasal)	Almotriptan 12.5mg Sumatriptan 50mg (brand name) Sumatriptan 50mg (generic) Zolmitriptan 2.5mg
Populations	Patients with migraine	Adult patients diagnosed with migraine according to International Headache Classification; patients unresponsive to analgesics or anti-inflammatory drugs
Time horizon	48 hours	2 hours
Type of model	Decision Tree	Decision trees (Scenario A B)
Efficacy inputs	Conversion of moderate or severe headache to mild or no headache after drug administration (response at 2 hours - for oral response at 1 hours - for subcutaneous) Recurrence	Effectiveness (freedom from pain at 2 hours without recurrence and no AE) Ineffectiveness (persistent pain at 2 hours recurrence or AE)
Adverse events	Not included	No costs associated with AE
Utilities	QWB	N/A

Discounting	N/A	N/A
Outcomes	Incremental cost per attack avoided Incremental cost per QALY Incremental net economic benefit	Average cost-effectiveness ratio
Results	Government perspective Oral Sumatriptan: ergotamine/caffeine $98 per migraine avoided; $29,400/QALY ASA/metoclopramide $154 per migraine avoided; $47,200/QALY Subcutaneous Sumatriptan: subcutaneous dihydroergotamine $201 per migraine avoided; $62,600/QALY intranasal butorphanol $210 per migraine avoided; $66,100/QALY oral sumatriptan $196 per migraine avoided; $56,400/QALY Societal Perspective Oral Sumatriptan: ergotamine/caffeine sumatriptan is dominant in terms of cost per attack and QALY; $42 [incremental net benefit] ASA/metoclopramide $32 per migraine avoided; $9,700/QALY; -$37[incremental net benefit] Subcutaneous Sumatriptan: subcutaneous dihydroergotamine $79 per migraine avoided; $24,500/QALY; -$159 intranasal butorphanol $87 per migraine avoided; $27,500/QALY; -$171[incremental net benefit] oral sumatriptan $74 per migraine avoided; $21,200/QALY; -$101[incremental net benefit]	Generic sumatriptan is most cost-effective Scenario A (lower effectiveness) Average cost of generic sumatriptan per unit of effectiveness: UK €14.50 France €21.92 Italy €22.50 Spain €36.67 Scenario B (higher effectiveness) Average cost of generic sumatriptan per unit of effectiveness: UK €9.16 France €13.84 Italy €14.21 Spain €23.16
Types of sensitivity analysis	Deterministic analysis (one-way) Drug acquisition costs Health service use costs Utility values Treatment effect Average earnings Frequency of attacks Probabilistic Analysis Unclear	N/A

Sensitivity analysis results	Deterministic analysis (one-way) Results sensitive to treatment effects Probabilistic Analysis Results not present; stated that results were not very sensitive to simultaneous and probable changes	N/A
Points to consider	Costs in CDN$ (1996) Generic prices are not considered Efficacy data from meta-analysis conducted by author No consideration of adverse events Utility values derived from QWB Distributions used in PSA are not specified and results are not presented Comparison to ergots and ASA plus antiemetic No comparison to no therapy or other non-triptan medications	All costs in € (2010 £ converted to €) Cost of sumatriptan (generic): €2.63 (France) €2.70 (Italy) €4.49 (Spain) €1.68 (UK) Only drug costs of single dose included in model No costs associated with the management of adverse events Efficacy data from published economic evaluations Reported average cost per outcome not ICER; Reviewer unable to calculate ICER Sensitivity analysis was not considered No consideration of utility values No comparison to no therapy or other non-triptan medications

Appendix A5: Characteristics of Reviewed Studies Continued

Study	Asseburg et al., 2012	National Clinical Guideline Centre, 2012
Sponsorship	Finnish Medicines Agency	National Institute for Health and Clinical Excellence
Country	Finland	UK
Perspective	Societal	UK NHS and Personal Social Services
Study Type	CEA/CUA	CUA
Comparators	Sumatriptan 100 mg Almotriptan 12.5 mg Eletriptan 40 mg Frovatriptan 2.5 mg Naratriptan 2.5 mg Rizatriptan 10 mg Sumatriptan 50 mg Zolmitriptan 2.5 mg Zolmitriptan 5 mg	NSAIDs Acetaminophen Ergots Triptans Triptan in combination with NSAIDs Triptan in combination with acetaminophen
Populations	Patients age 18-65 diagnosed with migraine using International Headache Society criteria, experiencing moderate or severe attacks	Patients aged 12 or over, experiencing acute migraine attack, indicated for oral treatment and diagnosed with migraine
Time horizon	24 hours	24 hours
Type of model	Decision tree	Decision tree

Efficacy inputs	2 hour response 2 hour pain-free recurrence [primary end point SNAE]	Sustained pain free at 24 hours Sustained headache response (for sensitivity analysis only)
Adverse events	No costs associated with AE	Not included
Utilities	QWB-SA	QWB
Discounting	N/A	N/A
Outcomes	Incremental cost per additional SNAE Incremental cost per QALY	Average cost, average QALY, net benefit [incremental cost per QALY and calculated by reviewer]
Results	Sumatriptan 100 mg is superior to all triptans except eletriptan In terms of incremental cost per additional SNAE, Sumatriptan 50 mg is subject to extended dominance, and rizatriptan is subject to dominance. In terms of cost per QALY, sumatriptan 100 mg dominated almotriptan, frovatriptan, naratriptan, rizatriptan , sumatriptan 50 mg, zolmitriptan 2.5 mg, and zolmitriptan 5 mg; ICER for eletriptan versus sumatriptan 100 mg is €43.65 per additional SNAE ICUR for eletriptan versus sumatriptan 100 mg is €19,659 per QALY	Base case through probabilistic analysis simulation <u>(Ranked order, treatment, mean cost, mean QALY, net benefit)</u> 1) Triptan + NSAIDs, £2.23, 0.000007, -2.099 2) Triptan+ acetaminophen, £2.20, -0.000048,-3.156 3) Triptan, £2.17, -0.000280, -7.763 4) Acetaminophen,£ 0.03, -0.000415, -8.334 5) NSAIDs, £0.06, -0.000447, -8.992 6) Ergot, £0.34, -0.000602, -12.373 <u>Reviewer's calculation</u> Acetaminophen, ergots, and NSAIDs are less costly, but less effective compared to triptans ICUR for triptans versus acetaminophen was £15,852 per QALY, versus NSAIDs was $12,635 and versus ergots was $683 ICUR for triptans + acetaminophen versus acetaminophen was £5,913 per QALY; and for triptans + NSAIDs versus NSAIDs was £4,780 per QALY
Types of sensitivity analysis	<u>Deterministic analysis (one-way)</u> Drug acquisition costs Assumption of wastage Utility values	<u>Deterministic analysis (One-way)</u> Utility values Drug acquisition costs (triptan) <u>Deterministic analysis (Scenario)</u> Sustained headache response at 24 hours as primary outcome <u>Probabilistic Sensitivity Analysis (PSA)</u> Treatment effect (log normal distribution)

Sensitivity analysis results	Deterministic Analysis (one-way) Results insensitive to drug acquisition costs and utility values Results regarding wastage assumption were not discussed	Deterministic analysis (One-way) Results sensitive to drug acquisition costs Deterministic analysis (Scenario) Results sensitivity to sustained headache response at 24 hours as primary outcome Probabilistic Sensitivity Analysis (PSA) Highest probability of being cost effective triptan in combination with NSAIDs and in combination with acetaminophen
Points to consider	Costs in € (2012) Cost of generic sumatriptan 100 mg is €18.38 per package, € 0.93 per dose Efficacy data from mixed treatment comparison conducted by authors No costs associated with the management of adverse events Utility values derived from QWB-SA, sensitivity analysis considered utility values derived from EQ-5D No comparison to no therapy or other non-triptan medications	Costs in £ (2011) Generic prices are not considered Efficacy data from NMA conducted by author No consideration of adverse events Results reported as average cost, average QALY, net benefit and ranked order Reviewer calculated ICUR Probabilistic sensitivity analysis considered log normal distribution for treatment effect Comparison of non-triptan medications and triptan in combination with non-triptan medications

Appendix A5: Characteristics of Reviewed Studies Continued

Study	Mullins et al., 2007	Kelman et al., 2006
Sponsorship	Pfizer Inc	Ortho-McNeil Pharmaceuticals Incorporated
Country	US	US
Perspective	Medicaid	Payer
Study Type	Informal analysis	Informal analysis
Comparators	Almotriptan 12.5 mg Eletriptan 20 mg Eletriptan 40 mg Naratriptan 2.5 mg Rizatriptan 5 mg Rizatriptan 10 mg Sumatriptan 25 mg Sumatriptan 50 mg Sumatriptan 100 mg Zolmitriptan 2.5 mg Zolmitriptan 5 mg	Almotriptan 12.5 mg Eletriptan 20 mg Eletriptan 40 mg Eletriptan 80 mg (2 tablets of 40 mg) Naratriptan 2.5 mg Rizatriptan 5 mg Rizatriptan 10 mg Sumatriptan 25 mg Sumatriptan 50 mg Sumatriptan 100 mg Zolmitriptan 2.5 mg Zolmitriptan 5 mg
Populations	Patients with migraine	Patients with migraine
Time horizon	24 hours	24 hours
Type of model	Decision tree	Decision analytic [Not specified]

Efficacy inputs	Headache relief at 2 hours Pain-free at 2 hours Recurrence of headache pain Sustained pain-free	Sustained pain-free (pain free at 2 hours post-dosing with no recurrence to moderate or severe headache and no rescue headache medication used for 2-24 hours)
Adverse events	Not included	No costs associated with AE
Utilities	N/A	N/A
Discounting	N/A	N/A
Outcomes	Cost to treat 100 migraine attacks Cost per successfully treated patient	Cost to attain 100 sustained pain-free patients Cost to attain 100 sustained pain free with no adverse events patients
Results	In 5 of 7 states, eletriptan 20 mg has lowest cost to treat 100 patients. In 2 of 7 states, eletriptan 40 mg has lowest cost to treat 100 patients. In all 7 states, eletriptan 40 mg has lowest cost per successfully treated patient.	Almotriptan 12.5 mg and rizatriptan 10 mg were most cost effective in terms of achieving 100 sustained pain-free patients ($7,120, $7,427 respectively). Almotriptan 12.5 mg and rizatriptan 10 mg were most cost effective in terms of attaining 100 sustained pain-free patients with no-adverse events patients ($8,298, $12,545 respectively).
Types of sensitivity analysis	Deterministic analysis (one-way) Dosing assumption	Deterministic analysis (one-way) Drug acquisition costs
Sensitivity analysis results	Deterministic analysis (one-way) In terms of costs to treat 100 patients, results sensitive to dosing assumption [data not shown] In terms of cost per successfully treated patient, results insensitive to dosing assumption[data not shown]	Deterministic analysis (one-way) Results insensitive to drug acquisition costs; almotriptan 12.5 mg and rizatriptan 10 mg remain most cost effective
Points to consider	Cost in USD$ (2005) Generic prices are not considered Efficacy data from published meta-analysis Only drug acquisition costs considered No consideration of adverse events Reported cost per outcome; not ICER Reviewer unable to calculate ICER Model was adapted from Perfetto et al. No consideration of utility values No comparison to no therapy or other non-triptan medications	Cost in USD$ (2004) Generic prices are not considered Efficacy data from published meta-analysis Only drug acquisition costs considered No costs associated with the management of adverse events Results reported as cost per outcome; not ICER Reviewer unable to calculate ICER No consideration of utility values No comparison to no therapy or other non-triptan medications

Appendix A5: Characteristics of Reviewed Studies Continued

Study	Mullins et al., 2005	Perfetto et al., 2005
Sponsorship	Pfizer Inc	Pfizer Pharmaceuticals
Country	US	US
Perspective	Payer	Payer
Study Type	Informal analysis	Informal analysis
Comparators	Almotriptan 12.5 mg Eletriptan 40 mg Naratriptan 2.5 mg Rizatriptan 5 mg Rizatriptan 10 mg Sumatriptan 50 mg Sumatriptan 100 mg Zolmitriptan 2.5 mg Zolmitriptan 5 mg	Almotriptan 12.5 mg Eletriptan 40 mg Naratriptan 2.5 mg Rizatriptan 5 mg Rizatriptan 10 mg Sumatriptan 50 mg Sumatriptan 100 mg Zolmitriptan 2.5 mg Zolmitriptan 5 mg
Populations	Patients with migraine	Patients with moderate or severe migraine
Time horizon	24 hours	24 hours
Type of model	Decision tree	Decision tree
Efficacy inputs	2-hour response therapeutic gain 2-hour pain-free therapeutic gain 24-hour sustained pain-free Recurrence	Response at 2 hours Pain free at 2 hours Sustained pain-free rate Recurrence rate in the 24 hour-period
Adverse events	Not included	Not included
Utilities	N/A	Not included
Discounting	N/A	N/A
Outcomes	Cost to successfully treat 100 patients	Cost to treat 100 migraine patient attacks Cost per successfully treated patient

Results	Eletriptan 40 mg has lowest cost to successfully treat 100 patients. Naratriptan 2.5 mg has highest cost to successfully treat 100 patients <u>Cost to successfully treat 100 patients</u> Almotriptan 12.5 mg, $9,073 Eletriptan 40 mg, $5,630 Naratriptan 2.5 mg, $ 11,136 Rizatriptan 5 mg, $10,579 Rizatriptan 10 mg, $8,246 Sumatriptan 50 mg, $7,779 Sumatriptan 100 mg, $8,549 Zolmitriptan 2.5 mg, $7,549 Zolmitriptan 5 mg, $8,499	Eletriptan has the lowest cost to treat 100 patient attack and lowest cost per successfully treated patient <u>Cost to treat 100 patient attack</u> Almotriptan 12.5 mg, $1,670 Eletriptan 40 mg, $1,560 Naratriptan 2.5 mg, $1,945 Rizatriptan 5 mg, $1,771 Rizatriptan 10 mg, $1,802 Sumatriptan 50 mg, $1,731 Sumatriptan 100 mg, $1,740 Zolmitriptan 2.5 mg, $1,629 Zolmitriptan 5 mg, $1,889 <u>Cost per successfully treated patient</u> Almotriptan 12.5 mg, $90.52 Eletriptan 40 mg, $56.39 Naratriptan 2.5 mg, $111.44 Rizatriptan 5 mg, $105.72 Rizatriptan 10 mg, $82.53 Sumatriptan 50 mg, $77.59 Sumatriptan 100 mg, $85.29 Zolmitriptan 2.5 mg, $75.62 Zolmitriptan 5 mg, $84.93
Types of sensitivity analysis	<u>Deterministic analysis (one-way)</u> Dosing assumption	<u>Deterministic analysis (scenario)</u> Dosing assumption
Sensitivity analysis results	<u>Deterministic analysis (one-way)</u> Results insensitive to dosing assumption	<u>Deterministic analysis (scenario)</u> Results insensitive to dosing assumption
Points to consider	Costs in USD$ (2004) Average wholesale price discounted at 15% to consider generic pricing Efficacy data from published meta-analysis Only drug acquisition costs considered No consideration of adverse events Results reported as cost per outcome; not ICER Reviewer unable to calculate ICER No consideration of utility values No comparison to no therapy or other non-triptan medications	Cost in USD$ (2004) Average wholesale price discounted by 15% for branded triptan Efficacy data from published meta-analysis No consideration of adverse events Reported cost per outcome considered, not ICER Reviewer unable to calculate ICER No consideration of utility values No comparison to no therapy or other non-triptan medications

Appendix A5: Characteristics of Reviewed Studies Continued

Study	Rambserg & Henriksson, 2005	Slof et al., 2005
Sponsorship	Unknown	Almirall Prodesfarma
Country	Sweden	Spain
Perspective	Societal	Payer
Study Type	CEA	CEA
Comparators	Eletriptan 40 mg Rizatriptan 10 mg Zolmitriptan 5 mg Almotriptan 12.5 mg Zolmitriptan 2.5 mg Sumatriptan 50 mg Sumatriptan 100 mg	Sumatriptan 100 mg Sumatriptan 50 mg Zolmitriptan 2.5 mg Zolmitriptan 5 mg Naratriptan 2.5 mg Rizatriptan 10 mg Eletriptan 40 mg Eletriptan 80 mg Almotriptan 12.5
Populations	Patients with migraine ; assumed entry in model at age 40 with mean migraine attack of 15 per year	Migraineurs 18-65 years of age
Time horizon	24 hours	24 hours
Type of model	Decision tree	Decision analytic model
Efficacy inputs	Pain-free at 2 hours Recurrence [primary outcome- SNAE]	Sustained pain-free (pain free by 2 hours post dose and not experiencing recurrence of moderate to severe headache nor using rescue headache medication at 2-24 hours post dose.)
Adverse events	No costs associated with AE	Included, chest related (chest pressure, chest pain, radiating pain in arm, other chest feeling, heavy arms, shortness of breath, palpitations and anxiety) and CNS related (asthenia, abnormal dreams, agitation, aphasia, ataxia, confusion, dizziness, somnolence, speech disorder, thinking abnormally, tremor, vertigo, and other focal neurological symptoms)
Utilities	N/A	N/A
Discounting	N/A	N/A
Outcomes	Incremental cost per SNAE	Average cost per sustained pain-free patient Incremental cost per sustained pain-free patient

Results	Eletriptan and rizatriptan dominated all triptans Eletriptan dominated all triptans with the exception of rizatriptan (€99.80 per SNAE)	Naratriptan 2.5 mg is the least costly treatment, with total costs of €3.64 Naratriptan 2.5 mg, sumatriptan 50 mg, and almotriptan 12.5 mg dominate all other triptans ICER for sumatriptan versus naratriptan 50 mg is €23.09 per sustained pain-free patient ICER for = almotriptan versus sumatriptan is €10.45 per sustained pain-free patient
Types of sensitivity analysis	<u>Deterministic analysis (one-way)</u> Treatment effect <u>Deterministic analysis (scenario)</u> Pain free at 2 hours as outcome Pain free at 2 hours , no adverse events as outcome No placebo adjustment using SNAE as outcome No placebo adjustment using pain free at 2 hours as outcome No placebo adjustment using pain free at 2 hours , no adverse events as outcome <u>Probabilistic Sensitivity Analysis</u> Transition probabilities (beta distribution)	<u>Deterministic analysis (scenario)</u> Low adverse events costs High adverse events costs
Sensitivity analysis results	<u>Deterministic analysis (one-way)</u> Results insensitive to treatment effects <u>Deterministic analysis (scenario)</u> Results insensitive to pain free at 2 hours and pain free at 2 hours , no adverse events as outcome Results sensitive to no placebo adjustment using SNAE as outcome; no placebo adjustment using pain free at 2 hours as outcome; and no placebo adjustment using pain free at 2 hours , no adverse events as outcome <u>Probabilistic Sensitivity Analysis</u> Eletriptan and rizatriptan have highest probability of being cost effective	<u>Deterministic analysis (scenario)</u> Results sensitive to low adverse events costs Results insensitive to high adverse events costs

Points to consider	Costs in € (Year not specified; costs converted from SEK, 1€=10SEK) Generic prices are not considered Efficacy data from published meta-analysis, considered published two meta-analyses in deterministic analysis Drug acquisition costs and cost of loss of productivity considered No costs associated with management of adverse events Probabilistic sensitivity analysis considered beta distribution for transition probabilities No consideration of utility values No comparison to no therapy or other non-triptan medications	Costs in € (2002) Retail price of treatments less 40% co-payment were considered Efficacy data from published meta-analysis Included adverse events; based on costs of chest-related AE and CAS-related AE derived from survey of 6 experts No consideration of utility values No comparison to no therapy or other non-triptan medications

Appendix A5: Characteristics of Reviewed Studies Continued

Study	Zhang & Hay, 2005	Belsey, 2004
Sponsorship	Merck	Merck and Co Inc.
Country	US	International (USA, UK, Canada, Germany, Italy, Netherlands)
Perspective	Societal	Payer [Not specified]
Study Type	CUA (stated as CEA)	CEA
Comparators	Rizatriptan 10 mg Cafergot (ergotamine 2mg/caffeine 200mg) Sumatriptan 50 mg	Almotriptan 12.5 mg Eletriptan 20 mg Eletriptan 40 mg Eletriptan 80 mg Frovatriptan 2.5 mg Naratriptan 2.5 mg Rizatriptan 10 mg Sumatriptan 50 mg Sumatriptan 100 mg Zolmitriptan 2.5 mg Zolmitriptan 5 mg
Populations	US migraine patient cohort	Patients with migraine
Time horizon	1 year	2 hours
Type of model	Decision tree (3 models: rizatriptan versus Cafergot, sumatriptan versus Cafergot, rizatriptan versus sumatriptan)	Decision analytic [Not specified]
Efficacy inputs	Headache response at 2 hours after medication Headache recurrence within 24 hours	Pain-free at 2 hours
Adverse events	Cardiovascular events	Not included

Utilities	QWB	Not included
Discounting	N/A	Not included
Outcomes	Incremental cost per QALY	Average drug costs per pain-free patient at 2 hours Incremental cost-effectiveness plots
Results	Rizatriptan and Sumatriptan dominated Cafergot Rizatriptan dominated Sumatriptan	<u>Average drug costs per pain-free patient at 2 hours</u> UK: $19.82 for rizatriptan 10 mg to $53.50 sumatriptan 100 mg USA: $47.32 for rizatriptan 10 mg to $153.47 frovatriptan 2.5 mg Canada: $25.79 for rizatriptan 10 mg to $67.29 naratriptan 2.5 mg Germany: $21.88 for rizatriptan 10 mg to $63.03 eletriptan 20 mg Italy: $18.21 for rizatriptan 10 mg to $41.60 zolmitriptan 5 mg Netherlands: $19.00 for rizatriptan 10 mg to $57.94 eletriptan 20 mg <u>Incremental cost-effectiveness plots</u> For five of six countries, rizatriptan 10 mg and eletriptan 40 mg dominated sumatriptan 100 mg; all other triptans were less costly and less effective than sumatriptan 100 mg. In Canada, rizatriptan 10 mg dominated sumatriptan 100 mg; all other triptans were less costly and less effective than sumatriptan
Types of sensitivity analysis	<u>Deterministic Analysis (one-way)</u> Drug acquisition costs Cost of hospitalization Utility association with each outcome (except hospitalization) Treatment effect Probability of relief in ER Probability of switching therapy	N/A

Sensitivity analysis results	Rizatriptan/Sumatriptan versus Cafergot Results insensitive to drug acquisition costs, costs of hospitalization, utility association with each outcome (except hospitalization), treatment effect, probability of relief in ER, probability of switching therapy Rizatriptan versus Sumatriptan Results sensitive to treatment effect	N/A
Points to consider	Costs USD$ (2003) Generic prices are not considered Efficacy data from published meta-analysis and 1 RCT, using indirect comparison Included adverse events; based on cost of hospitalization as a result of CV event Utility values derived from QWB Comparison to Ergot and triptan No comparison to no therapy or other non-triptan medications	Costs in USD$ (2003, all costs converted to USD) Generic price not considered Efficacy data from meta-analysis using informal comparison No consideration of adverse events Sensitivity analysis not considered No consideration of utility values No comparison to no therapy or other non-triptan medications

Appendix A5: Characteristics of Reviewed Studies Continued

Study	Williams & Reeder , 2004	Adelman & Besley, 2003
Sponsorship	Pharmacia Corporation	Merck & Co., Inc.
Country	US	US
Perspective	US healthcare payer	Population Health (Health care payer)
Study Type	CEA	Informal analysis
Comparators	Almotriptan 12.5 mg Sumatriptan 50 mg Sumatriptan 100 mg	Almotriptan 12.5 mg Zolmitriptan 2.5 mg Frovatriptan 2.5 mg Sumatriptan 50 mg Sumatriptan 100 mg Rizatriptan 10 mg Zolmitriptan 5 mg Naratriptan 2.5 mg
Populations	Patients with acute migraine	Patients with migraine
Time horizon	24 hours	2 hours
Type of model	Decision analytic (not specified)	Decision analytic [Not specified]
Efficacy inputs	Sustained pain-free rate [Composite endpoint SNAE]	Pain free at 2 hours after initial dosing
Adverse events	No costs associated with AE	Not included
Utilities	N/A	N/A
Discounting	N/A	N/A
Outcomes	Incremental cost per additional SNAE	Average cost to achieve pain-free status in one patient at 2 hours after initial dosing

Results	Almotriptan 12.5 mg is superior to sumatriptan 50 mg and 100mg though cannot determine if almotriptan superior to no therapy. ICER for almotriptan versus sumatriptan 50 mg is $11.60 per SNAE and versus sumatriptan 100 mg is $15.92 per SNAE	Rizatriptan 10 mg and almotriptan 12.5 mg were most cost effective and frovatriptan 2.5 mg was the least cost effective in terms of mean cost to achieve pain-free status in one patient at 2 hours after initial dosing ($48.34, $48.57, $162.49 respectively).
Types of sensitivity analysis	Deterministic Analysis (one-way) Relationship between efficacy and tolerability Health service use and costs Drug utilization Probabilistic Analysis (Monte Carlo analysis) Unclear	N/A
Sensitivity analysis results	Deterministic Analysis (one-way) Results insensitive to assumptions around efficacy and tolerability and health service use Results sensitive to drug utilization : if 2 tablets of almotriptan required: drugs are equivalent in terms of cost-effectiveness Probabilistic Analysis (Monte Carlo analysis) Results of PSA are unclear	N/A
Points to consider	Costs in USD$ (1999, except drug costs 2004) Generic prices are not considered Efficacy data from a published meta-analysis No costs associated with management of adverse events Distributions used in PSA are not specified, and results are not presented in conventional formats No consideration of utility values No comparison to no therapy or other non-triptan medications	Cost in USD$ (2002) Generic prices are not considered Efficacy data from meta-analysis using indirect comparison Only drug acquisition costs considered No consideration of adverse events Reported cost per outcome; not ICER Reviewer unable to calculate ICER Sensitivity analysis not considered No consideration of utility values No comparison to no therapy or other non-triptan medications

Appendix A5: Characteristics of Reviewed Studies Continued

Study	Wells et al., 2003	Williams & Reeder, 2003
Sponsorship	Pfizer Global Research and Development	Pharmacia Corporation
Country	UK	US
Perspective	Healthcare system	US healthcare payer
Study Type	Informal analysis	CEA

Comparators	Eletriptan 40 mg Eletriptan 80 mg Sumatriptan 50 mg Sumatriptan 100 mg	Almotriptan 12.5 mg Rizatriptan 10 mg
Populations	Patients with migraine less than 18 years of age to greater than 45 years of age	Patients with acute migraine
Time horizon	24 hours	24 hours
Type of model	Decision Tree	Decision analytic [Not specified]
Efficacy inputs	Response at 1 hour Pain-free headache status at 2 hours Recurrence 24-hour sustained pain-free [Success measure 1 (SM1) (pain-free headache status at 2 hours, no recurrence within 24 hours of the first dosing, and no requirement for recue medication) & Success measure 2 (SM2) (positive headache response at 1 hour, achievement of pain-free status by 2 hours)]	sustained freedom from pain [Composite endpoint SNAE]
Adverse events	Not included	No costs associated with AE
Utilities	N/A	N/A
Discounting	N/A	N/A
Outcomes	Cost per successfully treated attack	Incremental cost per additional SNAE
Results	In terms of SM1 and SM2, eletriptans have lowest cost per successfully treated attack <u>SM1 Cost per successfully treated attack</u> Eletriptan 40 mg, £17.55 Eletriptan 80 mg, £ 31.76 Sumatriptan 50 mg, £63.98 Sumatriptan 100 mg, £80.50 <u>SM2 Cost per successfully treated attack</u> Eletriptan 40 mg, £29.61 Eletriptan 80 mg, £48.13 Sumatriptan 50 mg, £95.63 Sumatriptan 100 mg, £124.28	Almotriptan 12.5 mg is superior to rizatriptan 10 mg though cannot determine if almotriptan superior to no therapy. ICER for almotriptan versus rizatriptan is $6.94 per SNAE
Types of sensitivity analysis	N/A	<u>Deterministic Analysis (one-way)</u> Relationship between efficacy and tolerability Health service use and costs Drug utilization <u>Probabilistic Analysis (Monte Carlo analysis)</u> Unclear

Sensitivity analysis results	N/A	Deterministic Analysis (one-way) Results insensitive to assumptions around efficacy and tolerability and health service use Results sensitive to drug utilization : if 2 tablets of almotriptan required: drugs are equivalent in terms of cost-effectiveness Probabilistic Analysis (Monte Carlo analysis) Results of PSA are unclear
Points to consider	Cost £ (2002) Generic prices are not considered Drug acquisition costs and rescue medication considered Efficacy data from one PL No consideration of adverse events Reported cost per outcome, not ICER Sensitivity analysis not considered No consideration of utility values No comparison to no therapy or other non-triptan medications	Costs in USD$ (1999, except drug costs 2003) Generic prices are not considered Efficacy data from published meta-analysis No costs associated with management of adverse events Distributions used in PSA are not specified, and results are not presented in conventional formats No consideration of utility values No comparison to no therapy or other non-triptan medications

Study	Belsey, 2002	Reeder et al., 2002
Sponsorship	Merck Sharp & Dohme Limited	Unknown
Country	UK	US
Perspective	Payer [Not specified]	Payer
Study Type	Informal analysis	Informal analysis
Comparators	Sumatriptan 100 mg Sumatriptan 50 mg Rizatriptan 10 mg Zolmitriptan 2.5 mg Zolmitriptan 5mg Naratriptan 2.5 mg Almotriptan 12.5 mg Eletriptan 40 mg Eletriptan 80 mg	Almotriptan 12.5 mg Rizatriptan 10 mg Sumatriptan 100 mg Zolmitriptan 5 mg Naratriptan 2.5 mg
Populations	Patients with migraine	Patients with migraine
Time horizon	2 hours	24 hours
Type of model	Decision analytic [Not specified]	Decision analytic [Not specified]
Efficacy inputs	Pain-free at 2 hours	Sustained pain-free (pain free at 2 hours post-dose, no headache recurrence up to 24 hours after initial dose, no use of rescue medications within the same 24-hour time frame)

Adverse events	Not included	Not included
Utilities	Not included	N/A
Discounting	N/A	N/A
Outcomes	Average cost per pain-free patient at two hours	Cost to attain 100 sustained pain-free patients Cost to attain 100 sustained pain free patients without adverse events
Results	Rizatriptan 10 mg the lowest mean cost per pain-free patient at two hours (£14.15) Sumatriptan 100mg the highest mean cost per pain-free patient at two hours (£37.61) <u>Average cost per pain-free patient at two hours</u> Sumatriptan 100 mg, £37.61 Sumatriptan 50 mg, £28.71 Rizatriptan 10 mg, £14.15 Zolmitriptan 2.5 mg, £20.22 Zolmitriptan 5mg, £33.56 Naratriptan 2.5 mg, £32.66 Almotriptan 12.5 mg, £15.06 Eletriptan 40 mg, £17.37 Eletriptan 80 mg, £28.17	Almotriptan the most cost effective in terms of cost to attain 100 sustained pain-free patients and cost to attain 100 sustained pain free patients without adverse events <u>Cost to attain 100 sustained pain-free patient [approximates, exact values not shown]</u> Almotriptan 12.5 mg, $ 4,000 Rizatriptan 10 mg, $6,000 Sumatriptan 100 mg, $,8000 Zolmitriptan 5 mg, $8,000 Naratriptan 2.5 mg, $12,000 <u>Cost to attain 100 sustained pain free patients without adverse events [approximates, exact values not shown]</u> Almotriptan 12.5 mg, $4,000 Rizatriptan 10 mg, $7,000 Sumatriptan 100 mg, $9,000 Zolmitriptan 5 mg, $10,000 Naratriptan 2.5 mg, $12,000
Types of sensitivity analysis	N/A	N/A
Sensitivity analysis results	N/A	N/A
Points to consider	Cost in £ (sumatriptan 50 mg, 2001; all other triptans 2002) Generic price not considered Efficacy data from meta-analysis by author No consideration of adverse events Reported as cost per outcome; not ICER Reviewer unable to calculate ICER Sensitivity analysis not considered No consideration of utility values No comparison to no therapy or other non-triptan medications	Costs in US (source unknown) Efficacy data from a published meta-analysis No consideration of adverse events Reported as cost per outcome; not ICER Reviewer unable to calculate ICER Sensitivity analysis not considered No consideration of utility values No comparison to no therapy or other non-triptan medications

Appendix A5: Characteristics of Reviewed Studies Continued

Study	Payne et al., 1996
Sponsorship	UK Department of Health
Country	US
Perspective	Societal
Study Type	CEA (stated as cost-efficacy analysis)
Comparators	Sumatriptan 6mg (subcutaneous) Dihydroergotamine mesylate 1 mg (subcutaneous)
Populations	Patients aged 18-65 with 1 year documented history of migraine with or without aura, 1-6 moderate-to-severe migraine headaches per month during 6 month preceding of participation
Time horizon	1 year
Type of model	Trial based
Efficacy inputs	11 Efficacy Measures Required no more than 1 dose of medication Able to carry on as normal 1 hour after first dose Complete response 1 hour after first dose Relief of nausea 1 hour after first dose Complete response at 1 hour after second dose Able to carry on as normal 1 hour after second dose Complete response 24 hours after first dose Able to carry on as normal 24 hours after first dose Did not require medication for headache recurrence Required no rescue medication
Adverse events	Included, nausea and vomiting
Utilities	N/A
Discounting	N/A
Outcomes	incremental cost per efficacy
Results	[Efficacy Measure, Incremental Cost-Efficacy] Required no more than 1 dose of medication, $5,702.90/Efficacy Able to carry on as normal 1 hour after first dose, $3,999.77/Efficacy Complete response 1 hour after first dose, $4,130.61/Efficacy Relief of nausea 1 hour after first dose, $6,696.59/Efficacy Complete response at 1 hour after second dose, not significant due to efficacy Able to carry on as normal 1 hour after second dose, not significant due to efficacy Complete response 24 hours after first dose, DHE is more efficacious and less costly Able to carry on as normal 24 hours after first dose, DHE is more efficacious and less costly Did not require medication for headache recurrence, DHE is more efficacious and less costly Required no rescue medication, not significant due to efficacy

Types of sensitivity analysis	Deterministic Analysis (One-way) Indirect costs Direct costs Assumption of requiring antiemetics Assumption of 2 dose medication Assumption of being unable to function 24 hours after first dose Deterministic Analysis (Scenario) Break-even point (cost of labour)
Sensitivity analysis results	Deterministic Analysis (One-way) Results are insensitive to indirect and direct costs, assumptions of requiring antiemetics, of 2 dose medication, and of being unable to function 24 hours after first dose Deterministic Analysis (Scenario) Results sensitive to cost of lost labour: if cost of lost labour is $10,900, incremental cost ratios would be equivalent
Points to consider	Costs in USD$ (1993) Generic prices are not considered Subcutaneous treatments Efficacy input from one clinical trial Included adverse events; based on costs of vomiting and nausea No consideration of utility values Comparison to ergot No comparison to no therapy or other non-triptan medications

Appendix B - Budget Impact Analysis

Research Question

What is the economic impact of alternative changes to the funding status of triptans (e.g. restricted vs. more open access)?

Reimbursement Based Economic Assessment

An applied, policy-oriented economic model focusing on financial impact was created to facilitate consideration of alternative reimbursement strategies for triptans. The analysis utilized OPDP data on usage of triptans (almotriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) and ergots (ergot and ergot alkaloid) from 2000-2012. Oral ergots were discontinued in 2013. Thus, without adequate data on the shift from oral ergots to non-oral ergot formulations, it was not possible to forecast ergot expenditure. The model was developed within Microsoft Excel.

Expenditures for triptans for the next three years, 2013-2015, were predicted using time series analysis. Four models were used to forecast expenditure.

1. A linear model whereby expenditure was assumed to increase by the same amount each year and also increase with each new triptan covered under OPDP.
2. An exponential model where an exponential relationship between expenditure and time and number of triptans covered was assumed.
3. A power model whereby a non-linear relationship between time and expenditure was allowed – this model also incorporated the number of triptans covered.
4. A constant growth model whereby a constant percentage increase in expenditure was assumed with the addition of a triptan to coverage also leading to a percentage increase.

Of the four models, the most suitable model for forecasting was selected based on the following procedure. The linear, exponential and constant growth models were compared in terms of mean square error (MSE) and the model with the lowest error chosen. The linear model was preferred for triptans due to the lower MSE. The significance of the power term within the power model was then assessed and as it had little impact on MSE, the linear model was still preferred (see Appendix B1: Model Details for model details).

Alternative reimbursement strategies varied according to the process of reimbursement – current EAP status, EAP with generic costs equivalent to 25% of branded costs, EAP with replacement of brand name agents with their generic formulation, when available, EAP with no coverage of brand products, GB/LU for all triptans and GB/LU for generic products only – and the imposition of quantity limits – no limit, no more than 6 per month, no more than 12 per month and no more than 18 per month. For all GB/LU strategies it was assumed that generic products would cost 25% of the branded equivalent and that replacement of brand name agents with their generic formulation, when available, would be required. For EAP strategies the cost of processing EAP claims in 2012 was obtained from OPDP and was used to

forecast costs in alternate years.

A total of 20 reimbursement strategies were considered (Table 1 Reimbursement Strategies)

Table 1: Reimbursement Strategies

REIMBURSEMENT STRATEGY	DETAILS
EAP 1	Generic costs will be equivalent to 25% of average branded cost
EAP 2	EAP 1 with required replacement of brand name agents with their generic formulation, when available
EAP 3	EAP 2 with no coverage from formulations without generic equivalent (assume transfer to equivalent reimbursed formulation)
EAP 4	EAP 1 with 6 per month quantity limit
EAP 5	EAP 2 with 6 per month quantity limit
EAP 6	EAP 3 with 6 per month quantity limit
EAP 7	EAP 1 with 12 per month quantity limit
EAP 8	EAP 2 with 12 per month quantity limit
EAP 9	EAP 3 with 12 per month quantity limit
EAP 10	EAP 1 with 18 per month quantity limit
EAP 11	EAP 2 with 18 per month quantity limit
EAP 12	EAP 3 with 18 per month quantity limit
GB/LU 1	All triptans GB/LU
GB/LU 2	Only generic triptans
GB/LU 3	GB/LU 1 with 6 per month quantity limit
GB/LU 4	GB/LU 2 with 6 per month quantity limit
GB/LU 5	GB/LU1 with 12 per month quantity limit
GB/LU 6	GB/LU 2 with 12per month quantity limit
GB/LU 7	GB/LU 1 with 18 per month quantity limit
GB/LU 8	GB/LU 2 with 18 per month quantity limit

For EAP1, when a patient is prescribed the generic formulation of atriptan this will be assumed to cost 25% of the current brand cost

For EAP2, when a patient is prescribed the generic formulation of a triptan this will be assumed to cost 25% of the current brand cost. Under EAP2, if a patient is prescribed the brand formulation this must be replaced with their generic formulation, when available, which will be assumed to cost 25% of the current brand cost.

For EAP3, only the triptans for which a generic equivalent is available (Option EAP3) will be covered under OPDP in combination with reduced generic costs with the requirement of replacement of brand name agents with their generic formulation. Under EAP3, it is assumed that migraineurs who previously received products without a generic equivalent would now be prescribed a different formulation of the same product for which a generic equivalent is available.

For EAP1, EAP2, and EAP3 the total number of triptans prescribed will be the same as the base scenario. Thus, the estimation of expenditure requires weighting use with different unit costs. The difference in cost between EAP1 and the base case is because in EAP1, generic formulations will cost 25% of the current brand cost. The difference in costs between EAP1 and EAP2 arises because under EAP2, all brand formulations will be replaced with their generic formulation, when available. The difference in costs between EAP2 and EAP3 arises because under EAP3, only generic formulation will be covered.

For GB/LU1, all products with a generic equivalent must be priced at 25% of the brand cost and replacement of brand name agents with their generic formulation, when available, is required.

The increase in prescription volume was estimated using utilization data for Alberta and Manitoba (provinces with less restrictive access to triptans with much higher usage) relative to Ontario. To estimate the volume of triptan use we took the forecasted volume of use in any given year and multiplied that by the ratio of the use of triptans by beneficiary for Alberta/Manitoba. The average unit cost for triptans forecasted for that year in Ontario is then applied to this cost to give the estimated costs of triptans under GB/LU. (Full details of calculations are provided in Appendix B3: Worked Example of Budget Impact under General benefit/limited use)

For GB/LU2, a similar approach to that adopted for estimating EAP3 was adopted: i.e., it is assumed that migraineurs who previously received products without a generic equivalent would now be prescribed a different formulation of the same product for which a generic equivalent is available.

For quantity limits under EAP, only usage up to the quantity limits based on Ontario data were considered. Thus, we weighted the estimated total expenditures by the proportion of usage below the quantity limits for Ontario in 2012.

For quantity limits under GB/LU, only usage up to the quantity limits based on Alberta and Manitoba data were considered. Thus, we weighted the estimated total expenditures by the proportion of usage below the quantity limits for Alberta/Manitoba in 2012 (see Appendix B3: Worked Example of Budget Impact under General benefit/limited use).

Using only current data for Ontario is not appropriate for the calculation of the impact of extending coverage given that it relates to EAP coverage. We therefore, used both current Ontario data to estimate the proportion of triptan use by product and weighted this by the increase in triptan use per beneficiary in Manitoba and Alberta.

Findings

Current Expenditure and Market Share

Expenditure, Units, and Users in 2012

Table 2: Forecast of Expenditure by Triptan

	YEAR	SUMATRIPTAN	NARATRIPTAN	RIZATRIPTAN	ZOLMITRIPTAN	ALM0TRIPTAN	TOTAL
Actual	2000	$565,578	$0	$0	$0	$0	$565,578
	2001	$588,530	$26,363	$32,154	$1,454	$0	$648,502
	2002	$624,648	$59,156	$100,074	$25,107	$0	$808,985
	2003	$656,011	$83,077	$123,671	$36,926	$0	$899,685
	2004	$655,065	$72,375	$154,308	$45,153	$2,027	$928,927
	2005	$648,103	$72,727	$216,383	$50,670	$29,210	$1,017,094
	2006	$768,084	$85,633	$281,449	$54,377	$60,722	$1,250,266
	2007	$793,143	$100,866	$330,469	$37,140	$69,193	$1,330,811
	2008	$855,497	$89,867	$328,395	$34,004	$77,981	$1,385,745
	2009	$862,681	$90,229	$376,905	$35,501	$75,070	$1,440,385
	2010	$766,529	$81,283	$386,339	$22,669	$84,450	$1,341,270
	2011	$767,929	$80,538	$448,184	$29,014	$120,494	$1,446,158
	2012	$853,036	$77,825	$510,415	$28,578	$152,565	$1,622,418
Predicted	2013	$876,883	$80,000	$524,684	$29,377	$156,830	$1,667,774
	2014	$915,039	$83,482	$547,515	$30,655	$163,654	$1,740,344
	2015	$953,195	$86,963	$570,345	$31,934	$170,478	$1,812,914

In 2012, expenditure by OPDP on triptans was $1.62 million. In 2012, triptans expenditure ranged from $29 thousand for zolmitriptan to $853 thousand for sumatriptan.

Summary of Findings for Table 2

- Triptan expenditure has increased at a steady rate from $0.57 million in 2000 to $1.62 million in 2012.
- The proportion of sumatriptan usage over time has declined from 100% in 2000 to 53% in 2012, whilst the proportion of usage for rizatriptan and almotriptan has increased over time (for rizatriptan from 12% in 2002 to 31% in 2012, for almotriptan from 3% in 2005 to 9% in 2012).
- Sumatriptan has always been the most widely used, whilst rizatriptan is established as the second most widely used treatment and zolmitriptan is the least used treatment.

Table 3: User and Units in 2012

	USERS N (%)	UNITS N (%)	UNITS PER USER N
Total	2628	364361	
Ergots	1538 (59%)	255126 (70%)	166
Triptans	1090 (41%)	109235 (30%)	100
Almotriptan	131 (5%)	10408 (3%)	79
Naratriptan	76 (3%)	6782 (2%)	89
Rizatriptan	400 (15%)	33235 (9%)	83
Sumatriptan	484 (18%)	56740 (16%)	117
Zolmitriptan	7 (0%)	2070 (1%)	296

The number of units per user was 100 for triptans and 166 for ergots.

Summary of Findings for Table 3

- Total users were 2628, 1090 for triptans and 1538 for ergots. Triptans accounted for 41% of users, while ergots accounted for 59% of users.
- Total units were 364361, 109235 for triptans and 255126 for ergots. Triptans accounted for 30% of units, while ergots accounted for 30% of units.
- Triptans number of units per user ranged from 83 for naratriptan to 296 for zolmitriptan.

Table 4: Number of Prescription in 2012

	PRESCRIPTIONS N	TRIPTANS UNITS %	TOTAL TRIPTAN AND ERGOT EXPENDITURE %
Ergots	5689		14%
Triptans	8641		
Almotriptan	773	10%	8%
Naratriptan	610	6%	4%
Rizatriptan	2600	30%	27%
Sumatriptan	4583	52%	45%
Zolmitriptan	75	2%	2%

The most commonly prescribed triptan was sumatriptan.

Summary of Findings for Table 4

- The most commonly prescribed triptan was sumatriptan (52% of total triptan units) which also contributed most of the budget impact (45% of total triptan and ergot expenditure).
- The least prescribed triptan was zolmitriptan (2% of total triptan units) while almotriptan contributed the least of the budget impact (2% of total triptan and ergot expenditure).

Table 5: Total Cost in 2012

	TOTAL COST IN 2012 $	AVERAGE COST PER UNIT $
Ergots	$261,589	$1.03
Triptans	$1,622,418	$14.85
Almotriptan	$152,565	$14.66
Naratriptan	$77,825	$11.48
Rizatriptan	$510,415	$15.36
Sumatriptan	$853,036	$15.03
Zolmitriptan	$28,578	$13.81

In 2012, ergots cost an average of $1.03 per unit whilst triptans varied from $11.48 for naratriptan to $15.36 for rizatriptan.

Summary of Findings for Table 5

- The average cost per unit was $14.85 for triptans and $1.03 for ergots.
- The average cost per unit for triptans ranged from $11.48 for naratriptan to $15.36 for rizatriptan.

Table 6: Total EAP Processing Cost for Triptans

	YEAR	TOTAL EAP PROCESSING COST
Estimated	2000	$3,910
	2001	$4,484
	2002	$5,593
	2003	$6,220
	2004	$6,422
	2005	$7,032
	2006	$8,644
	2007	$9,201
	2008	$9,581
	2009	$9,958
	2010	$9,273
	2011	$9,998
Actual	2012	$11,217
Predicted	2013	$11,531
	2014	$12,032
	2015	$12,534

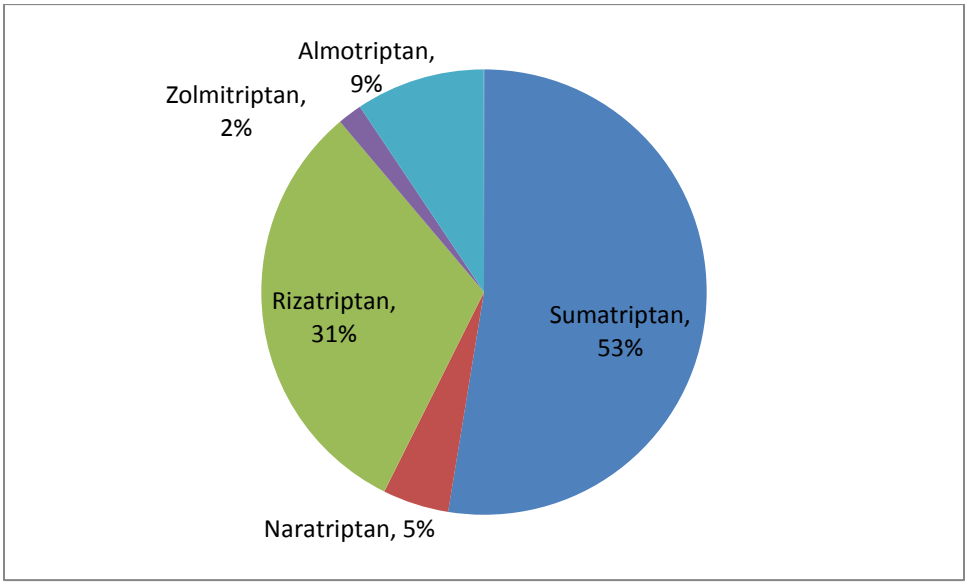
In 2012, the total EAP processing cost (Exceptional Access Program) for triptans was estimated to be $11,217.

Summary of Findings for Table 6

- Total EAP processing cost for triptans is estimated to increase time from $3,910 in 2000 to $11,217 in 2012.

Triptan Market Share in 2012

Figure 1: Triptan Market Share in 2012



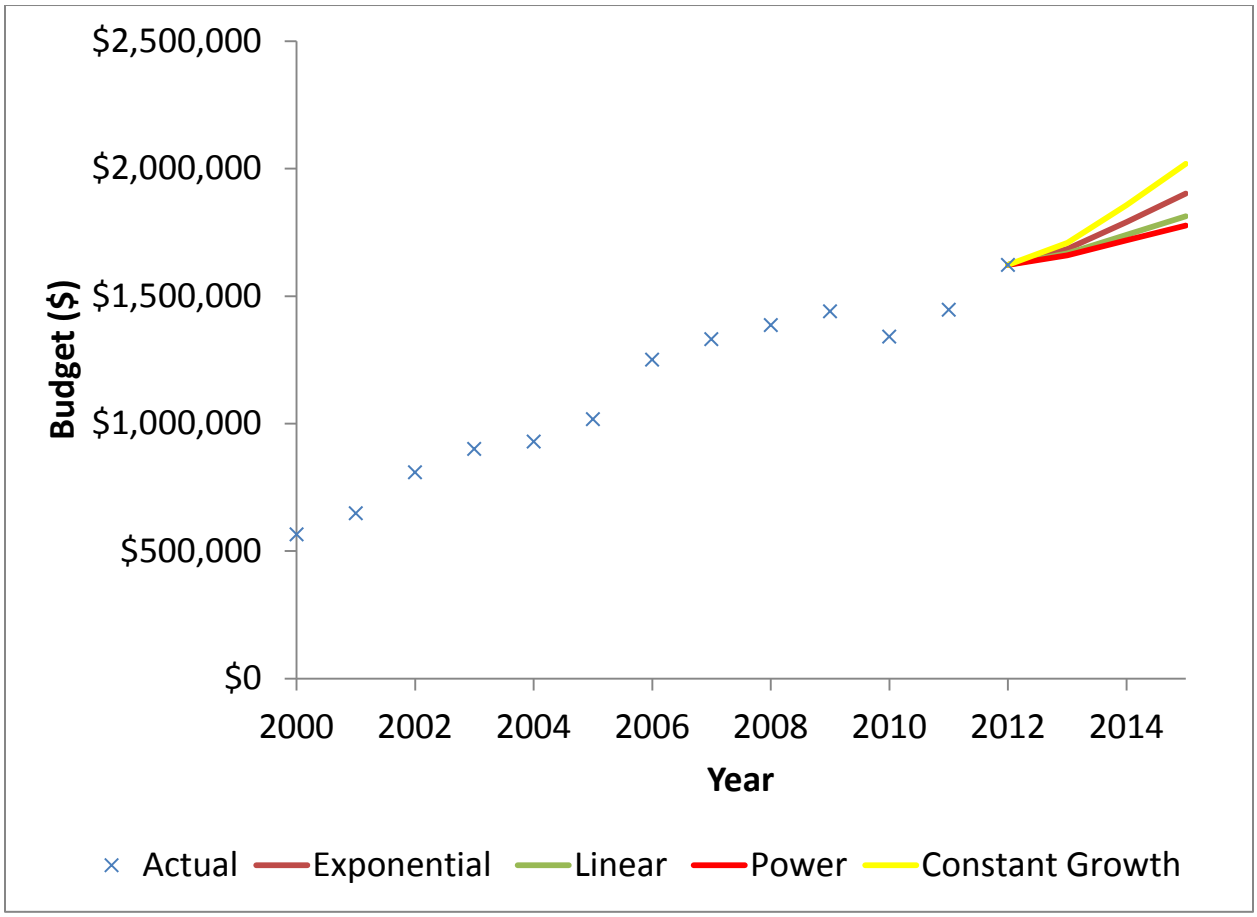
Based on expenditure in 2012, sumatriptan had the largest market share at 53%, whilst zolmiriptan had the smallest market share at 2%.

Summary of Findings for Figure 1

- In 2012, sumatriptan had the largest market share, whilst rizatriptan had the second largest market share, and zolmitriptan had the smallest market share.

Forecasting Expenditure

Figure 2: Forecast of Triptan Expenditure



Triptan expenditure has increased over time since 2000 and will continue to increase for the next three years.

Summary of Findings for Figure 2

- The cost of triptans is expected to rise over the next three years.
- All four models (exponential, linear, power and constant growth) follow an upward trend. The linear model, however, appears as the most suitable model for forecasting triptan expenditure.

Forecast of Expenditure By Triptans

Without any change in reimbursement for triptans, it is forecasted that expenditure on triptans will rise over the next three years; $1.67 million followed by $1.74 million followed by $1.81 million. In 2015, the forecasted number of units of triptans prescribed is 122,061. Without any change in reimbursement for

triptans, it is expected that sumatriptan expenditure will remain the largest, while zolmitriptan expenditure will remain the least. For sumatriptan, expenditure will be $877 thousand followed by $915 thousand followed by $953 thousand. For zolmitriptan, expenditure will be $29 thousand followed $31 thousand by followed by $32 thousand (Table 2 Forecast of Expenditure by Triptan).

Impact of Alternative Approaches to Reimbursement

A linear model was used to forecast the expenditure of triptan under various strategies for reimbursement (Appendix B1: Model Details).

A summary of the predicted expenditure and budget impact for the selected strategies are presented below:

Table 7: Summary of Predicted Expenditure and Budget Impact (Without Quantity Limits)

	YEAR		
	2013	2014	2015
Base Case			
	$1,679,305	$1,752,377	$1,825,448
EAP1			
Predicted Total $	$1,405,743	$1,467,247	$1,529,366
Budget Impact, N (%)	-$273,562(16%)	-$285,129(16%)	-$296,082(16%)
EAP2			
Predicted Total $	$527,001	$550,268	$574,150
Budget Impact, N (%)	-$1,152,304(69%)	-$1,202,108(69%)	-$1,251,298(69%)
EAP3			
Predicted Total $	$514,779	$537,515	$560,865
Budget Impact, N (%)	-$1,164,526(69%)	-$1,214,862(69%)	-$1,264,583(69%)
ALBERTA			
GB/LU1			
Predicted Total $	$6,756,681	$7,050,685	$7,344,689
Budget Impact, N (%)	$5,077,377(302%)	$5,298,309(302%)	$5,519,241(302%)
GB/LU2			
Predicted Total $	$6,596,480	$6,883,513	$7,170,546
Budget Impact, N (%)	$4,917,175(293%)	$5,131,137(293%)	$5,345,098(293%)
MANITOBA			
GB/LU1			
Predicted Total $	$4,994,316	$5,211,634	$5,428,952
Budget Impact, N (%)	$3,315,011(197%)	$3,459,257(197%)	$3,603,504(197%)
GB/LU2			
Predicted Total $	$4,875,901	$5,088,066	$5,300,231
Budget Impact, N (%)	$3,196,596(190%)	$3,335,689(190%)	$3,474,783(190%)

Of the alternative approaches to reimbursement of triptans, the results of EAP strategies without quantity limits suggest a reduction in total costs (16%, 69%, 69% respectively), while results of GB/LU strategies (based on Alberta usage) without quantity limits suggest an increase in total costs (302%, 293% respectively). Results of GB/LU strategies (based on Manitoba usage) without quantity limits suggest an increase in total costs (197%, 190% respectively).

Under the EAP1 , EAP2 and EAP3 strategies the number of units of triptans prescribed and the number of users will be the same as the base case: 122,061 and 1,218 respectively. Under GB/LU1 and GB/LU2 the number of units of triptans prescribed will be 1.6 million based on Alberta usage and 1.2 million based on Manitoba data whilst the number of users will be 24,344 and 32,428 respectively.

Table 8: Summary of Predicted Expenditure and Budget Impact (With Quantity Limits)

	YEAR		
	2013	2014	2015
Base Case			
	$1,679,305	$1,752,377	$1,825,448
EAP2			
Predicted Total $	$527,001	$550,268	$574,150
Budget Impact, N (%)	-$1,152,304(69%)	-$1,202,108(69%)	-$1,251,298(69%)
EAP5			
Predicted Total $	$265,130	$277,003	$289,491
Budget Impact, N (%)	-$1,414,175(84%)	-$1,475,373(84%)	-$1,535,958(84%)
EAP8			
Predicted Total $	$381,672	$398,617	$416,175
Budget Impact, N (%)	-$1,297,632(77%)	-$1,353,760(77%)	-$1,409,273(77%)
EAP11			
Predicted Total $	$470,182	$490,977	$512,387
Budget Impact, N (%)	-$1,209,123(72%)	-$1,261,399(72%)	-$1,313,061(72%)
ALBERTA			
GB/LU2			
Predicted Total $	$6,596,480	$6,883,513	$7,170,546
Budget Impact, N (%)	$4,917,175(293%)	$5,131,137(293%)	$5,345,098(293%)
GB/LU4			
Predicted Total $	$3,929,938	$4,100,941	$4,271,945
Budget Impact, N (%)	$2,250,633(134%)	$2,348,565(134%)	$2,446,497(134%)
GB/LU6			
Predicted Total $	$5,268,097	$5,497,328	$5,726,559
Budget Impact, N (%)	$3,588,792(214%)	$3,744,951(214%)	$3,901,111(214%)
GB/LU8			
Predicted Total $	$5,858,328	$6,113,241	$6,368,155
Budget Impact, N (%)	$4,179,023(249%)	$4,360,865(249%)	$4,542,707(249%)
MANITOBA			
GB/LU2			
Predicted Total $	$4,875,901	$5,088,066	$5,300,231
Budget Impact, N (%)	$3,196,596(190%)	$3,335,689(190%)	$3,474,783(190%)
GB/LU4			
Predicted Total $	$3,795,383	$3,960,532	$4,125,681
Budget Impact, N (%)	$2,116,078(126%)	$2,208,155(126%)	$2,300,232(126%)
GB/LU6			
Predicted Total $	$4,591,130	$4,790,905	$4,990,679
Budget Impact, N (%)	$2,911,826(173%)	$3,038,528(173%)	$3,165,230(173%)

GB/LU8			
Predicted Total $	$4,746,928	$4,953,481	$5,160,034
Budget Impact, N (%)	$3,067,623(183%)	$3,201,105(183%)	$3,334,586(183%)

Of the alternative approaches to reimbursement of triptans, the results of EAP2 strategies with quantity limits suggest a modest reduction in total costs - 84%, 77% and 72% compared to 69% with no quantity limits. The results of GB/LU2 strategies (based on Alberta usage) with quantity limits suggest an increase in total costs -134%, 214% and 249% compared to 293% without quantity limits.

Under EAP2, the imposition of quantity limits of 6, 12 and 18 per month will reduce the number of units of triptans prescribed from 122,061 to 61,071 (50% decrease), 88,687 (27% decrease) and 108,681 (11% decrease) respectively.

Under GB/LU2, the imposition of quantity limits of 6, 12 and 18 per month will reduce the number of units of triptans prescribed from 1.6 million to 0.9 million (41% decrease), 1.3 million (21% decrease) and 1.4 million (11% decrease) respectively.

Under both EAP and GB/LU the number of users will be as previously as only the volume per user will decline.

Summary of Findings for Table 7 and Table 8

- Without any change in reimbursement for triptans, it is expected that expenditure on triptans will rise over the next three years.
- Requiring that under EAP generic triptans should be 25% of brand cost is forecasted to reduce expenditure on triptans by 16% (a reduction of $0.30 million in 2015).
- Combining reduced generic costs with the requirement of replacement of brand name agents with their generic formulation, when available, of branded products will reduce expenditure by 69% (a reduction of $1.25 million in 2015).
- Based on current prescribing in Alberta where triptans are available similar to general benefit/limited use, coverage of triptans through general benefit/limited use is forecasted to lead to an increase in the expenditure of triptans in Ontario by 302% (an increase of $5.52 million in 2015). Restricting coverage under GB/LU to only generic products will lead to an increase of 293% (an increase of $5.35 million in 2015).
- Similarly, based on current prescribing in Manitoba where triptans are available with a passive quantity limit of 12, coverage of triptans through general benefit/limited use is forecasted to lead to an increase in the expenditure of triptans in Ontario by 197% (an increase of $3.60 million in 2015). Restricting coverage under GB/LU to only generic products will lead to an increase of 190% (an increase of $3.47 million in 2015).
- Imposition of quantity limits when triptans are available through EAP will lead to small absolute decreases in total triptan expenditures. For example, for strategy EAP2 the incremental reduction in triptan expenditure through imposing a quantity limit of 6 per month compared to no quantity limits would be approximately $285 thousand (a reduction of $1.54 million compared to a reduction of $1.25 million).
- However, for strategies involving access to triptans through GB/LU based on Alberta usage, the impact of quantity limits is much greater. For strategy GB/LU2, the incremental reduction in triptan expenditure through imposing a quantity limit of 6 per month compared (strategy GB/LU4) to no quantity limits (strategy GB/LU2) would be approximately $2.90 million. For strategy GB/LU2, the incremental reduction in triptan expenditure through imposing a quantity limit of 12 per month (strategy GB/LU6) compared to no quantity limits would be approximately $1.44 million. However, overall expenditure on triptans would still be significantly greater than if they remained on EAP (an increase of $2.45 million under GB/LU4, $3.90 million under GB/LU6 and $5.35 million under GB/LU2).
- Similarly, for strategies involving access to triptans through GB/LU based on Manitoba usage, the impact of quantity limits is much greater. For strategy GB/LU2, the incremental reduction in triptan expenditure through imposing a quantity limit of 6 per month compared (strategy GB/LU4) to no quantity limits (strategy GB/LU2) would be approximately $1.17 million. For strategy GB/LU2, the incremental reduction in triptan expenditure through imposing a quantity limit of 12 per month (strategy GB/LU6) compared to no quantity limits (strategy GB/LU2) would be approximately $0.31 million. However, overall expenditure on triptans would still be significantly greater than if they remained on EAP (an increase of $2.30 million under GB/LU4, $3.17 million under GB/LU6 and $3.47 million under GB/LU2).

For the predicted expenditure and budget impact for all strategies refer to Appendix B2: Alternative Approaches to Reimbursement Results.

Discussion

Data from Alberta and Manitoba were used to forecast future expenditure on triptans should a change in listing allow greater ease of access to triptans. This is a necessary limitation of the study given that there is no Ontario data which would allow forecast. The population covered by provincial drug plans will differ by province and, hence, the results of the study may be inexact.

To in some way validate the estimates obtained, it is possible to compare the use of triptans in Alberta and Manitoba with forecasted use based on migraine prevalence and uptake of triptans. However, it should be noted that although intuitively attractive, a limitation of such an approach is that it ignores the potential use of triptans outside of the migraine population.

Analysis of the 2012 CCHS provides age specific prevalence of migraine of 11.8% for those under 65 (12.7% for those under 60)and 9.2% for those over 65 (8.9% for those over 60).[80] A US study suggests that triptans were used by 19.4% of migraineurs aged under 60 and 12.7% of those over 60.[81] These figures would suggest uptake of 2.5% in those under 60 and 0.8% in those over 60.Triptan use by beneficiaries was 2.3% in Alberta and 1.2% in Manitoba for those under 65 and 0.3% in both provinces for those over 65. This suggests that given the forecasted data are in line with prevalence and usage data, the estimates derived from Alberta and Manitoba are not under estimates of the potential budget increase should migraineurs have more easy access to triptans.

Overall Conclusions

In 2012, expenditure by OPDP on triptans was $1.62 million. Without any change in reimbursement for triptans, it is expected that expenditure on triptans will rise over the next three years.

Alternative EAP strategies relating to generic pricing suggest a reduction in total costs, while alternative GB/LU based strategies suggest an increase in total costs.

Overall Summary

An applied, policy oriented model was created to forecast expenditure for triptans. Using OPDP data on usage of triptans and time series analysis, costs for the next three years were estimated with four models (exponential, linear, power and constant growth). Without any change in reimbursement for triptans, it is forecasted that expenditure on triptans will rise over the next three year. Alternative approaches to reimbursement of triptans were identified and budget expenditure on triptans for each alternative reimbursement strategy was forecasted. All strategies which included generic costs equivalent to 25% of average branded cost (without GB/LU) would lead to a reduction in total cost ranging from 16%-84%. All strategies which included GB/LU based on Alberta usage would lead to an increase in total costs ranging from 134%-302%. All strategies which included GB/LU based on Manitoba usage would lead to an increase in total costs ranging from 126%-197%.

Conclusions

Without any change in reimbursement for triptans, it is expected that expenditure on triptans will rise over the next three year.

If triptans were available at a generic price of 25% of average branded cost, regardless of a quantity limit reimbursement status, there would be a reduction in expenditure by OPDP, with a significantly greater reduction when replacement of brand name agents with their generic formulation, when available, is required.

Changing the reimbursement status of all triptans to general benefit/limited use with or without quantity limits would lead to a significant increase in expenditure by OPDP, even with a generic price of 25% of average branded cost.

Appendix B - Appendices

Appendix B1: Model Details

The following are details of each model used to forecast ergot and triptan expenditure.

Table 9: Model Details

	CONSTANT	NO. OF TRIPTANS FUNDED	QUARTER	NEW TRIPTAN AVAILABLE
ERGOTS				
LINEAR MODEL				
Coefficient	116146.88	-10101.94	-126.66	#N/A
Std. error	3852.85	1134.07	305.52	#N/A
R^2	0.81			
Mean prediction error	51900809			
LOGEST MODEL				
Coefficient	123235.24	0.88	1.00	#N/A
Std. error	0.05	0.02	0.00	#N/A
R^2	0.79			
Mean prediction error	53231590.405			
POWER MODEL				
Coefficient	75584.98	-5963.61	33000.62	#N/A
Std. error	20655.60	2332.80	16301.05	#N/A
R^2	0.82			
Mean prediction error	45104733.351			
CONSTANT GROWTH MODEL				
Coefficient	-0.01	#N/A	#N/A	-0.04
Std. error	0.005	#N/A	#N/A	0.02
R^2	0.05			
Mean prediction error	73076110.863			
TRIPTANS				
LINEAR MODEL				
Coefficient	102320.65	12974.54	18142.49	#N/A
Std. error	15723.73	4628.21	1246.85	#N/A
R^2	0.93			
Mean prediction error	595890177.338			
LOGEST MODEL				
Coefficient	114934.67	1.11	1.06	#N/A
Std. error	0.06	0.02	0.00	#N/A
R^2	0.94			
Mean prediction error	660084948.346			
POWER MODEL				
Coefficient	76011.42	-698.64	68166.56	#N/A
Std. error	14014.45	4976.66	4325.20	#N/A
R^2	0.94			
Mean prediction error	555152116.876			
CONSTANT GROWTH MODEL				
Coefficient	0.021	#N/A	#N/A	0.02
Std. error	0.005	#N/A	#N/A	0.02
R^2	0.01			
Mean prediction error	1079027502.711			

The linear model was the most suitable model for forecasting triptan and ergot expenditure.

Appendix B2: Alternative Approaches to Reimbursement Results

The following tables present the forecasted expenditure and budget impact for each alternative approach to reimbursement.

Table 10: EAP 1- Generic costs will be equivalent to 25% of average branded cost

	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$693,669	$723,852	$754,036
Naratriptan	$61,082	$63,739	$66,397
Rizatriptan	$460,553	$480,593	$500,633
Zolmitriptan	$22,079	$23,040	$24,001
Almotriptan	$156,830	$163,654	$170,478
EAP	$11,531	$12,369	$13,821
Total	$1,405,743	$1,467,247	$1,529,366
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	-$273,562	-$285,129	-$296,082
% reduction	16%	16%	16%

EAP 1 would lead to a 16% reduction in triptan expenditure.

Table 11: EAP 2- EAP 1 with required replacement of brand name agents with their generic formulation, when available

	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$292,297	$305,015	$317,734
Naratriptan	$28,351	$29,585	$30,819
Rizatriptan	$141,422	$147,576	$153,730
Zolmitriptan	$14,192	$14,810	$15,427
Almotriptan	$39,207	$40,914	$42,620
EAP	$11,531	$12,369	$13,821
Total	$527,001	$550,268	$574,150
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	-$1,152,304	-$1,202,108	-$1,251,298
% reduction	69%	69%	69%

EAP2 would lead to a 69% reduction in triptan expenditure.

Table 12: EAP 3- EAP 2 with no coverage for formulations without generic equivalent

	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$282,363	$294,649	$306,936
Naratriptan	$28,351	$29,585	$30,819
Rizatriptan	$141,422	$147,576	$153,730
Zolmitriptan	$11,904	$12,422	$12,940
Almotriptan	$39,207	$40,914	$42,620
EAP	$11,531	$12,369	$13,821
Total	$514,779	$537,515	$560,865
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	-$1,164,526	-$1,214,862	-$1,264,583
% reduction	69%	69%	69%

EAP 3 would lead to a 69% reduction in triptan expenditure.

Table 13: EAP 4- EAP 1 with 6 per month quantity limit

	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$314,720	$328,414	$342,108
Naratriptan	$35,657	$37,209	$38,760
Rizatriptan	$256,869	$268,046	$279,223
Zolmitriptan	$4,800	$5,009	$5,218
Almotriptan	$89,885	$93,796	$97,707
EAP	$11,531	$12,369	$13,821
Total	$713,461	$744,842	$776,838
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	-$965,844	-$1,007,534	-$1,048,611
% reduction	58%	57%	57%

EAP 4 would lead to a 57% reduction in triptan expenditure.

Table 14: EAP 5- EAP 2 with 6 per month quantity limit

	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$132,616	$138,386	$144,157
Naratriptan	$16,551	$17,271	$17,991
Rizatriptan	$78,877	$82,309	$85,741
Zolmitriptan	$3,085	$3,220	$3,354
Almotriptan	$22,471	$23,449	$24,427
EAP	$11,531	$12,369	$13,821
Total	$265,130	$277,003	$289,491
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	-$1,414,175	-$1,475,373	-$1,535,958
% reduction	84%	84%	84%

EAP 5 would lead to a 84% reduction in triptan expenditure.

Table 15: EAP 6- EAP 3 with 6 per month quantity limit

	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$128,109	$133,683	$139,258
Naratriptan	$16,551	$17,271	$17,991
Rizatriptan	$78,877	$82,309	$85,741
Zolmitriptan	$2,588	$2,700	$2,813
Almotriptan	$22,471	$23,449	$24,427
EAP	$11,531	$12,369	$13,821
Total	$260,126	$271,781	$284,051
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	-$1,419,179	-$1,480,595	-$1,541,398
% reduction	85%	84%	84%

EAP 6 would lead to a 84% reduction in triptan expenditure.

Table 16: EAP 7- EAP 1 with 12 per month quantity limit

	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$475,884	$496,591	$517,299
Naratriptan	$50,050	$52,228	$54,406
Rizatriptan	$361,265	$376,985	$392,704
Zolmitriptan	$7,744	$8,081	$8,418
Almotriptan	$121,889	$127,192	$132,496
EAP	$11,531	$12,369	$13,821
Total	$1,028,362	$1,073,446	$1,119,144
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	-$650,942	-$678,931	-$706,305
% reduction	39%	39%	39%

EAP 7 would lead to a 39% reduction in triptan expenditure.

Table 17: EAP 8- EAP 2 with 12 per month quantity limit

	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$200,527	$209,253	$217,978
Naratriptan	$23,231	$24,242	$25,253
Rizatriptan	$110,934	$115,761	$120,588
Zolmitriptan	$4,978	$5,194	$5,411
Almotriptan	$30,472	$31,798	$33,124
EAP	$11,531	$12,369	$13,821
Total	$381,672	$398,617	$416,175
Base Total	$1,679,305	$1,752,377	$1,825,448

Budget Impact			
$	-$1,297,632	-$1,353,760	-$1,409,273
% reduction	77%	77%	77%

EAP 8 would lead to a 77% reduction in triptan expenditure.

Table 18: EAP 9- EAP 3 with 12 per month quantity limit

	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$193,712	$202,141	$210,570
Naratriptan	$23,231	$24,242	$25,253
Rizatriptan	$110,934	$115,761	$120,588
Zolmitriptan	$4,175	$4,357	$4,538
Almotriptan	$30,472	$31,798	$33,124
EAP	$11,531	$12,369	$13,821
Total	$374,055	$390,668	$407,894
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	-$1,305,250	-$1,361,709	-$1,417,554
% reduction	78%	78%	78%

EAP 9 would lead to a 78% reduction in triptan expenditure.

Table 19: EAP 10- EAP 1 with 18 per month quantity limit

	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$616,030	$642,835	$669,640
Naratriptan	$53,060	$55,369	$57,678
Rizatriptan	$425,056	$443,551	$462,046
Zolmitriptan	$17,584	$18,349	$19,114
Almotriptan	$130,468	$136,145	$141,822
EAP	$11,531	$12,369	$13,821
Total	$1,253,728	$1,308,618	$1,364,122
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	-$425,577	-$443,759	-$461,326
% reduction	25%	25%	25%

EAP 10 would lead to a 25% reduction in triptan expenditure.

Table 20: EAP 11- EAP 2 with 18 per month quantity limit

	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$259,581	$270,877	$282,172
Naratriptan	$24,628	$25,700	$26,771
Rizatriptan	$130,522	$136,202	$141,881
Zolmitriptan	$11,303	$11,795	$12,286
Almotriptan	$32,617	$34,036	$35,455
EAP	$11,531	$12,369	$13,821
Total	$470,182	$490,977	$512,387
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	-$1,209,123	-$1,261,399	-$1,313,061
% reduction	72%	72%	72%

EAP 11 would lead to a 72% reduction in triptan expenditure.

Table 21: EAP 12- EAP 3 with 18 per month quantity limit

	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$250,759	$261,671	$272,582
Naratriptan	$24,628	$25,700	$26,771
Rizatriptan	$130,522	$136,202	$141,881
Zolmitriptan	$9,481	$9,893	$10,306
Almotriptan	$32,617	$34,036	$35,455
EAP	$11,531	$12,369	$13,821
Total	$459,538	$479,870	$500,816
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	-$1,219,767	-$1,272,507	-$1,324,632
% reduction	73%	73%	73%

EAP 12 would lead to a 73% reduction in triptan expenditure.

Table 22: GB/LU 1- All triptans GB/LU with GB/LU based on Alberta usage

ALBERTA	Year 2013	2014	2015
TRIPTAN			
Sumatriptan	$3,831,368	$3,998,083	$4,164,797
Naratriptan	$371,624	$387,795	$403,965
Rizatriptan	$1,853,736	$1,934,398	$2,015,060
Zolmitriptan	$186,029	$194,123	$202,218
Almotriptan	$513,924	$536,287	$558,649
Total	$6,756,681	$7,050,685	$7,344,689
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	$5,077,377	$5,298,309	$5,519,241
% increase	302%	302%	302%

GB/LU 1 would lead to a 302% increase in triptan expenditure.

Table 23: GB/LU 2- Only generic triptans GB/LU with GB/LU based on Alberta usage

ALBERTA	Year 2013	2014	2015
TRIPTAN			
Sumatriptan	$3,701,159	$3,862,207	$4,023,256
Naratriptan	$371,624	$387,795	$403,965
Rizatriptan	$1,853,736	$1,934,398	$2,015,060
Zolmitriptan	$156,037	$162,827	$169,617
Almotriptan	$513,924	$536,287	$558,649
Total	$6,596,480	$6,883,513	$7,170,546
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	$4,917,175	$5,131,137	$5,345,098
% increase	293%	293%	293%

GB/LU 2 would lead to a 293% increase in triptan expenditure.

Table 24: GB/LU 3- GB/LU 1 with 6 per month quantity limit

ALBERTA	Year 2013	2014	2015
TRIPTAN			
Sumatriptan	$2,159,305	$2,253,263	$2,347,221
Naratriptan	$248,054	$258,848	$269,641
Rizatriptan	$1,198,805	$1,250,969	$1,303,133
Zolmitriptan	$69,725	$72,759	$75,793
Almotriptan	$338,674	$353,411	$368,148
Total	$4,014,563	$4,189,249	$4,363,935
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	$2,335,258	$2,436,872	$2,538,487
% increase	139%	139%	139%

GB/LU 3 would lead to a 139% increase in triptan expenditure.

Table 25: GB/LU 4- GB/LU 2 with 6 per month quantity limit

ALBERTA	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$2,085,920	$2,176,685	$2,267,450
Naratriptan	$248,054	$258,848	$269,641
Rizatriptan	$1,198,805	$1,250,969	$1,303,133
Zolmitriptan	$58,484	$61,028	$63,573
Almotriptan	$338,674	$353,411	$368,148
Total	$3,929,938	$4,100,941	$4,271,945
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	$2,250,633	$2,348,565	$2,446,497
% increase	134%	134%	134%

GB/LU 4 would lead to a 134% increase in triptan expenditure.

Table 26: GB/LU 5- GB/LU 1 with 12 per month quantity limit

ALBERTA	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$2,965,096	$3,094,117	$3,223,137
Naratriptan	$323,290	$337,357	$351,425
Rizatriptan	$1,565,937	$1,634,075	$1,702,214
Zolmitriptan	$99,046	$103,355	$107,665
Almotriptan	$431,466	$450,240	$469,014
Total	$5,384,834	$5,619,145	$5,853,456
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	$3,705,529	$3,866,768	$4,028,007
% increase	221%	221%	221%

GB/LU 5 would lead to a 221% increase in triptan expenditure.

Table 27: GB/LU 6- GB/LU 2 with 12 per month quantity limit

ALBERTA	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$2,864,327	$2,988,963	$3,113,598
Naratriptan	$323,290	$337,357	$351,425
Rizatriptan	$1,565,937	$1,634,075	$1,702,214
Zolmitriptan	$83,078	$86,692	$90,307
Almotriptan	$431,466	$450,240	$469,014
Total	$5,268,097	$5,497,328	$5,726,559
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	$3,588,792	$3,744,951	$3,901,111
% increase	214%	214%	214%

GB/LU 6 would lead to a 214% increase in triptan expenditure.

Table 28: GB/LU 7- GB/LU 1 with 18 per month quantity limit

ALBERTA	Year 2013	2014	2015
TRIPTAN			
Sumatriptan	$3,328,444	$3,473,274	$3,618,105
Naratriptan	$353,157	$368,524	$383,891
Rizatriptan	$1,719,968	$1,794,809	$1,869,650
Zolmitriptan	$118,585	$123,745	$128,905
Almotriptan	$470,410	$490,879	$511,348
Total	$5,990,564	$6,251,231	$6,511,899
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	$4,311,259	$4,498,855	$4,686,451
% increase	257%	257%	257%

GB/LU 7 would lead to a 257% increase in triptan expenditure.

Table 29: GB/LU 8- GB/LU 2 with 18 per month quantity limit

ALBERTA	Year 2013	2014	2015
TRIPTAN			
Sumatriptan	$3,215,326	$3,355,235	$3,495,143
Naratriptan	$353,157	$368,524	$383,891
Rizatriptan	$1,719,968	$1,794,809	$1,869,650
Zolmitriptan	$99,467	$103,795	$108,123
Almotriptan	$470,410	$490,879	$511,348
Total	$5,858,328	$6,113,241	$6,368,155
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	$4,179,023	$4,360,865	$4,542,707
% increase	249%	249%	249%

GB/LU 8 would lead to a 249% increase in triptan expenditure.

Summary of Findings for Tables 11-29

- Without any change in reimbursement for triptans, it is expected that expenditure on triptans will rise over the next three years.
- All EAP strategies (without GB/LU) would lead to a reduction in total cost ranging from 16%-84%.
- All GB/LU strategies based on Alberta usage would lead to an increase in total costs ranging from 134%-302%.
- Requiring that under EAP generic triptans should be 25% of brand cost is forecasted to reduce expenditure on triptans by 16% (a reduction of $0.30 million in 2015).
- Combining reduced generic costs with the requirement of replacement of brand name agents with their generic formulation, when available, of branded products will reduce expenditure by 69% (a reduction of $1.25 million in 2015).
- Based on current prescribing in Alberta where triptans are available similar to general benefit, coverage of triptans through general benefit is forecasted to lead to an increase in the expenditure of triptans in Ontario by 302% (an increase of $5.52 million in 2015). Restricting coverage under GB/LU to only generic products will lead to an increase of 293% (an increase of $5.35 million in 2015).
- Imposition of quantity limits when triptans are available through EAP will lead to small absolute decreases in total triptan expenditures. For example, for strategy EAP2 the incremental reduction in triptan expenditure through imposing a quantity limit of 6 per month compared to no quantity limits would be approximately $285 thousand (a reduction of $1.54 million compared to a reduction of $1.25 million).
- However, for strategies involving access to triptans through GB/LU based on Alberta usage, the impact of quantity limits is much greater. For strategy GB/LU2, the incremental reduction in triptan expenditure through imposing a quantity limit of 6 per month compared (strategy GB/LU4) to no quantity limits (strategy GB/LU2) would be approximately $2.90 million. For strategy GB/LU2, the incremental reduction in triptan expenditure through imposing a quantity limit of 12 per month (strategy GB/LU6)compared to no quantity limits would be approximately $1.44 million. However, overall expenditure on triptans would still be significantly greater than if they remained on EAP (an increase of $2.45 million under GB/LU4, $3.90 million under GB/LU6 and $5.35 million under GB/LU2).

Table 30: GB/LU 1- All triptans GB/LU with GB/LU based on Manitoba usage

MANITOBA	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$2,832,021	$2,955,251	$3,078,481
Naratriptan	$274,692	$286,645	$298,598
Rizatriptan	$1,370,221	$1,429,843	$1,489,466
Zolmitriptan	$137,506	$143,490	$149,473
Almotriptan	$379,876	$396,405	$412,935
Total	$4,994,316	$5,211,634	$5,428,952
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	$3,315,011	$3,459,257	$3,603,504
% increase	197%	197%	197%

GB/LU 1 would lead to a 197% increase in triptan expenditure.

Table 31: GB/LU 2- Only generic triptans GB/LU with GB/LU based on Manitoba usage

MANITOBA	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$2,735,774	$2,854,816	$2,973,858
Naratriptan	$274,692	$286,645	$298,598
Rizatriptan	$1,370,221	$1,429,843	$1,489,466
Zolmitriptan	$115,338	$120,356	$125,375
Almotriptan	$379,876	$396,405	$412,935
Total	$4,875,901	$5,088,066	$5,300,231
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	$3,196,596	$3,335,689	$3,474,783
% increase	190%	190%	190%

GB/LU 2 would lead to a 190% increase in triptan expenditure.

Table 32: GB/LU 3- GB/LU 1 with 6 per month quantity limit

MANITOBA	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$2,154,479	$2,248,227	$2,341,975
Naratriptan	$224,620	$234,394	$244,168
Rizatriptan	$1,104,834	$1,152,909	$1,200,984
Zolmitriptan	$90,378	$94,311	$98,244
Almotriptan	$308,862	$322,302	$335,741
Total	$3,883,174	$4,052,143	$4,221,112
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	$2,203,869	$2,299,767	$2,395,664
% increase	131%	131%	131%

GB/LU 3 would lead to a 131% increase in triptan expenditure.

Table 33: GB/LU 4- GB/LU 2 with 6 per month quantity limit

MANITOBA	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$2,081,259	$2,171,821	$2,262,383
Naratriptan	$224,620	$234,394	$244,168
Rizatriptan	$1,104,834	$1,152,909	$1,200,984
Zolmitriptan	$75,808	$79,106	$82,405
Almotriptan	$308,862	$322,302	$335,741
Total	$3,795,383	$3,960,532	$4,125,681
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	$2,116,078	$2,208,155	$2,300,232
% increase	126%	126%	126%

GB/LU 4 would lead to a 126% increase in triptan expenditure.

Table 34: GB/LU 5- GB/LU 1 with 12 per month quantity limit

MANITOBA	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$2,646,315	$2,761,464	$2,876,614
Naratriptan	$264,331	$275,833	$287,334
Rizatriptan	$1,308,524	$1,365,462	$1,422,400
Zolmitriptan	$118,859	$124,031	$129,203
Almotriptan	$362,199	$377,959	$393,720
Total	$4,700,228	$4,904,750	$5,109,271
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	$3,020,923	$3,152,373	$3,283,823
% increase	180%	180%	180%

GB/LU 5 would lead to a 180% increase in triptan expenditure.

Table 35: GB/LU 6- GB/LU 2 with 12 per month quantity limit

MANITOBA	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$2,556,380	$2,667,616	$2,778,852
Naratriptan	$264,331	$275,833	$287,334
Rizatriptan	$1,308,524	$1,365,462	$1,422,400
Zolmitriptan	$99,697	$104,035	$108,373
Almotriptan	$362,199	$377,959	$393,720
Total	$4,591,130	$4,790,905	$4,990,679
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	$2,911,826	$3,038,528	$3,165,230
% increase	173%	173%	173%

GB/LU 6 would lead to a 173% increase in triptan expenditure.

Table 36: GB/LU 7- GB/LU 1 with 18 per month quantity limit

MANITOBA	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$2,744,148	$2,863,554	$2,982,961
Naratriptan	$271,466	$283,278	$295,090
Rizatriptan	$1,346,848	$1,405,454	$1,464,059
Zolmitriptan	$125,722	$131,193	$136,663
Almotriptan	$372,273	$388,472	$404,670
Total	$4,860,457	$5,071,950	$5,283,444
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	$3,181,152	$3,319,574	$3,457,995
% increase	189%	189%	189%

GB/LU 7 would lead to a189% increase in triptan expenditure.

Table 37: GB/LU 8- GB/LU 2 with 18 per month quantity limit

MANITOBA	Year		
	2013	2014	2015
TRIPTAN			
Sumatriptan	$2,650,888	$2,766,236	$2,881,584
Naratriptan	$271,466	$283,278	$295,090
Rizatriptan	$1,346,848	$1,405,454	$1,464,059
Zolmitriptan	$105,453	$110,042	$114,631
Almotriptan	$372,273	$388,472	$404,670
Total	$4,746,928	$4,953,481	$5,160,034
Base Total	$1,679,305	$1,752,377	$1,825,448
Budget Impact			
$	$3,067,623	$3,201,105	$3,334,586
% increase	183%	183%	183%

GB/LU 8 would lead to a 183% increase in triptan expenditure.

Summary of Findings for Tables 30-37

- All GB/LU strategies based on Manitoba usage would lead to an increase in total costs ranging from 126%-197%.
- Based on current prescribing in Manitoba where triptans are available with a passive quantity limit of 12, coverage of triptans through general benefit is forecasted to lead to an increase in the expenditure of triptans in Ontario by 197% (an increase of $3.60 million in 2015). Restricting coverage under GB/LU to only generic products will lead to an increase of 190% (an increase of $3.47 million in 2015).
- For strategies involving access to triptans through GB/LU based on Manitoba usage, the impact of quantity limits is much greater. For strategy GB/LU2, the incremental reduction in triptan expenditure through imposing a quantity limit of 6 per month compared (strategy GB/LU4) to no quantity limits (strategy GB/LU2) would be approximately $1.17 million. For strategy GB/LU2, the incremental reduction in triptan expenditure through imposing a quantity limit of 12 per month (strategy GB/LU6) compared to no quantity limits (strategy GB/LU2) would be approximately $0.31 million. However, overall expenditure on triptans would still be significantly greater than if they remained on EAP (an increase of $2.30 million under GB/LU4, $3.17 million under GB/LU6 and $3.47 million under GB/LU2).

Appendix B3: Worked Example of Budget Impact under General Benefit/Limited Use

The following table present the methods adopted to estimate the budget in 2015 based on Alberta data should triptans be listed under GB/LU – scenario GB/LU1.

Table 38: Forecasted Budget in 2015 under Scenario GB/LU1

	Methods	Results
Estimate of total triptan expenditure in 2015 if no change in listing		$1,825,448
Estimate if same usage but generic pricing and replacement of brand name agents with their generic formulation, when available (EAP 2)		$574,150
Triptan use per beneficiary in Ontario (2012)		
Triptan use per beneficiary in Alberta (2012)	245,213/503,192	0.487
Relative triptan use per beneficiary Alberta: Ontario	0.487/0.037	13.11
Forecasted cost of managing EAP under triptans		$13,821
Estimated triptans cost under GB/LU1	(574,150-13,821)*13.11	$7,344,689
Forecasted Increase in Budget Expenditure	(7,344,689-1,825,448)/1,825,448	302%

GB/LU 1 would lead to a 302% increase in triptan expenditure.

The following table present the methods adopted to estimate the budget in 2015 based on Alberta data should triptans be listed under GB/LU with a quantity limit of 12 per month per user GB/LU5.

Table 39: Forecasted Budget in 2015 under Scenario GB/LU1

	Methods	Results
Estimated triptans cost under GB/LU1		$7,768,015
Proportion of triptan use over the 12 per month limit in Ontario		
All triptans	29,990/109,235	0.27
Almotriptan	2236/10036	0.22
Naratriptan	1188/6578	0.18
Rizatriptan	7094/32906	0.22
Sumatriptan	17686/56332	0.31
Zolmitriptan	1344/2070	0.65
Proportion of triptan use over the 12 per month limit in Alberta	48,349/245,213	0.20
Ratio of triptan over use with 12 per month limit: Alberta: Ontario	0.20/0.27	0.72
Forecasted triptan use over the 12 month limit if GB/LU based on Alberta data		
Almotriptan	0.22*0.72	0.16
Naratriptan	0.18*0.72	0.13
Rizatriptan	0.22*0.72	0.16
Sumatriptan	0.31*0.72	0.23
Zolmitriptan	0.65*0.72	0.47
Forecasted cost under GB/LU5 by triptan		
Almotriptan	558,649*(1-0.16)	$469,014
Naratriptan	403,965*(1-0.13)	$351,425
Rizatriptan	2,015,060*(1-0.16)	$1,702,214
Sumatriptan	4,164,797*(1-0.23)	$3,223,137
Zolmitriptan	202,218*(1-0.47)	$107,665
Estimated triptans cost under GB/LU5		$5,853,456
Forecasted Increase in Budget Expenditure	(5,853,456-1,825,448)/1,825,448	221%

GB/LU 5 would lead to a 221% increase in triptan expenditure.