

Treatment for Overactive Bladder

Stakeholder Review

March 2016

GENERAL

Comment: ODPN should consider more prominently identifying one of the key limitations in their assessment and recommendations; namely, the potential impact of pre-existing product listing agreements on the ICERs and, therefore, the relative ranking of products in the options presented.

Response: *Thank you for your response. If the manufacturer wishes to allow us to make any pre-existing product listing agreements available publicly, we would happily revise our analyses to include these.*

Comment: I am surprised that Myrbetriq is not considered first line treatment of overactive bladder. In my practice, many patients who are elderly, I see a lot of issues with confusion and worsening dementia in patients on antimuscarinic meds. Oxybutynin is the worst of the class. Oxybutynin should not need to be tried prior to writing a script for a different antimuscarinic (e.g., solifenacin) or beta 3 agonist (i.e. Myrbetriq). Personally I use a lot of Myrbetriq in my practice with great success and minimal side effects. If the patient feels they still need better symptom control then I offer an antimuscarinic (usually solifenacin) in addition to Myrbetriq but tell them that they may have dry mouth, constipation and dry eyes (common antimuscarinic side effects) as a trade-off.

Response: *In our systematic review, there was no evidence that mirabegron was more efficacious than anticholinergics. Mirabegron (a beta3-adrenoceptor agonist) is better tolerated than most anticholinergics, especially for dry mouth. However, beta3-adrenoceptors are located in other tissues such as heart and brain, and the long-term effects of mirabegron on cardiovascular function and cognition are not yet known. Therefore, based on the available evidence, mirabegron is not considered a first-line agent in most patients. Note that the therapeutic note that is associated with anticholinergics on the ODB formulary states that anticholinergics should be used with caution in certain populations (e.g., frail elderly); other options to consider for these patients may be mirabegron.*

Comment: I have extreme concerns with respect to the possible limitations that have been suggested in the new policy drafted for OAB prescriptions. Firstly, as a Canadian physician I have been trained to always prescribe the best agent for each patient. There are important nuances between the OAB medications currently available, most importantly their effects on cognition. Only two agents have even been tested in elderly subjects (the largest demographic being prescribed these agents.) It is not safe nor good practice to extrapolate data from one agent to another and assume the same outcome or safety. It would appear to be highly nondemocratic to force a physician to prescribe a medication they are not even comfortable with. Where is the evidence-based medicine for safety in elderly from which these proposals came from? Secondly, there is only one B agonist and there are many patients with underlying conditions in which they are best served by this class which has no generic equivalent.

This agent has now been available for three years in this country and I believe withdrawing access to it is utterly unacceptable.

Response: *Thank you for your comment. In response to the feedback from the various stakeholders including clinicians and reviewing the evidence, our final recommendation to OPDP is to list oxybutynin IR, solifenacin, tolterodine as general benefit with other agents on Limited Use. The criteria for Limited Use include use of oxybutynin IR, solifenacin OR tolterodine (only one needs to be tried) before moving on to the drugs listed as Limited Use.*

Comment: I have been working in LTC for 25 years as an ‘attending physician’ as well as a Medical Director in Ontario. Trying to lessen the ‘anticholinergic burden’ in geriatrics is an ‘ongoing issue’. Although there are no studies to show that an anti-muscarinic agent on its own causes cognitive decline, in theory, it is indeed a ‘real risk’. Add other drugs that the resident may be on (e.g., digoxin, nortriptyline, furosemide and warfarin), this translates into a score of 6 on the anticholinergic cognitive burden scale; adding oxybutynin or solifenacin increases this score to 9. I have stopped anti-muscarinic OAB agents on new admissions to long-term care facilities many times in the past and have seen their cognition improve significantly (as judged by the MMSE score). To emphasize this observational finding, I believe some jurisdictions will not even cover the cost of a ChEI, if the patient is on an ‘anti-cholinergic agent’. Even the *current* ODB LU criteria mentions that: “Antimuscarinic agents should be used with caution in the elderly due to potentially serious adverse effects (e.g. confusion, psychosis, acute urinary retention, constipation). Antimuscarinic agents should be avoided in older adults with pre-existing cognitive impairment (e.g. dementia) and those who are already using other drugs with significant anticholinergic effects (e.g. tricyclic antidepressants) in order to avoid a high overall anticholinergic drug burden”. Most confusing (and unclear) when reviewing all the current ODB ‘limited use criteria’. So, if one is considering prescribing an OAB medication in a LTCF resident where quality of life and dignity is still an issue and would be felt to be of benefit for that resident, may I suggest another option (or ‘add-on’): Give mirabegron an additional ‘Limited Use code’ for use in patients with ‘MCI’ or mild/moderate dementia.

Response:

Thank you for your comments. We agree that the anticholinergic effects of these medications are of particular concern in the elderly and have noted this in our report. As well, we have recommended that a Therapeutic Note be added to each of the anticholinergics listed on the ODB formulary, as some agents (e.g., oxybutynin immediate release) currently do not have this note included. As well, we have recommended that the note that is currently part of the Limited Use criteria for LU code 290 be removed.

Comment: There is no available clinical outcome evidence to support the enforced step-wise use of successive anticholinergic (ACH) medications after failure of a first-line ACH drug. The lack of clinical evidence supporting enforced sequential use of two ACH drugs means that the cost- effectiveness rationale

currently underpinning most of the reimbursement options proposed by the ODP RN is not grounded in the available evidence, thus creating a fundamental challenge to their validity.

Response: *Thank you for your comment. In response to the feedback from the various stakeholders including clinicians and reviewing the evidence, our final recommendation to OPDP is to list oxybutynin IR, solifenacin, tolterodine as general benefit with other agents on Limited Use. The criteria for Limited Use include use of oxybutynin IR, solifenacin OR tolterodine (only one needs to be tried) before moving on to the drugs listed as Limited Use.*

Comment: a. The ODP RN's Qualitative Research Report speaks clearly to the need for flexibility in determining which treatment will best meet individual patient needs. Insights from patients and their prescribers should be reflected more prominently in the reimbursement options.

b. We were disappointed to see that the opinions of both consumers and specialist clinicians were largely ignored in favour of purely cost of drug considerations in the suggested recommendations for oxybutynin use; why was this considered to be of over-riding importance?

Response: *A number of factors are taken into consideration in the development of potential reimbursement options, including efficacy and safety data, patient and prescriber insights, real-world utilization and cost-effectiveness. In addition, there are clinician and patient representatives who are members of our research team, and provide valuable input throughout the review process.*

Comment: The proposed recommendations do not address the particular needs of the elderly population (i.e., a significant proportion of beneficiaries covered by OPDP), and contain no provisions in cases where patients may have unacceptable adverse events with one anti-muscarinic drug, or who have contraindications for the use of ACH drugs.

Response: *The note that is currently embedded in the LU clinical criteria states: "Antimuscarinic agents should be used with caution in the elderly due to potentially serious adverse effects (e.g. confusion, psychosis, acute urinary retention, constipation). Antimuscarinic agents should be avoided in older adults with pre-existing cognitive impairment (e.g. dementia) and those who are already using other drugs with significant anticholinergic effects (e.g. tricyclic antidepressants) in order to avoid a high overall anticholinergic drug burden". This provides rationale for prescribers who wish to avoid the use of antimuscarinic agents in the elderly. Our final recommendations recommend that this note be added to all antimuscarinic agents (e.g., oxybutynin IR) that are listed as General Benefit as well as those that are available as LU.*

Comment: The draft recommendations are not consistent with the Beers Criteria, which specifically do not recommend the use of drugs with strong ACH properties (e.g. darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine and trospium) because of the risk of impaired cognitive and physical function, and the risk of dementia. This concern is not addressed by reimbursement options that force the sequential use of two ACH agents.

Response: *We made a recommendation that the note that is currently embedded in the LU clinical criteria be added to all antimuscarinic agents, including those that are listed as General Benefit (e.g., oxybutynin IR) and those available as Limited Use. i.e., “Antimuscarinic agents should be used with caution in the elderly due to potentially serious adverse effects (e.g. confusion, psychosis, acute urinary retention, constipation). Antimuscarinic agents should be avoided in older adults with pre-existing cognitive impairment (e.g. dementia) and those who are already using other drugs with significant anticholinergic effects (e.g. tricyclic antidepressants) in order to avoid a high overall anticholinergic drug burden”. This provides rationale for prescribers who wish to avoid the use of antimuscarinic agents in the elderly.*

Comment: Two alternative reimbursement options are suggested based on a number of factors including efficacy/safety data, patient and prescriber insights and observational and real-world data.

Option 1:

- Generic OAB medications (i.e., oxybutynin, solifenacin, tolterodine) listed as General Benefit (GB). All other OAB drugs listed as Limited Use (LU).
- Use one of the GB OAB medications as first line treatment; use LU OAB drugs if there is a documented contraindication, failure to respond, or intolerance to one first line OAB medication.

Option 2:

- Oxybutynin IR OR solifenacin as General Benefit, all other OAB medications Limited Use.
- Use oxybutynin IR OR solifenacin as first line treatment; use LU OAB drugs if there is a documented contraindication, failure to respond, or intolerance to one first line OAB medication.

Response: *Thank you for your suggestions. These alternative options were considered by our Citizen’s Panel and included in our final report.*

Comment: Why is there no consideration of expert clinician clinical judgement in the recommendations; the influence of comorbidities and other patient related factors which might favour the use of one drug over another are not considered. These are not expensive medications with potentially major benefits for sufferers of the condition; the effort going into rationing of these drugs seems disproportionate.

Response: *There are clinician and patient representatives on the research team, and they provide input throughout the review process. A recommendation has been made in the final report suggesting that all antimuscarinic agents should include the therapeutic note cautioning of their use in the elderly. Finally, cost was not the only factor that was considered in the development of the recommendations; other factors such as efficacy and safety, patient and prescriber preferences and real-world utilization data were also included.*

Comment: All Limited Use (LU) codes control for some component of prescribing, whether it be clinical implications, cost etc. If the issue is cost, then perhaps all generics should be available as general benefit and brand name products should be available under LU. This would provide patients/physicians with choice (although it is difficult to determine how much of prescribing is patient choice versus physician prescribing habits). If there are 3 or 4 generic agents where research findings have demonstrated that they are all clinically effective, shouldn't patients at least try several of these agents prior to being prescribed brand named agents?

Response: *If patients exhibit some type of serious adverse event in response to a generic anticholinergic, then physicians may be more inclined to prescribe them a brand name agent with a different mechanism of action, for example mirabegron. The therapeutic notes related to anticholinergics for the treatment of OAB addresses the clinical implications of potential adverse events in the elderly patient populations. It is important to note that the ODPRN is not recommending the removal of the therapeutic notes; therefore potential clinical adverse events as well as underlying medical conditions (e.g., frail elderly) should still be addressed before prescribing anticholinergic medications. Currently, there is no strong evidence to suggest that patients should not try another agent if they previously failed on one.*

Comment: How does the ODPRN envision the LU code being implemented in Ontario?

Response: *A step therapy approach where the pharmacy system has the ability to review past prescriptions has been implemented in other jurisdictions. The ODPRN is*

beginning to identify these various options for the MOHLTC in order to potentially recommend existing strategies that have been effective in other jurisdictions.

Comment: Patents for certain drugs, such as darifenacin, will be expiring in the coming years. How will this be addressed by the ODPRN?

Response: *The ODPRN will recommend a review of recommendations/reimbursement options on an ongoing basis in order to remain abreast of any developments including availability of generics and new products.*

Comment: Do members of the Citizen's Panel review a copy of the report that includes changes from the stakeholder review after feedback and changes have been incorporated?

Response: *Members of the Citizen's Panel are provided with copies of the draft report and recommendations as well as a lay summary of findings. They were provided with updated reports.*

Comment: The evidence demonstrates that many patients are only trying 1 agent. It is important to consider why these patients are not trying a second agent. Possible reasons could be the side effects associated with the medications, stigma etc. It would be interesting to determine how many general practitioners (GP) are starting therapy versus refilling prescriptions from a specialist (urologist). It was felt that many GPs may not be aware of the various options and side effects and therefore may be more reluctant to initiate therapy.

Response: *Thank you for your comments. At this point, we are unable to provide additional analyses.*

Comment: We see a great need for improved GP incontinence education and awareness of available incontinence medications, (it was highlighted that they over prescribe oxybutynin, likely due to not being aware of newer drugs available), this is a common theme internationally. They also are not well trained on incontinence and the pathways to diagnosis and treatment.

Response: *Thank you for your comment. We agree that education of general practitioners is important. However, the focus of our review was formulary modernization for the Ontario Public Drug Programs. As such, we did not review use of non-pharmacologic therapies, nor did we review diagnosis of the condition. Therefore, no additional recommendation on GP incontinence education was made in our report.*

Comment: When it comes to the, “and/or”, option on approved drugs, we recommend the “Or”, option, meaning a choice between oxybutynin, Vesicare or Detrol before trying a LU drug. Rather than having to try them all first. In addition I would prefer to see oxybutynin taken off the list.

Response: *Thank you for your comment. Our final recommendation is based on efficacy and safety data, patient and prescriber preference, real-world utilization, cost-effectiveness, and stakeholder comments.*

Comment: We would like to reiterate the importance of considering the evidence specific to the population aged over 65 years old before issuing any recommendation to the Ministry. We believe that the final recommendations should give a much greater weight to the output of the subgroup analyses evaluating the efficacy and safety of OAB drugs in the population aged in the following age groups (≥ 65 , 65 to 75, ≥ 75) than anything else.

Response: *We are currently completing the subgroup analyses and these findings are still being reviewed internally by the research team prior to being summarized in the online reports. Based on preliminary results of a meta-analysis for micturitions in a very limited data set, those aged 65 to 75 and those over 75 experienced significantly fewer micturitions (based on a mean difference) than with placebo. No studies reported incontinence episodes in these age subgroups, and data for safety is still under internal review following analyses.*

Comment: In the context of geriatric medicine, the stakeholder believes that fesoterodine is the only antimuscarinic agent proven safe and effective to manage the symptoms of OAB. This is based on pharmacological characteristics as well as clinical evidence in the population aged 65 years and older.

Response: *The three studies cited by the stakeholder were considered for inclusion in the systematic review: two were included in the network meta-analysis (Wagg et al JAGS 2013;61:185-93; DuBeau CE et al. J Urol 2014;191:395-404) and one was excluded (Wagg et al. Neurourol Urodyn 2014;33:106-114.). The systematic review team is completing the subgroup analysis (using a very limited data set) for those aged 65 to 75 and those over 75; preliminary results indicate that for micturitions, this group of patients experienced significantly fewer micturitions than with placebo. However, no studies reported incontinence episodes in these age subgroups.*

Environmental Scan

Comment: The International Continence Society and International Urology Association have guidelines that address the treatment of OAB. The ODPRN should consider reviewing these guidelines.

Response: *Thank you for your comment. We are unable to identify current guidelines produced by either the International Continence Society or the International Urology Association.*

Comment: For example, the different mechanisms of action (MOAs) for the various medications in this drug class are not fully articulated in any of the reports. As you are aware, these MOAs are linked to the differing side effect profiles of the various agents. In particular, both the ODPRN OAB Report and the OPDP's reimbursement policy for LU OAB medications make note of several cautions relating to the use of antimuscarinic agents. Why are these differences in MOA and policy-based cautions not reflected in the reimbursement options proposed?

Response: *A section has been added to the Environmental Scan report describing the pharmacology of anticholinergics and mirabegron. In addition, a recommendation has been made to add a therapeutic note outlining the potential safety concerns of the antimuscarinic agents to all antimuscarinic agents including those that are listed as General Benefit as well as those that are available as LU.*

Comment: The International Consultation on Incontinence represents an authoritative set of recommendations spanning all aspects of management of frail older persons with urinary incontinence. The updated the recommendations have been published in 2015.

Response: *The summary information on use of pharmacotherapy in the frail elderly has been included in the Environmental Scan report.*

Comment: The results of a systematic literature review and international consensus validation process (LUTS-FORTA 2014) for the appropriateness of oral

drugs for long-term treatment of lower urinary tract symptoms in older persons have also been published recently.

Response: *Thank you for your comment. The Environmental Scan team reviewed and only summarized guidelines (not systematic reviews) related to the management of OAB.*

Qualitative Team

Comment: Generally, findings from the qualitative analysis of patients reflect the perspectives of what is seen through the Canadian Continence Foundation. However, it was felt that although the qualitative analyses included patient perspectives of conservative measures, patients through the Foundation feel that these treatment options are not effective and OAB symptoms can only be treated with medications.

Response: *Thank you for your comment. It is acknowledged that many patients require pharmacotherapy in addition to non-pharmacological treatment options.*

Comment: In the qualitative analysis, the term ‘popular’ is used to describe certain agents. The ODPRN should consider that patients should be given a choice as to which agent they are prescribed.

Response: *The term ‘popular’ has been removed to avoid any misunderstanding regarding patient choice. We have replaced it with “commonly used”.*

Systematic Review Team

Comment: In clinical practice, patients need to try more than one therapy or multiple therapies in order to determine which agent is most effective for them. How has this been integrated into the systematic review?

Response: *Thank you for your comment and question. The systematic review addressed the issue of trying sequential or multiple therapeutic options in a couple of different ways. We aimed to compare the efficacy and safety of the available therapeutic agents in subpopulations of patients with OAB who were either treatment-experienced or treatment-naïve; however, most of the included studies randomized a mixed group of both treatment-experienced and -naïve patients. There are a limited number of studies that allow us to explore efficacy and safety in solely treatment-experienced and treatment-naïve patient groups through subgroup analyses and, data permitting, these analyses are currently underway.*

We also studied the efficacy and safety of multiple therapies, namely the combination of mirabegron with an anticholinergic agent. We are currently vetting results internally with our clinician experts and results will be added to the online report when they become available (www.odprn.ca)

Comment: Would it be possible to circulate the results for the odds ratios?

Response: *The aim of this report is to present a high-level summary of results from the systematic review. Detailed results, including odds ratios, will be presented in comprehensive technical report available on the ODPRN website (www.odprn.ca) and/or through peer-reviewed publication(s) in approximately 6 months. For transparency, all data that contributed to the pharmacoeconomic modelling for this drug class review are provided in the appendices of the OAB report produced by the ODPRN Pharmacoeconomics Unit.*

Comment: Was there any data available on the oxybutynin gel formulations?

Response: *Of the included studies, one involved comparison with oxybutynin gel (Staskin 2009); however, not all outcomes of interest were reported. No data were available for oxybutynin gel for quality of life, urgency, or withdrawals due to lack of response.*

Comment: Without seeing the actual model and details of the Network Meta-Analysis (NMA), it has proven difficult to provide useful comments. While we understand that a NMA was conducted to evaluate the efficacy and safety outcomes, the methodologies behind the analyses are not clearly outlined in the draft reports. More specifically, the synthesis lacks relevant information on the relative effect between drug therapies including odds ratios, confidence intervals, mean differences, probability of being the best treatment out of all compared, etc. In addition, the SR also fails to distinguish between various strengths of the OAB drugs making it more difficult to interpret the results.

Response: *Thank you for your comments. The aim of the draft report is to provide a high-level overview of the systematic review and associated Bayesian network meta-analyses (NMA). While we aim to be transparent and comprehensive in all of our conduct and reporting, it is difficult to produce a complete scientific record within the abbreviated time line of the ODPRN Drug Class Reviews. As per the ODPRN Drug Class Review process, complete results will be available in a complete technical report on the ODPRN website within approximately 6 months (www.odprn.ca), or will be made available in a peer-reviewed publication.*

In addition, certain data (mean differences and standard deviations, odds ratios and associated credible or confidence intervals) are censored from the initial draft report so as not to preclude peer-reviewed publication by our team. We believe we have adequately described the methodology used for the Bayesian NMA in the report, but may have inadvertently neglected to report that the results discussed in the report reflect results from the random effects model. For transparency, all data contributing to the pharmacoeconomics models has been provided in the appendices of the OAB report produced by the ODPRN Pharmacoeconomics Unit.

The decision to group all strengths of the OAB agents into a single node for the base case analysis was made in consultation with the ODPRN research team and the clinical experts who advise our Drug Class Review process. Due to the accelerated time line of the ODPRN Drug Class Reviews, we were unable to conduct sensitivity analyses based on dosing or strength.

There are varying opinions on the utility of the probability rankings from the Bayesian NMA. These statistics are available and can be added to the final report following a consultation with the ODPRN OAB research team.

Comment: The NMA was conducted as an indirect/mixed treatment comparison and the majority of studies (63%) included were placebo-controlled trials and not head-to-head comparative studies. Therefore, it is misleading to suggest superiority of a drug in statements like *“When compared head-to-head, extended-release oxybutynin was superior to transdermal oxybutynin, tolterodine, extended-release tolterodine and mirabegron.”* The lack of details in the synthesis of the results makes it difficult to determine the credibility of how “head-to-head” comparisons were made and how certain drugs were ascertained to be superior to others. For instance, the NMA claims solifenacin and fesoterodine to be superior to mirabegron for the outcome of quality of life (QoL). The analysis also suggests that tolterodine ER significantly improves QoL compared to solifenacin and fesoterodine. It is unclear as to how these conclusions were reached, considering the evidence from the publications by Pavesi (2013) and Khullar (2015).²³ In addition, it is not clear how ODPRN addressed the potential heterogeneity of studies included in the SR.

Response: *Thank you for your comment. The aim of the draft report is to provide a high-level overview of the systematic review and associated Bayesian network meta-analyses (NMA). While we aim to be transparent and comprehensive in all of our conduct and reporting, it is not possible to produce comprehensive scientific reports within the abbreviated time line of the ODPRN Drug Class Reviews. A more detailed narrative and/or graphical description of the studies contributing to the network meta-analyses will be provided in the full scientific report and/or peer-reviewed publication. It is important to note that although many of the included studies are placebo-controlled, a large number of these studies employ multiple treatment arms with placebo control. Along with placebo, these studies generally report an OAB agent compared to one or more alternative OAB agents. Based on our experience with multiple treatment comparisons, the OAB agents offer a proportionately higher than average number of studies reporting direct head-to-head evidence across agents, which enhances the strength of the Bayesian network meta-analyses.*

The language used to describe ‘head-to-head comparisons’ in the systematic review report

references the comparative results from the indirect treatment comparisons. Following a review of the presented results, we agree that this language may be ambiguous, and will amend the text in the final report to better reflect the consideration of both direct and indirect evidence in our analyses. Detailed data will be included in the subsequent full scientific report and/or peer-reviewed publication in approximately 6 months.

The Pavesi 2013 report mentioned in the stakeholder comment was included in our review as a post-hoc analysis of three individual randomized controlled trials. Data for the quality of life outcome were extracted individually from the primary reports of each trial (Herschorn 2013, Khullar 2013, Nitti 2013). Our comparative results for quality of life are consistent with the results of the individual studies. In our analysis, both mirabegron and tolterodine ER significantly improved quality of life compared to placebo.

The Khullar 2015 report mentioned in the stakeholder comment was not included in this systematic review because the publication date (August 19, 2015) was later than the date of our primary literature search (August 15, 2015). Khullar 2015 provides the quality of life data from the SCORPIO trial; the primary record for the SCORPIO trial was included in our systematic review (Khullar 2013). The health-related quality of life data from this trial were provided in the [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/results/NCT00689104?sect=Xn0156#outcome17) record for this study, and were included in our analysis (Last updated Jun 5, 2015 - See NCT00689104, Secondary outcome 17 in the Study Results tab: <https://clinicaltrials.gov/ct2/show/results/NCT00689104?sect=Xn0156#outcome17>).

Clinical and statistical heterogeneity were explored in sensitivity analyses and will be presented in the full scientific report and/or peer-reviewed publication along with details on the evaluation of inconsistency and the overall robustness of the results. At the individual study level, population characteristics were extracted and assessed to explore the comparability of the intervention arms.

Comment: The SR included 55 (63%) placebo controlled studies (\pm active control) and 23 (26%) active-control studies. We assume that randomization does not hold across all of the included studies. Therefore, there may be a risk of confounding bias that can compromise the internal validity of the SR. It is worth mentioning that CADTH does not consider active control studies as direct evidence of head-to-head comparisons. Thus, it is not clear why ODPRN would have a different interpretation of the results generated by a NMA.

Response: Thank you for your comment. As per the previous comment, although many of the included studies are placebo-controlled, a large number of these studies employ multiple treatment arms with placebo control. Along with placebo, these studies generally report an OAB agent compared to one or more alternative OAB agents. Based on our experience with multiple treatment comparisons, the OAB agents offer a proportionately higher than average number of studies reporting direct head-to-head evidence across agents, which enhances the strength of the Bayesian network meta-analyses.

We acknowledge that randomization is not preserved when conducting network meta-analyses (NMA). Our methods for Bayesian NMA aim to produce valid, unbiased

estimates of effect based on the most robust statistical techniques available. The underlying assumptions dictate that the individual studies of different treatments are not subject to the influence of effect modification across studies or between comparisons. We check these assumptions by carefully evaluating heterogeneity, similarity and consistency. The robustness of the findings are additionally explored through sensitivity and subgroup analyses. Results of these analyses will be fully reported in the peer-reviewed publication and/or full scientific report.

HTA agencies appear to be evolving in their views of indirect evidence. To our knowledge, CADTH considers both indirect and direct evidence in their Therapeutic Review and Optimal Use HTA products. It would be inappropriate for us to comment on CADTH use or valuation of evidence without a reference to support this. There is an information gain resulting from the use of Bayesian network meta-analysis to compare evidence for all available treatment options in a statistical network. Interpretation of results should be based on valid methodology, transparent reporting, and a solid understanding of the evidence base, clinical area, and limitations of the methodologies employed. ODPRN considers all of these facets from a systematic review perspective in context with the other research unit reports.

Comment: While the Environmental Scan report does review some of the evidence available, the absence of cognitive impairment as a safety parameter within the SR, appears to be a significant gap within this report.

Response: Thank you for your comment. Potential outcomes for inclusion in the systematic review were discussed a priori in consultation with the ODPRN research team and clinical experts who inform our processes. The selected outcomes were prioritized by the research team and detailed in the comprehensive research plan. While we agree that an evaluation of cognitive outcomes would be value-added, the accelerated time line of the ODPRN Drug Class Review precludes the assessment of all relevant outcomes of interest.

Pharmacoepidemiology Unit

Comment: To provide clarity and help put things into perspective for readers, ODPRN may want to consider including a description of the changes in the state of the market during the time period of analysis given the significant changes in terms of availability of new innovative as well as generic products. This would help put into context some of the results in the analysis (e.g., the primary focus on anticholinergic products, the limited data available for mirabegron, Botox).

Response: Thank you for this feedback. We recognize the dynamic changes in the utilization of OAB agents over the past 10 years. Many of the analysis in our report explore the changing trends in use and this is a major finding of our report that is

highlighted throughout. We have added discussion of when products were introduced to the formulary.

Comment: While a good overview of data sources is provided on pages 8-9, there are no direct/specific sources attributed in the exhibits and tables in the report. In the absence of references to where the data have come from for the results presented in the document, it is difficult to understand which data sources are being sourced and, thus, provide thoughtful comment.

Response: *We thank the stakeholder for this feedback. We have now added notes to all figures citing the specific data source.*

Comment: ODPN has made comments related to utilization trends based on highly limited data for new products. In particular, comments were made regarding mirabegron utilization that are important to put into context. The embargoed graphic presented at the Stakeholder Session clearly demonstrated that there is significant early uptake for all new agents when they come to market, a clear reflection of the unmet need of patients who have typically tried several OAB treatment options (as per the data submitted and presented at the session). While the ODPN flagged the mirabegron uptake curve, it should also be noted that this curve is very similar – but of a lower magnitude - to those products that came before it (i.e., parallel to but lower magnitude to solifenacin). In the case of these other products, there was a significant levelling-off of the curve once the initial unmet need was addressed and there is no objective evidence to suggest that the same will not also be true for mirabegron in the near future. In fact, data on file (Astellas, February 2016) demonstrates that this levelling-off effect has already started to occur in both the Canadian private payer and public markets.

Response: *We will adopt a time horizon of 1 year for the base case with 5 years in sensitivity analysis. We thank the stakeholders for their comments and insight. To explore the potential for leveling off we conducted an extension of our analysis to the end of 2015 for all publicly-funded mirabegron prescriptions in Ontario and found the rate of use continued to increase. In Q4-2015 there were 14,943 users up from 11,353 users in Q3 2015. This trend of continued growth also continued into January of 2016. We agree that similar to previous OAB treatments when first introduced to market there is often a rapid uptake followed by a leveling off; previous medications had a plateau occur 2 to 3 years after market entry. There is no current evidence from our analysis that in the publically-funded population this has yet occurred. The utilization of mirabegron should continue to be monitored as more data and a longer window of observation is available. We have added language to our report to support the need for updated monitoring of utilization.*

Comment: The side effect profile and intolerability of immediate release oxybutynin not only renders it the least favourable drug for patients with OAB but also leads to their withdrawal from treatment altogether, leaving large numbers of people thought to warrant treatment untreated. There are data from Canada which

support this, not simply analyses from dated clinical trials of oxybutynin use. Why was the adverse event profile not considered more seriously in your knowledge syntheses?

Response: *Safety of these agents was considered in our network meta-analysis, as well as through a review of observational literature investigating comparative safety, specifically for falls and cognitive effects. Our results indicate that oxybutynin IR was the least tolerated agent with regards to dry mouth, but the best tolerated agent for constipation. For the review of the observational literature, due to the limited evidence available, no conclusive statements can be made regarding differences in safety or between OAB medications based on observational data.*

Comment: **With respect with the Limited Use (LU) cod, the ODPRN should consider that this code was created to address both clinical and policy expectations.**

Response: *The ODPRN will consider this comment and notes that overall findings demonstrated low proper utilization of the LU code.*

Pharmacoeconomics Unit

Comment: **Why was there no costs assigned to ‘no therapy’ in the de novo model pharmacoeconomic model.**

Response: *The pharmacoeconomic model only included costs that were assumed to vary by treatment regimen; therefore, as there was no evidence which suggested differential resource use based on therapy, the model did not assign a cost to ‘no therapy’. Analyses did however include the physician costs associated with treatment switching.*

Comment: **The costs of implementing recommendations that require enforced use of sequential ACH agents in first line treatment need to be incorporated into the report. This will ensure full accounting and disclosure of the impact of all options presented (i.e. challenges of and costs of modifying the OPDP’s adjudication system; and/or, pharmacist fees for monitoring/enforcement of a more complex LU code at the pharmacy level).**

Response: *Given that all treatments other than oxybutynin IR are currently subject to LU codes and analysis explored strategies reducing such requirements, we do not foresee any additional costs relating to the proposed changes.*

Comment: The most critical gap in the model is that the NMA does not support how the information was used in the economic evaluation. In order to consider different lines of therapy in a sequenced or stepped approach as ODPN has proposed, the economic model should have incorporated corresponding clinical data. Given that the trials included in the NMA were not separated out by line of drug treatment, use of networked data from heterogeneous patient populations for estimates of safety and efficacy outcomes to reflect first-, second-, and third-line treatment recommendations is of concern. Such an analysis should have included distinct clinical data to support each of these lines of therapy. This is of particular concern for drugs with a different mechanism of action, where relative safety and efficacy might differ substantially across lines or sequences of therapy. As previously stated, it cannot be assumed that efficacy with a different ACH therapy in second-line treatment is the same as the efficacy of a beta-3 adrenergic agonist following a failure to respond to an ACH therapy.

Response: *Thank you for your comment. You are correct in pointing out that efficacy data relating to second and third-line therapy with the currently available OAB agents is lacking. As a result, we relied on the available data from the companion network meta-analysis (first line use only) to estimate possible ICERs relating to the sequencing of products (second or third-line use) for the proposed reimbursement options. An alternative course of action would have been to limit the proposed reimbursement options to first-line therapies only, consistent with the lack of clinical data to support assumptions regarding second and third-line treatments. Should this data become available, further analysis would be possible.*

Comment: In the economic model it is assumed that treatment effectiveness beyond 3 months would remain constant at 12 months. This is an assumption that is not supported by the current evidence. Therefore, the assumptions around effectiveness for the base case analysis should be changed to reflect existing evidence. In a similar fashion, the rate of adverse events and treatment discontinuations were assumed to be zero after 3 months until 12 months. Moreover, it was assumed that patients whose symptoms are resolved no longer need treatment. However, it is reasonable to expect that symptoms would reappear once treatment is discontinued. There is no evidence to support the assumptions used in the model. Specific to this point, it is not clear why the ODPN did not use evidence from longer-term and longitudinal studies submitted to support the assumptions regarding treatment effectiveness, adverse events, and treatment discontinuations beyond 3 months.

Response: *The de novo cost-effectiveness model was populated by the results of the network meta-analysis which was conducted by the systematic review team. In their analysis, they included randomized controlled trials that compared OAB agents to each other or to placebo or no treatment; there were studies that ranged from 2 weeks to 52 weeks. Analysis found evidence suggesting a consistency in effect for trials with duration greater than 6 weeks.*

Comment: We noted that persistence to treatment with mirabegron was assumed to be equivalent to that of solifenacin. However, there are studies conducted in Canada that demonstrate that persistence is higher with mirabegron than with ACH drugs. In addition, the assumption that the rate of adverse events with mirabegron is similar to that of solifenacin is not accurate and is not supported by current evidence.

As part of its analysis, the ODRPN was provided with, and also gathered its own, real-world evidence (RWE) related to OAB products and their use (e.g., real-world persistence data, lines of therapy data, etc.). However, much of this RWE does not appear to have been incorporated into the base-case and/or sensitivity analyses carried out in this assessment. Since the ODRPN's work is intended to be holistic and ultimately be used for "real world" public policy decision making, it is critical that the base case of any analysis be reflective of the real world data that have been collected. Why did the assumptions used in the base case PE model not integrate the published RWE analyses provided and/or collected by ODRPN? What was the rationale for not including this component of the evidence gathered through the process?

Response: *No real-world utilization data for Ontario Public Drugs Program was available for mirabegron, due to the recent inclusion of mirabegron on the ODB formulary. Although one paper described persistence rates for antimuscarinics and mirabegron in Canada, the population that was included in this study was significantly different than the publically-funded population and as such, the data was not included in our model. For example, persistence rates were calculated using data from private drug plans (versus OPDP which is publically funded) and only included 20% of patients 65 years and older (vs. OPDP where the average age is 73 years). In addition, the mean number of days to discontinuation in the published study for antimuscarinics varied considerably from our real-world analysis of OPDP data, suggesting that the two populations may differ in adherence rates (e.g., in published study mean number of days to discontinuation for solifenacin was 169 days compared to 248 days in our study). (Reference: Wagg et al. Persistence and adherence with the new beta-3 receptor agonist, mirabegron, versus antimuscarinics in overactive bladder: early experience in Canada. Can Urol Assoc J 2015;9:343-50.)*

Comment: It is not clear why "no therapy" was used as the comparator against other OAB drugs in the economic evaluation (NOTE: using "no therapy" as a reference for the NMA is not the same as the usual "no therapy" as a formal comparator in an economic evaluation). As per CADTH's economic evaluation guidelines, the reference treatment or strategy should be usual care or standard of care; however, this was not the approach used. If it is argued that "no therapy" is a relevant comparator, then it should not be the reference case and it would need to be modelled out properly like other comparators included in the analysis. QALYs were calculated for "no therapy", but it is not transparent how these QALYs were derived from the results of the NMA.

Response: *We defined "no therapy" as the usual management of patients without the addition of a pharmacotherapy.*

Comment: Another concern with the analysis is that “no therapy” was assigned a cost of zero in the model. Given the burden of OAB and the costs observed in the other treatment arms, this appears to be an erroneous assumption. The costs of “no therapy” (including additional doctor visits, other use of health care resources) need to be included. This is an important consideration, as the pharmacoeconomic analysis compare the incremental costs and effects of each treatment relative to “no therapy” and the base case ICER results as a means of ranking treatments in terms of cost-effectiveness.

Response: *We are unaware that there is evidence to suggest that patients not treated by a pharmacotherapy will have additional health care resources. If the reviewer has such evidence to share, we would happily revise our analysis.*

Comment: We would like to point out that the tolterodine unit cost used in all the different economic evaluations is inaccurate. This greatly impacts the orientation of the conclusion of the cost-effectiveness analyses and the perception that the scenario “enforced step therapy for ACh medications” (i.e. Oxybutynin IR and solifenacin as General Benefit, all other OAB medications Limited Use) is the only one that can lead to cost savings for the OPDP. Based on information from the ODB e-formulary, the amount that the MOHLTC currently pays for Detrol LA/ Mylan-Tolterodine ER represents 75% of the brand price. As multiple generic competitors come to market in 2016, a significant price reduction (representing ~25% of the brand reference price) should be used for tolterodine in the various economic evaluations. Doing so would allow the ODPRN to demonstrate that even a coverage scenario in which all the remaining patented therapies would be upgraded to a first-line General Benefit status could bring savings to the OPDP budget for OAB drugs.

Response: *In our sensitivity analysis, assuming generic pricing for tolterodine at 25% of the brand costs does improve its cost effectiveness relative to no therapy but it remains dominated by solifenacin. The manufacturer is wrong in assuming that a policy of moving all therapies to general benefit would be cost saving; as comparing this strategy to a policy of moving solifenacin to general benefit or both solifenacin and tolterodine to general benefit would show that the strategy suggested by the manufacturer would be clearly more costly. No change is therefore required to the report.*