Medicines Management Programme

Oral Medicines for the Management of Urinary Incontinence, Frequency & Overactive Bladder

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Abbreviations

AUA American Urological Association

ACP American College of Physicians

CEBM Centre for Evidence-Based Medicine

CYP Cytochrome P450

DDD Defined daily dose

DPS Drug Payments Scheme

GMS General Medical Services scheme

EAU European Association of Urology

EMA European Medicines Agency

ER Extended-release

IR Immediate-release

HSE Health Service Executive

LUTS Lower Urinary Tract Symptoms

MMP Medicines Management Programme

NICE National Institute of Health and Care Excellence

OAB Overactive bladder syndrome

PCRS Primary Care Reimbursement service

P-gp P-glycoprotein

QoL Quality of life

RCT Randomised controlled trial

RR Relative risk

SMD Standardised mean difference

UI Urinary incontinence

UUI Urge urinary incontinence

WMD Weighted mean difference

1. Introduction

The International Continence Society–International Urogynecological Association defines urinary incontinence (UI) as the complaint of any involuntary loss of urine.[1] UI can have a significant detrimental impact on the physical, psychological and social wellbeing of a person.[2] In general, UI is approximately twice as common in women as in men, and is more common in older than younger persons.[3]

There are three main subtypes of UI[2]:

- **Stress urinary incontinence:** involuntary leakage on effort or exertion, or on sneezing or coughing. The management of stress urinary incontinence is not addressed in this evaluation.
- **Urgency incontinence** (or urge urinary incontinence): involuntary leakage accompanied by, or immediately proceeded by, a sudden compelling desire to pass urine which is difficult to defer (urgency).
- **Mixed urinary incontinence:** involuntary leakage associated with both urgency and also physical stress (exertion, effort, sneezing, or coughing). Mixed UI may be stress or urge dominant.

Urinary frequency is generally considered as ≥ 8 micturitions during waking hours, though this number is variable depending on hours of sleep, fluid intake and co-morbidities etc.[4]

Overactive bladder (OAB) syndrome is defined as urgency, usually with increased frequency and nocturia, which may occur with or without urgency incontinence.[1, 2] About 20% of women aged 40 years or older have a "healthcare requirement" for OAB and this increases to 36% of women aged 80 years or older.[5] Prevalence rates among men range from 7% to 27%.[4] For women, conservative management options for OAB include lifestyle interventions such as reducing caffeine intake, altering fluid intake and losing weight; physical therapies such as pelvic floor muscle training; and pharmacological treatment.[5] Although most studies have been conducted in women, behavioural therapies are also valuable in men.

Troublesome **lower urinary tract symptoms** (LUTS) occur in up to 30% of men over the age of 65 years, and are categorised into voiding, storage or post-micturition symptoms.[6] For

men with LUTS suggestive of OAB, or where OAB is the predominant symptom, supervised bladder training, advice on fluid intake, lifestyle advice and containment products may be offered. If such management options prove unsuccessful or are not appropriate, pharmacological therapy should be offered.[6]

Drugs for the treatment of urge urinary incontinence, frequency and overactive bladder syndrome represent a significant cost to the health service, approximately €16.5 million in 2013, representing a slight increase in expenditure since 2012.[7] On average, 31,400 prescriptions for these medications are filled on the General Medical Services (GMS) scheme every month, with a further 4,200 prescriptions filled on the Drugs Payments Scheme (DPS).[7]

2. Aim

There are eight oral drugs currently licensed and marketed for the treatment of urge urinary incontinence (UI), frequency and overactive bladder syndrome (OAB) in Ireland, all of which are reimbursed by the Health Service Executive (HSE) Primary Care Reimbursement Service (PCRS).[8, 9] Seven of these drugs are antimuscarinics, which work through competitive antagonism of acetylcholine at postganglionic muscarinic receptors, causing a relaxation of bladder smooth muscle.[10] By this action, they increase the maximum urinary capacity and the volume to the first detrusor contraction and decrease the urgency and frequency of incontinence episodes and voluntary urination.[10] Mirabegron, a beta$_3$-agonist, is a novel agent first authorised in 2012.[11] Mirabegron exerts it effect by activating beta adrenoceptors in the detrusor muscle and trigone area of the bladder, facilitating urine storage through the relaxation of the detrusor.[12]

The Medicines Management Programme (MMP) conducted a review of drugs for UI, frequency and OAB as part of the Preferred Drugs initiative. The selection of a preferred drug for the treatment of these conditions under the MMP is designed to support prescribers in choosing a medicine of proven safety, efficacy and cost effectiveness in the management of patients with these symptoms.

As with previous MMP Preferred Drugs initiatives, prescribers are encouraged to consider the preferred drug when initiating pharmacotherapy for UI, frequency and OAB. However,

the selection of a preferred drug serves as guidance only. Prescribers remain autonomous in prescribing and should always take the individual patient, and in particular factors such as age, co-morbidities and concomitant medications, into account when selecting a drug to prescribe.

2.1 Definitions

For the purposes of this evaluation, urinary incontinence (UI) refers to urge urinary incontinence or urge dominant mixed urinary incontinence. Medications under review refer exclusively to oral medications, unless otherwise stated. Antimuscarinic drugs are referred to in some international guidelines as anticholinergic drugs; for the purposes of this evaluation, the terms antimuscarinic and anticholinergic are considered interchangeable. Unless otherwise stated, the cost is the reimbursed cost of a drug, as listed on the HSE PCRS website (www.pcrs.ie) on 6th October 2014. Where two or more preparations of the same drug (excluding parallel imports) are listed, or where there are generic preparation(s) available, the least expensive preparation has been selected for the evaluation. The terms XL, ER and SR denote extended-release preparations and the terms are considered interchangeable for the purpose of this document.

3. Preferred drug for urgency incontinence and overactive bladder

Under the MMP, the preferred drug for UI, frequency and OAB is EXTENDED–RELEASE (ER) TOLTERODINE.

Where there are issues of tolerability and/or lack of effect with ER tolterodine, an alternative antimuscarinic (oral or transdermal), or mirabegron may be considered second line treatment. Cost should be considered when selecting a second line agent.

4. Consultation

An eight-week period of consultation, subsequently extended to 13 weeks, was undertaken in which submissions from relevant stakeholders, including the pharmaceutical industry and professional bodies representing clinicians and healthcare professionals, were invited. This consultation period closed on Friday 22nd August 2014.

5. Selection criteria

Five key selection criteria were considered as part of the evaluation process:

1. Clinical efficacy
2. Patient factors, i.e. dosing and administration, adverse effects, drug interactions
3. Cost
4. National and international clinical guidelines
5. National prescribing trends

5.1 Clinical efficacy

All of the authorised, reimbursed drugs under evaluation have been shown to be effective in relieving the symptoms of UI, frequency and OAB in placebo-controlled randomised controlled trials (RCTs) of varying duration. Typical outcome measures used to determine efficacy include frequency of incontinence episodes, frequency of urgency episodes, and frequency of micturition. Secondary outcomes typically involve safety and tolerability data. A limited number of clinical trials assessed quality of life using health-related quality of life outcomes, e.g. OAB-q Symptom Bother score.

There are a limited number of head-to-head RCTs comparing different antimuscarinics. Mirabegron has been compared to placebo only in RCTs; in one RCT of mirabegron, tolterodine was included as an active control, however, the study was not designed to detect statistically significant differences in efficacy between mirabegron and tolterodine.[3] For details of RCTs see Appendix 1.[i]

Head-to-head trials comparing two or more drugs or dosages are very useful. However, differences in clinical trial design can make meaningful comparisons between individual

[i] Only RCTs included in a submission are listed in Appendix 1.

clinical trial results difficult. Individual trials must be interpreted in the context of the body of literature.[13] Systematic reviews and meta-analyses utilise pooled data from clinical trials and provide an additional means of assessing the general and comparative efficacy of drugs for UI, urinary frequency and OAB. A strength of the meta-analytic technique is that it provides an overall perspective of differences between efficacy and safety among individual antimuscarinic agents using all suitable data and large numbers of participants, and is therefore less susceptible to the weaknesses of individual studies.[13] The Centre for Evidence Based Medicine (CEBM) Method of Oxford University considers systematic review and meta-analysis of RCTs the highest grade (Level 1a) of evidence.[14] The clinical usefulness of drugs for the treatment of UI, frequency and OAB represents a balance between efficacy and adverse effects, and consequently, most meta-analyses consider both of these factors when comparing these drugs. The results of four systematic reviews and meta-analyses of antimuscarinic drugs for UI, frequency and OAB, which contain a degree of overlap in the studies included, are discussed in section 5.1.1.

5.1.1 Meta-analyses

In 2012, Buser *et al* published two network meta-analyses summarising the efficacy and adverse events of antimuscarinics in the treatment of OAB.[15] Neither mirabegron nor flavoxate were included in the analyses. The efficacy network meta-analysis was limited to six outcome measures: perception of cure or improvement; urgency episodes per 24 hours; leakage episodes per 24 hours; urgency incontinence episodes per 24 hours; micturitions per 24 hours; and nocturia per 24 hours.[15] For the adverse events network meta-analysis, adverse events were classified according to the Common Terminology for Adverse Events (v.3.0) into seven categories and then graded using a visual analogue scale based on expert consensus. In a trade-off analysis (i.e. a trade-off between efficacy and adverse events), the outcomes were ranked and weighted by experts, with urgency episodes per 24 hours considered the most important outcome, and nocturia the least important. Individual outcomes are not discussed in detail in this evaluation, though in general, higher doses of antimuscarinics resulted in greater mean reductions in urgency episodes per 24 hours compared with lower doses.[15] Contrary to the findings of previous studies, no consistent pattern showing superiority of ER

formulations over immediate-release (IR) formulations was found. Higher doses also resulted in more adverse events.[15]

Of greater interest is the trade-off between efficacy and adverse events.

- The authors concluded that in general, the efficacy of antimuscarinics is at best moderate, and no treatment stands out in all assessed outcomes.
- Currently prescribed antimuscarinics seem to be an equivalent choice in terms of adverse events, perhaps with the exception of higher oral doses of oxybutynin and propiverine, which have more unfavourable adverse events profiles.
- In a trade-off analysis, 40 mg trospium, 100 mg/day oxybutynin gel, 4 mg solifenacin and fesoterodine 4 mg appeared to strike the best balance between efficacy and adverse events. Other antimuscarinics which showed a favourable efficacy-adverse event relationship included tolterodine ER 4 mg and oxybutynin ER 15 mg.

A Cochrane review entitled *'Which anticholinergic drug for overactive bladder symptoms in adults'* (2012) compared individual anticholinergic drugs for the treatment of UI and OAB, different formulations (e.g. IR vs. ER, oral vs. transdermal) of anticholinergic drugs (excluding flavoxate), and different doses of the same and different anticholinergic drugs. Some of the outcome measures assessed included quality of life, frequency of micturition and urgency/incontinence episodes.[16] Some of the outcome comparisons are discussed as follows:

Solifenacin vs. tolterodine

Five trials comparing different doses of solifenacin with different doses and formulations of tolterodine were included in the analysis. Four of these trials compared IR tolterodine 4 mg with solifenacin (5 mg and 10 mg dosages) and one compared ER tolterodine 4 mg with solifenacin 5 mg.

- Meta-analysis of four trials showed statistically significantly fewer leakage episodes with solifenacin (weighted mean difference [WMD] -0.30, 95% CI -0.53 to -0.08) at 12 weeks.
- Meta-analysis showed no statistically significant difference in micturition in 24 hours between the groups at 12 weeks.

- Four trials reported on urgency episodes per 24 hours, which showed a statistically significant difference favouring solifenacin (WMD -0.43, 95% CI -0.74 to -0.13) at 12 weeks.
- With regard to withdrawals from clinical trials due to adverse events, the combined results of five clinical trials were not statistically significant at 3 and 12 weeks. Overall results for dry mouth were not statistically significant at 3 and 12 weeks. When one trial was removed from the analysis, dry mouth rates were significantly lower with solifenacin when compared to IR tolterodine (RR 0.69, 95% CI 0.51 to 0.94). However, a separate analysis of ER tolterodine versus solifenacin found the risk of dry mouth was statistically significantly lower with ER tolterodine than with solifenacin, but there were no significant differences in the number of withdrawals due to adverse events.

Fesoterodine vs. tolterodine ER

Three 12-week trials compared an oral preparation of fesoterodine with ER oral tolterodine.

- Meta-analysis was possible for comparison of fesoterodine 8 mg and tolterodine ER 4 mg. The analysis showed a statistically significantly better QoL with fesoterodine 8 mg vs. tolterodine ER 4 mg, however, the details of the measurement method(s) are not given.
- Meta-analysis showed statistically significantly lower end-of-treatment leakage episodes per 24 hours (WMD -0.19, 95% CI -0.30 to -0.09), micturition per 24 hours (WMD -0.27, 95% CI -0.47 to -0.06) and urgency per 24 hours (WMD -0.44, 95% CI -0.72 to -0.16) favouring fesoterodine 8 mg.

Tolterodine vs. oxybutynin

Thirteen parallel-arm studies and one cross-over study compared various doses and formulations (e.g. IR, ER) of tolterodine and oxybutynin; one of the studies included in the analysis compared ER tolterodine 4 mg to transdermal oxybutynin 3.9 mg daily.

- Three trials, one of which used transdermal oxybutynin, collected QoL data. Two of these trials reported data, which when combined showed no significant difference between oxybutynin and tolterodine (SMD -0.00, 95% CI -0.18 to 0.18).
- There were no statistically significant differences for patient reported cure or improvement, or leakage episodes or voids in 24 hours, but fewer withdrawals due to

adverse events with tolterodine (RR 0.52, 95% confidence interval, CI 0.40 to 0.66, data from eight trials) and less risk of dry mouth with tolterodine as compared to oxybutynin (RR 0.65, 95% CI 0.60 to 0.71, data from 10 trials).

- There were no statistically significant differences between ER and IR preparations of oxybutynin or tolterodine for cure or improvement, leakage episodes or micturitions in 24 hours or withdrawals due to adverse events, but data were limited.

In an earlier systematic review and meta-analysis, Novara *et al* (2008) evaluated and compared the efficacy and safety of different doses, formulations and routes of administration of the available antimuscarinic drugs.[17] Flavoxate was not included in this analysis. Some of the main findings are discussed below:

Oxybutynin vs. tolterodine

- Twelve RCTs comparing oxybutynin and tolterodine were identified, eight of which compared IR preparations of either drug, and four of which were suitable for meta-analysis. Efficacy was similar for both IR preparations, though significantly more patients stopped taking oxybutynin IR than tolterodine IR due to adverse effects.
- A single study comparing ER preparations of oxybutynin and tolterodine found similar efficacy for weekly urge urinary incontinence episodes and incontinence episodes of any type.
- The incidence of dry mouth was significantly less in those on tolterodine, though in most cases it was mild in nature.

Oxybutynin vs. trospium

- A 52-week RCT comparing oxybutynin and trospium found similar efficacy for both drugs in terms of mean change in micturitions and the number of urgency episodes per 24 hours.
- Adverse effects, including dry mouth, were less common in those receiving trospium.

Tolterodine vs. trospium

A single unpublished RCT comparing tolterodine IR 2 mg twice daily and trospium 20 mg twice daily showed similar efficacy and adverse event rates for the two drugs.

Tolterodine vs. solifenacin

- A study comparing solifenacin IR 5 mg and 10 mg to tolterodine ER found that solifenacin IR was non-inferior to tolterodine with regard to several outcome measures, including frequency of micturition, reduction in number of urgency episodes per day and urge incontinence episodes per day.
- Dry mouth was more common in those receiving solifenacin. However, despite limitations in the data, meta-analysis of this and earlier trial found that only constipation was more common with solifenacin.

Tolterodine vs. fesoterodine

- In a placebo-controlled trial of fesoterodine 4 mg and 8 mg, tolterodine ER 4 mg was included as an active control. Fesoterodine 8 mg was found to outperform tolterodine ER 4 mg, while fesoterodine 4 mg showed similar efficacy to tolterodine ER 4 mg.
- Adverse effects were similar for fesoterodine 4 mg and tolterodine ER 4 mg, but occurred more frequently with the higher dose of fesoterodine.

In 2008, Chapple *et al* updated a previous systematic review and meta-analysis of the efficacy, safety, tolerability of the antimuscarinics in OAB. [13] Impact on health-related quality of life was considered but was published in a separate analysis. Similar outcome measures as those used by Buser *et al* were employed, i.e. change in the number of micturitions, urgency and incontinence episodes per day. Flavoxate was not included in the analysis.

- In terms of the mean number of urgency episodes per day, fesoterodine, propiverine, solifenacin and tolterodine were significantly more effective than placebo. Meta-analysis was not possible for oxybutynin and trospium. There was evidence favouring solifenacin 5 mg per day over ER tolterodine 4 mg per day (mean difference: 0.80, 95% CI 1.17-1.43, p=0.01).
- Antimuscarinics were also more effective than placebo in reducing the mean number of micturitions per day. There was some evidence favouring solifenacin 10 mg over tolterodine IR 4 mg per day (mean difference 0.73, 95% CI 0.19-1.27, p=0.01) , and evidence favouring solifenacin 10 mg over solifenacin 5 mg per day (mean difference: 0.30, 95% CI 0.04-0.55, p=0.02).

- Tolterodine ER 4 mg was found to be associated with a statistically significantly lower risk than placebo of withdrawal due to an adverse event (RR 0.71, 95% CI 0.53-0.95, p=0.02). Oxybutynin IR 7.5-10 mg per day, oxybutynin IR 15 mg per day, propiverine ER 20 mg per day and solifenacin 10 mg per day were associated with a significantly higher risk of withdrawal than placebo due to adverse events.
- Dry mouth was found to be more common with all interventions than placebo. A dose-related effect was seen for fesoterodine, solifenacin and tolterodine, though not so for oxybutynin and propiverine. The risk of mild dry mouth was less in those treated with tolterodine ER 4 mg than those treated with oxybutynin 7.5 mg IR per day.

Summary – Clinical Efficacy

- ✓ Based on the results of published meta-analyses, the MMP does not believe there to be compelling evidence of the clinically meaningful superiority of one antimuscarinic drug over another for the treatment of UI, frequency and OAB.
- ✓ While discreet differences between antimuscarinic drugs have been found in terms of certain clinical outcome measures, these differences have generally been modest, and though statistically significant, the MMP does not consider them to be of major clinical importance.
- ✓ Flavoxate was largely excluded from systematic reviews and meta-analyses of antimuscarinics for UI, frequency and OAB.
- ✓ The treatment of UI, frequency and OAB involves a trade-off between clinical efficacy and adverse effects. The MMP believes there to be sufficient evidence to support choosing an ER or once daily antimuscarinic preparation over an IR preparation requiring multiple daily doses on the basis of a more favourable adverse effect profile.
- ✓ At present, the clinical efficacy data for mirabegron for the treatment of UI, frequency and OAB are limited to placebo-controlled RCTs.

Preferred drug: No preference

- ✓ **IR preparations disfavoured – increased adverse effects**
- ✓ **Flavoxate disfavoured – excluded from key meta-analyses**
- ✓ **Clinical efficacy data for mirabegron currently limited to placebo-controlled RCTs**

5.2 Patient factors

5.2.1 Dosing and administration

Some antimuscarinics used in the treatment of urgency incontinence, frequency and OAB syndrome are available as immediate-release (IR) and extended-release (ER) formulations, the ER preparations allowing for once daily administration. Solifenacin is available as a film-coated tablet but its long terminal half-life allows for once-daily dosing.[18] Flavoxate and trospium are available as IR preparations only and require thrice and twice daily administration, respectively.[19, 20] Mirabegron is administered as a single daily dose.[11]

In general, preparations administered once daily are preferred over drugs requiring multiple daily administrations due to their association with improved treatment compliance. The available evidence suggests that IR preparations may be less well tolerated than ER formulations.[21] A number of meta-analyses determined that IR oxybutynin may be associated with more severe adverse effects than ER oxybutynin and IR/ER formulations of other antimuscarinics.[15, 22]

5.2.2 Adverse effects

There may be differences in the adverse effect profiles of the antimuscarinics and different formulations of the antimuscarinics. Some of these are discussed in Section 5.1. Typical antimuscarinic side effects include dry mouth, constipation, blurred vision and drowsiness.[21] However, as a whole the antimuscarinics are not particularly well tolerated and adherence to and persistence with antimuscarinic treatment is generally low.[23, 24]

A network meta-analysis to quantify and compare the adverse events profiles of antimuscarinic drugs for OAB found similar overall results for solifenacin, trospium, tolterodine and fesoterodine.[25] Oral oxybutynin was associated with a statistically significant higher adverse events score than these agents. Darifenacin[ii], fesoterodine, oral oxybutynin, propiverine and solifenacin showed a positive correlation between increasing dose and adverse events. However, several limitations limit the clinical significance of these findings, including that most of the studies included were fixed dose studies. In practice, many of these drugs are titrated according to response and tolerability.[22] The number of people

[ii] Not marketed in Ireland

withdrawing from treatment due to adverse events was not measured; this is often a useful indicator of adverse effects and tolerability.

A systematic review of long-term (≥6 months) adherence to antimuscarinic treatment determined that regardless of the specific antimuscarinic drug used, persistence rates are usually poor.[24] Median persistence rates ranged from 12% to 39.4% at 12 months, 8% to 15% at 18 months, and 6% to 12% at 24 months. At 36 months persistence rates ranged from 0% (darifenacin) to 16% (trospium). Risk factors for discontinuation were identified, with the most important being younger age group, use of oxybutynin and use of IR formulations. Reasons given for discontinuing treatment included lack of effect, 'learning to get by' without medication, medication switch and adverse events. [24]

A Danish registry study of persistence with antimuscarinic drugs for OAB found significantly higher persistence rates with trospium compared to darifenacin, flavoxate, solifenacin, oxybutynin and tolterodine.[25] With the exception of trospium, all drugs had continuation rates of < 50% after 6 months of treatment, < 25% at 1 year and < 10 % after 2 years or more; with trospium the continuation rates were 46% and 36% after 6 months and one year, respectively, and 22% after 2 years.[25] Possible reasons for these differences in persistence rates between antimuscarinics suggested by the authors included adverse effects, the availability of generic trospium during the study period, and lack of treatment efficacy. An analysis of Irish prescribing data is presented in section 5.5.

As discussed in Section 5.2.1, there is evidence that ER preparations of antimuscarinics such as oxybutynin and tolterodine are better tolerated than IR preparations. While side effects are among the causes of relatively high rates of discontinuation, a belief by patients that the drug is not working as well as it should has been found in some cases to be a more significant factor.[23, 24]

Prolongation of the QT interval has occurred in controlled studies using both therapeutic and higher doses of tolterodine, and although changes from baseline did not cross the threshold of concern, the clinical implications are unclear.[27] The tolterodine SmPC therefore warns that tolterodine should be used with caution in patients with QT prolongation or relevant risk factors, such as electrolyte disturbances, bradycardia, pre-existing cardiac

disease, or the concomitant use of other drugs known to prolong the QT interval.[28] With the exceptions of oxybutynin (Lyrinel® XL, Cystrin®) and propiverine (Detrunorm® XL), the other antimuscarinics evaluated here also carry warning regarding a possible increased risk of QT prolongation.[19, 20, 29-33]

Owing to its novel mechanism of action, mirabegron may be lacking some of the adverse effects typically associated with the antimuscarinics, in particular dry mouth. Dry mouth was reported in < 3% of patients taking mirabegron. At therapeutic doses, mirabegron has not demonstrated clinically relevant QT prolongation in clinical studies.[11] However, patients with known or risk factors for QT prolongation were excluded from clinical studies, therefore, the effects of mirabegron in these patients is as yet unknown.[11] Other common adverse effects of mirabegron are tachycardia and urinary tract infection (UTI).[11 , 21]

5.2.3 Drug interactions

5.2.3.1 Pharmacodynamic drug interactions

Owing to their common mode of action and adverse effect profiles, certain pharmacodynamic drug interactions are common to all the antimuscarinics, e.g. inhibition of prokinetic drugs such as metoclopramide.[21] Furthermore, many drugs not classified as antimuscarinics have inherent antimuscarinic activity, e.g. tricyclic antidepressants. Concomitant use with antimuscarinics for urgency incontinence, urinary frequency and overactive bladder syndrome may result in additive antimuscarinic effects resulting in increased sedation, dry mouth and constipation. [21] Therefore, caution is advised when prescribing an antimuscarinic for UI, frequency and OAB with other drug(s) that have antimuscarinic activity. [21]

Because of a concern over possible QT prolongation with tolterodine, caution is advised where there is concomitant administration of tolterodine and drugs known to prolong QT-interval including Class IA (e.g. quinidine, procainamide) and Class III (e.g. amiodarone, soltalol) anti-arrhythmics.[28]

Analysis of Irish prescribing data[iii] by the MMP (Section 5.5.4) found relatively low rates of co-prescribing of tolterodine (IR/ER) with drugs known to prolong the QT interval; approximately 5% of pharmacy claims were suggestive of co-prescribing of potentially interacting drugs.[34] These results were similar to rates of co-prescribing of QT-prolonging drugs alongside oxybutynin (all preparations), fesoterodine and solifenacin (Section 5.5.4).

5.2.3.2. Pharmacokinetic drug interactions

Most antimuscarinics are substrates for the cytochrome P450 (CYP) isoenzymes CYP3A4 and/or CYP2D6. Consequently, concomitant administration of antimuscarinics with potent inhibitors or inducers of these enzyme systems may to result in altered serum concentrations.[19, 20, 29-33] However, the importance of such interactions is generally uncertain and dose adjustments are generally unnecessary. However, caution should be exercised when such drugs are co-administered.

Mirabegron is a weak inhibitor of CYP3A4 and a moderate inhibitor of CYP2D6. At high doses it inhibits the efflux transporter P-glycoprotein (P-gp). Clinically relevant drug interactions between mirabegron and medicinal products that inhibit, induce or are substrates for one of the CYP isozymes or transporters are not expected except for the inhibitory effect of mirabegron on the metabolism of CYP2D6 substrates.[11] No dose adjustment of mirabegron is necessary where there is concomitant administration of potent CYP3A inhibitors, e.g. itraconazole, except in cases of renal and/or hepatic impairment. Caution is advised if mirabegron is co-administered with medicinal products with a narrow therapeutic index that are significantly metabolised by CYP2D6, such as type 1C antiarrhythmics, e.g. flecainide, propafenone, and tricyclic antidepressants, e.g. imipramine, desipramine.[11] The European Medicines Agency (EMA) has recommended specific post-marketing surveillance of mirabegron in relation to its concomitant administration with CYP2D6 substrates with a narrow therapeutic index.[3]

[iii] Data from July 2013 – June 2014

Summary – Patient factors

Dosing and administration; Adverse effects

- ✓ Certain characteristic adverse effects are typical of the antimuscarinics, e.g. dry mouth, constipation. In general, adherence to antimuscarinic therapy for UI, frequency and OAB is low; however, this may not be due entirely due to adverse effects. Mirabegron may be lacking some of the adverse effects typically seen with the antimuscarinics
- ✓ The MMP believes there to be sufficient evidence to support choosing an ER or once daily preparation over an IR preparation on the basis of adverse effect profile. Additionally, preparations administered once daily are generally preferred over drugs requiring multiple daily administrations due to their association with improved treatment compliance.

Drug interactions

- ✓ Caution is advised where there is concomitant administration of some antimuscarinics with drugs that prolong the QT interval. However, an analysis of Irish prescribing data indicates that the rate of co-prescribing is low.

Preferred Drug: No preference (IR preparations disfavoured)

5.3 Cost

There is some variability in drug costs across this therapeutic area. Of the eight drugs included in this evaluation, four remained under patent protection at the time of publication, namely fesoterodine (Toviaz®), propiverine (Detrunorm® XL), solifenacin (Vesitirim®) and mirabegron (Betmiga®). Some preparations (e.g. ER/XL) of other antimuscarinics remain under patent protection. None of the drugs under review had undergone reference pricing as of 17th October 2014.[35]

The MMP accepts that factors other than acquisition cost contribute to the costs of treatment UI and OAB. Return visits to GPs and specialists for reassessment of symptoms and drug treatment, as well as the cost of incontinence pads, which is often borne by patients, also contribute to the cost to the patient and the health service.

The MMP compared the drug acquisition cost of individual agents.[iv] The position of the MMP is that in general, the cheaper of two drugs is preferred unless the more expensive drug has a clear and proven advantage in terms of clinical efficacy, adverse effect profile and/or potential for drug interactions. The defined daily dose (DDD), as listed by the World Health Organisation (WHO) Collaborating Centre for Drugs Statistics Methodology (www.whocc.no), was used in the comparison of the reimbursed costs of individual drugs.[36] Costs per DDD (Figure 1) were calculated by dividing the reimbursed cost per pack by the number of dosage units per pack and multiplying by the relevant factor in order to obtain the DDD.[9]

The costs per 30 days' treatment are displayed in Figure 2 and were calculated by multiplying the cost per DDD by 30. For tolterodine and oxybutynin, only ER preparations are included in the cost comparison, because evidence suggests they are better tolerated than IR preparations (see Section 5.2.1. and 5.2.2), and ER preparations of these drugs are therefore viewed by the MMP as more suitable for consideration as the preferred drug.

Figures 1 and 2 represent the reimbursed drug costs and are exclusive of pharmacist fees and mark-up.

[iv] Prices based on the reimbursed price as listed on PCRS website, www.pcrs.ie, 6th October 2014.

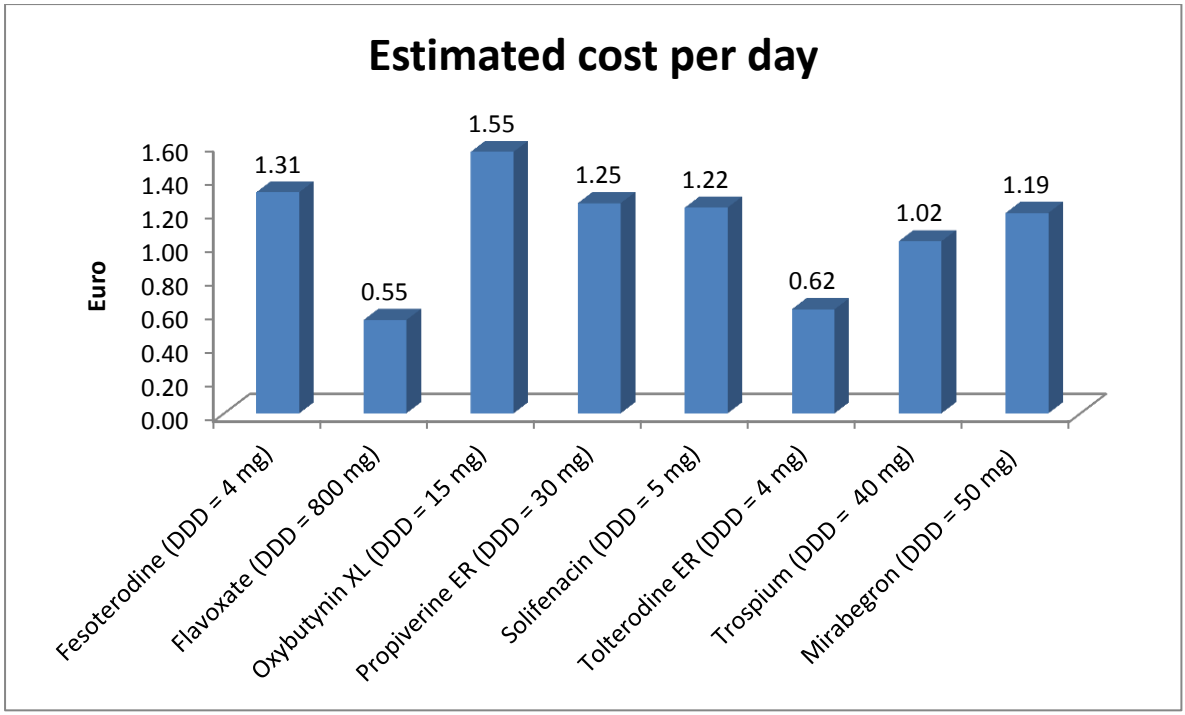

Figure 1. Estimated reimbursed cost per day (DDD).[v]

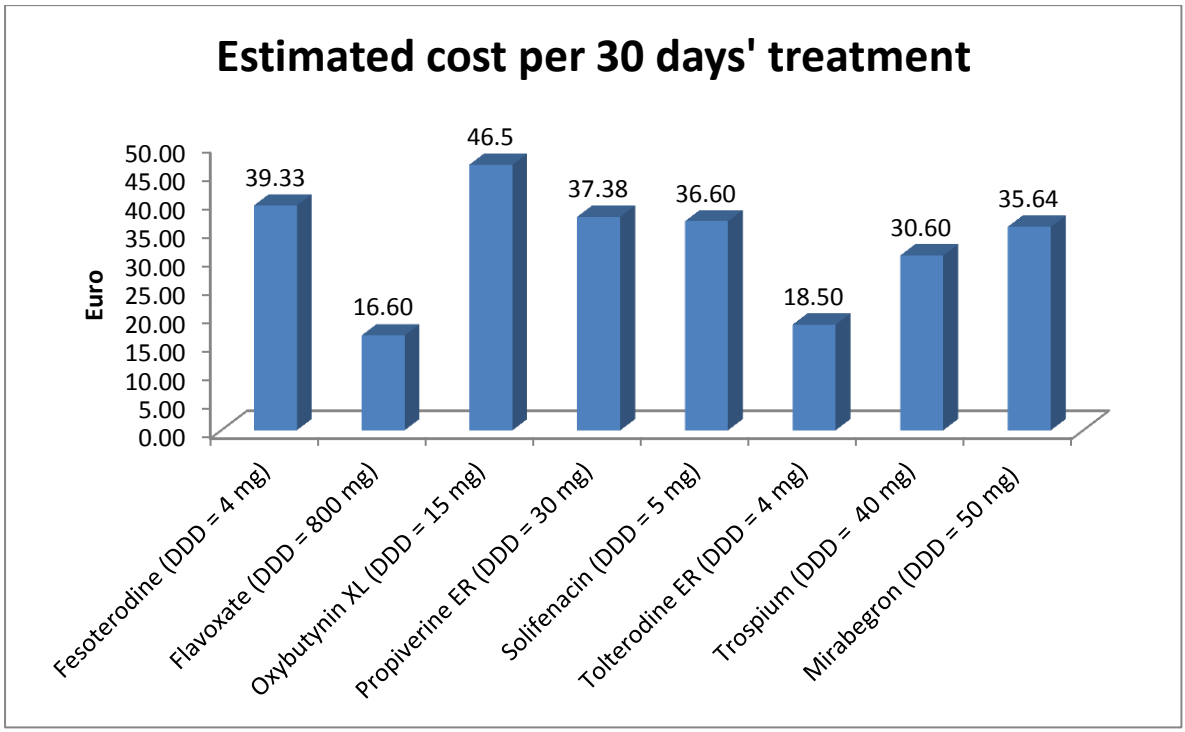

Figure 2. Estimated reimbursed cost per 30 days' treatment (DDD).[v]

[v] Fesoterodine (Toviaz®); Flavoxate (Urispas®); Oxybutynin ER (Lyrinel® XL 5 mg + 10 mg) [Lyrinel XL 15 mg preparation not reimbursed by PCRS, October 2014]; Propiverine (Detrunorm® XL); Solifenacin (Vesitirim®); Tolterodine ER (Trusitev); Trospium (Regurin®); Mirabegron (Betmiga®).

The MMP conducted analyses of GMS pharmacy claims data to help inform the present review (see Section 5.5). As part of these analyses, the average PCRS expenditure per pharmacy claim was determined for each of the eight drugs under review using the most recent data (June 2014). This expenditure is displayed in Figure 3 as the level of ingredient cost per claim item. Variation in ingredient cost per item reflects the range of doses prescribed across the patient population and the availability of generic products.

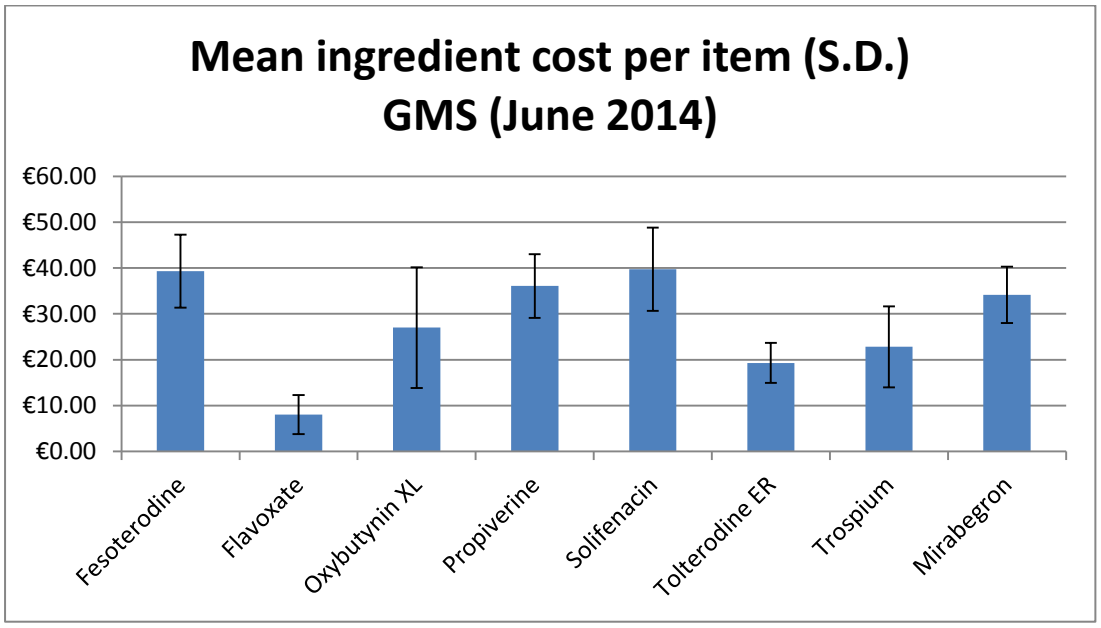

Figure 3. Expenditure in terms of mean ingredient cost per dispensed item. Error bars display standard deviation. (Pharmacy fees excluded).

Summary – Cost

Based on the reimbursed cost *and* the mean ingredient cost paid per dispensed item, tolterodine ER and flavoxate are considerably less expensive than the other antimuscarinics and mirabegron.

Preferred drug: Tolterodine ER and flavoxate

5.4 Clinical Guidelines

In the absence of Irish clinical guidelines on the management of UI, frequency and OAB, international guidelines from the UK, Europe and the USA were consulted. Details are in Table 1.

Table 1. Clinical guidelines

Group and Guideline	*Preferred drug(s)*	*Relevant excerpt/comment*
European Association of Urology Guidelines on Urinary Incontinence, 2009 (updated March 2013) [37]	Not specified	**Antimuscarinics:** 'There is no consistent evidence for the superiority of one antimuscarinic agent over another for cure or improvement of UI. There is good evidence that ER, once daily, and transdermal preparations are associated with lower rates of dry mouth than IR preparations, although discontinuation rates are similar. There is no evidence that any particular antimuscarinic agent is superior to another for improvement in quality of life". **Mirabegron:** The use of mirabegron resulted in modest reduction (improvement) in episodes of urge urinary incontinence compared to placebo. Offer mirabegron to people with urge urinary incontinence depending on local licensing arrangements'.
European Association of Urology Guidelines on Urinary Incontinence, (text update 2014) [38]	Not specified	**Antimuscarinics:** "Offer IR or ER formulations of antimuscarinic drugs as initial therapy for adults with urgency UI. If IR formulations of antimuscarinic drugs are unsuccessful for adults for adults with urgency UI, offer ER formulations or longer-acting

		antimuscarinic agents. Consider using transdermal oxybutynin if oral antimuscarinic cannot be tolerated due to dry mouth". **Mirabegron:** "Offer mirabegron to people with urgency UI, but warn patients receiving mirabegron that the possible long-term side effects remain uncertain".
American Urological Association AUA/SUFU Guideline: Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults, 2014.[4]	Not specified	**Antimuscarinics:** An extensive review of the randomised controlled trials that evaluated pharmacologic therapies for OAB (including trials with placebo controlled groups as well as trials with active treatment comparison groups) revealed no compelling evidence for differential efficacy across medications. This finding is consistent with the conclusions of several published systematic reviews". . . "Due to the similar efficacy observed for all oral anti-muscarinic medications, the choice of medication for a particular patient depends on the patient's history of antimuscarinic use, information regarding adverse events experienced in the past, the impact on the patient of the adverse events, patient preferences, comorbidities, use of other medications". **Mirabegron:** "Overall, the panel interpreted the mirabegron data to indicate that mirabegron appears to be similar in efficacy to the antimuscarinics and has lower rates of dry mouth than with any of these medications. Mirabegron may produce lower rates of constipation than some of the antimuscarinics . . . The body of

		evidence strength for the benefits and risks/burdens of mirabegron is Grade B".
American College of Physicians (ACP) Nonsurgical Management of Urinary Incontinence in Women (2014) [39]	No preference	Clinicians should base the choice of pharmacologic agents on tolerability, adverse effect profile, ease of use, and cost of medication. Pharmacologic therapies were effective and equally efficacious at managing urgency UI and had a moderate magnitude of benefit in achieving continence rates. However, they were associated with adverse effects and evidence showed that some patients were likely to discontinue pharmacologic treatment because of these effects. Solifenacin was associated with the lowest risk for discontinuation due to adverse effects, whereas oxybutynin was associated with the highest risk. For urgency UI, oxybutynin, tolterodine, darifenacin, solifenacin, fesoterodine, and trospium increased continence rates and improved UI.
National Institute for Health and Care Excellence (NICE) The Management of Urinary Incontinence in Women (Clinical Guideline 171), 2013.[2]	Oxybutynin (IR) Tolterodine (IR) Darifenacin[vi]	"Do not use flavoxate, propantheline or imipramine for the treatment of UI or OAB in women. Do not offer oxybutynin (IR) to frail older women. Offer a transdermal OAB drug to women unable to tolerate an oral preparation."

[vi] Not reimbursed by PCRS

National Institute for Health and Care Excellence (NICE) Lower Urinary Tract Symptoms in Men (Clinical Guideline 97), 2010.[6]	Not specified	Offer an anticholinergic to men to manage the symptoms of OAB. Review men taking anticholinergics every 4–6 weeks until symptoms are stable, and then every 6–12 months.
National Institute for Health and Care Excellence (NICE) Mirabegron for treating symptoms of overactive bladder – NICE Technology Appraisal [TA290], 2013.[40]	See comment	"Mirabegron is recommended as an option for treating the symptoms of overactive bladder only for people in whom antimuscarinic drugs are contraindicated or clinically ineffective, or have unacceptable side effects".

Summary – Clinical guidelines

International clinical guidelines do not identify a preferred agent for UI, frequency and OAB. Most suggest using an oral antimuscarinic as first line drug treatment, with consideration given to transdermal oxybutynin or mirabegron should the patient experience unacceptable adverse effects. Factors such as cost and patient preference should be considered also.

Preferred drug: No obvious preference – use oral antimuscarinic first line

5.5 National prescribing trends

In order to examine national prescribing trends for the eight drugs under review, analyses of PCRS pharmacy claims data were performed by the MMP. For the purposes of this review the analyses focused on the GMS scheme. The most recent available data at the time of writing were used and comprised dispensing claims data for the years 2013 and 2014 (up to and including June 2014). Mirabegron, the most recent drug to enter the market, was first reimbursed under the GMS scheme in May 2013.

5.5.1 Market share

Figure 4 represents the GMS market share for each drug based on the number of claims received in the month ending June 2014.

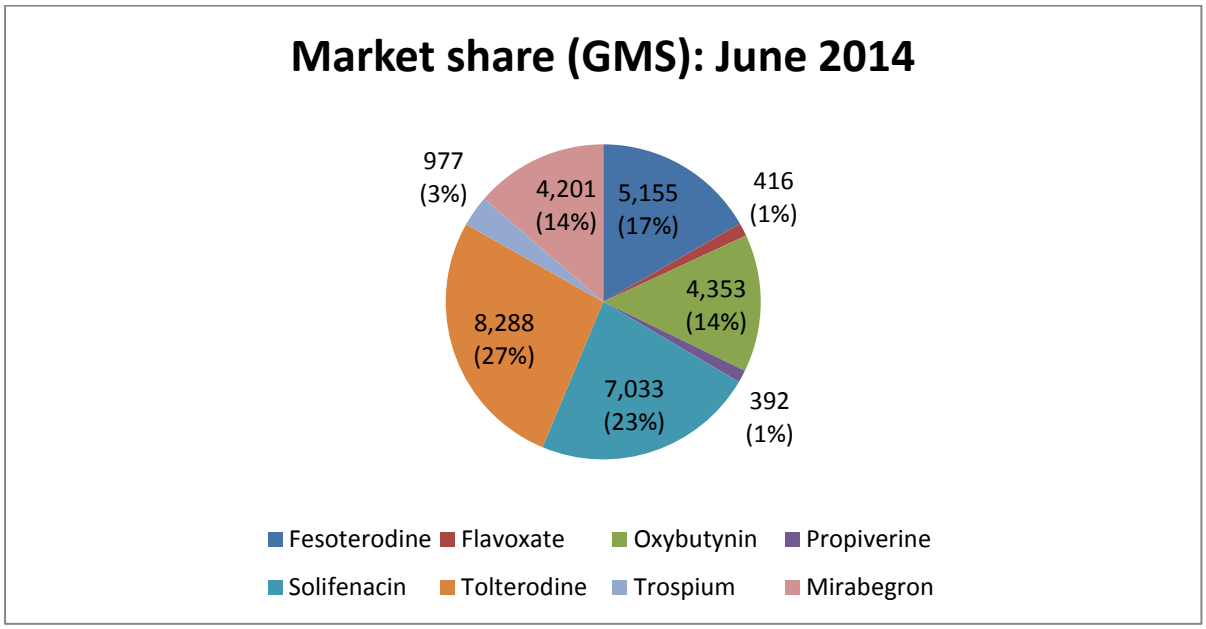

Figure 4. Market share as per number of dispensing claims (June 2014).

Figure 5 represents the number of patients who received drugs for UI, frequency and OAB under the GMS scheme from January 2013 to June 2014 inclusive. As is evident from Figure 5 (Page 24), since its introduction there has been a steady month-on-month increase in the number of patients prescribed mirabegron. Therefore, it is likely that the 14% market share of mirabegron in June 2014 (Figure 4) has increased since that time.

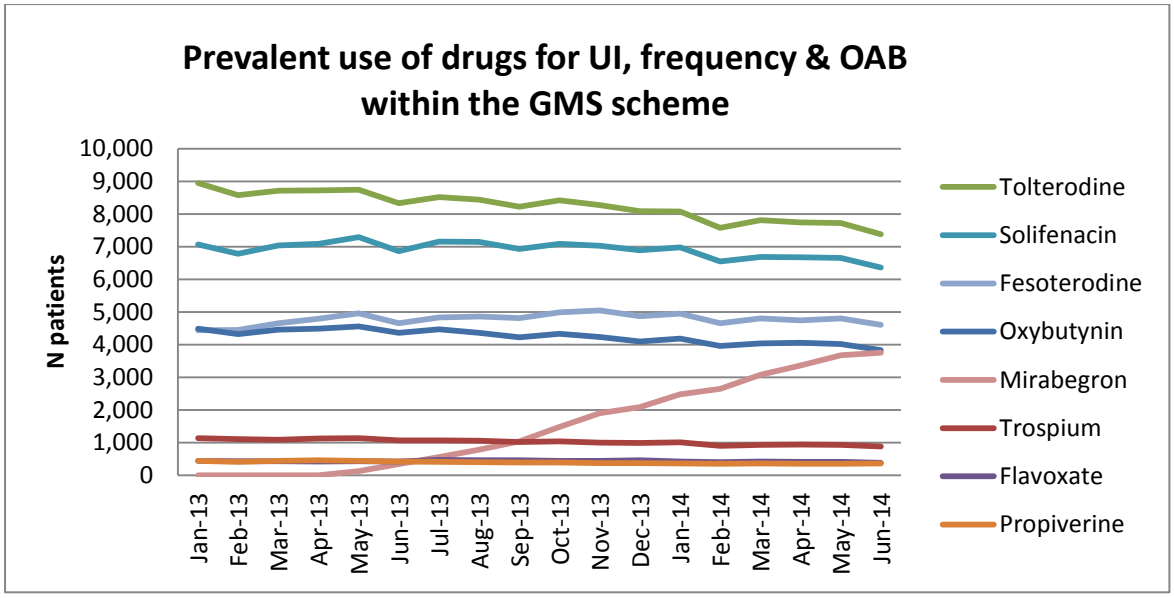

Figure 5. Number of GMS patients dispensed drugs for UI, frequency and OAB (January 2013 - June 2014)

5.5.2 Total expenditure

The monthly total expenditure for each of the eight drugs under review is depicted in Figure 6 (GMS data, May 2013 – June 2014). Total expenditure takes into account pharmacist fees.

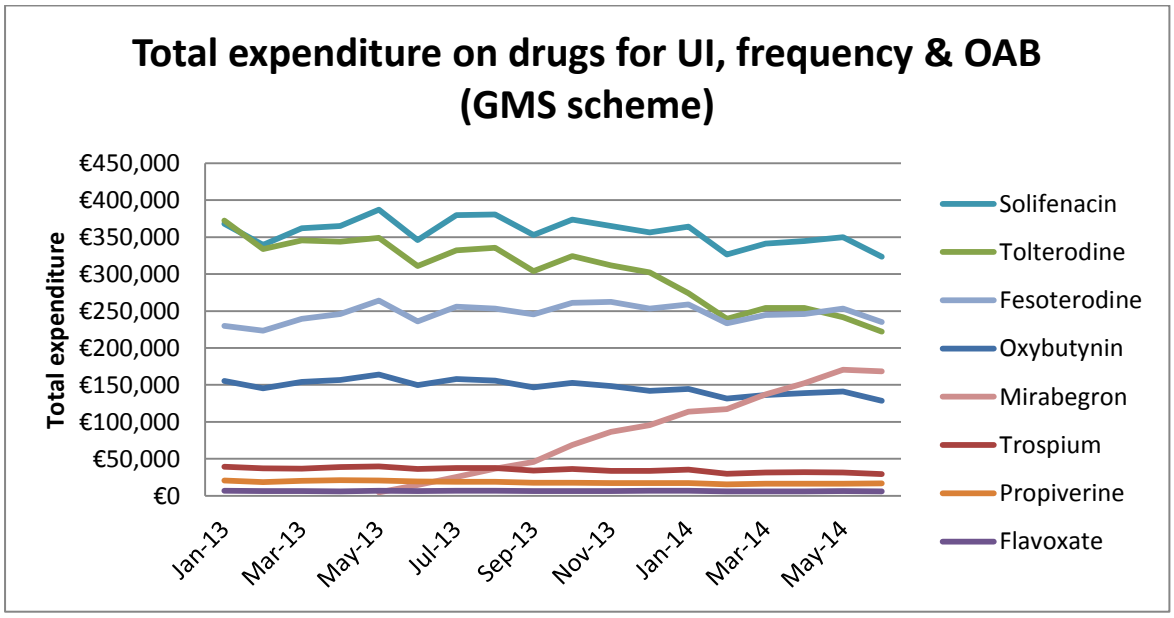

Figure 6. Total monthly expenditure on drugs for UI, frequency and OAB from January 2013–June 2014 (GMS).

5.5.3 Duration of use

Published evidence suggests that on the whole, adherence to antimuscarinic treatment in patients with UI and OAB syndrome is poor (Section 5.2.2). A cross-sectional analysis of PCRS dispensing data was performed to investigate rates of persistence among patients newly initiated on any of the drugs under review during May 2013.[7] Patients were followed for 12 months to determine the number of subsequent months in which they filled a prescription for the drug on which they had been initiated.

For each drug, the majority of patients did not persist on the drug on which they had been initiated beyond three months of treatment (Figure 7). The drugs with the highest proportions of patients persisting (i.e. ≥15% of patients persisting) on therapy for ≥10 months were mirabegron, solifenacin, fesoterodine and tolterodine. It should be noted that the patient numbers involved in this analysis were small for some drugs. Therefore, it may not be possible to derive meaningful differences in persistence rates between the drugs from these data.

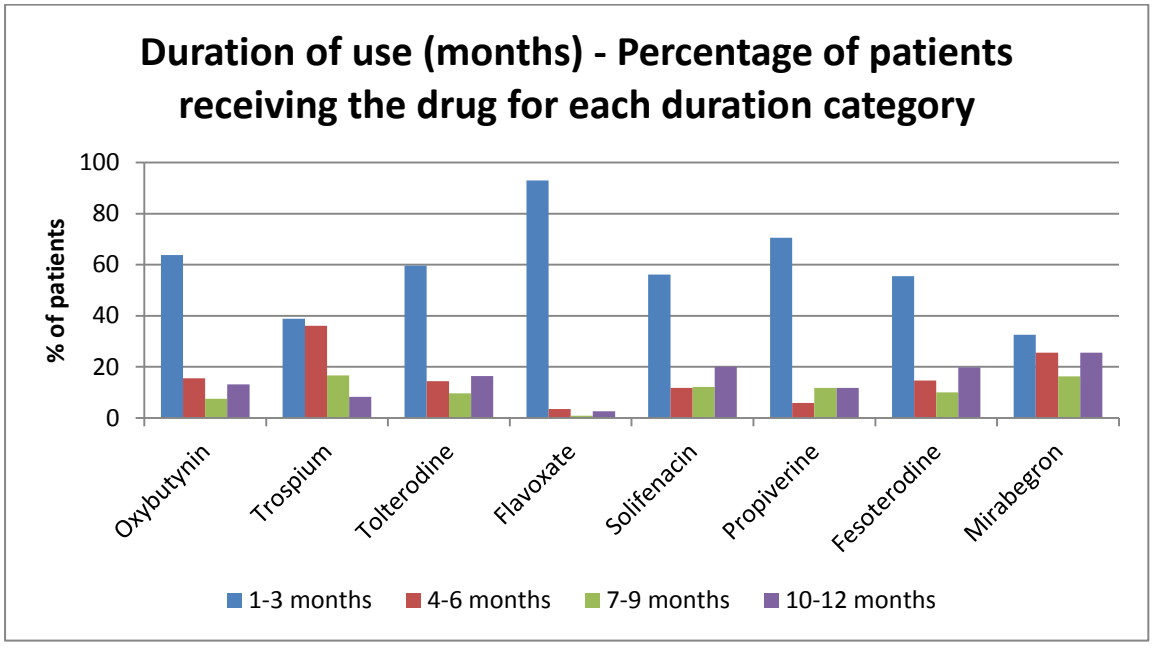

Figure 7. Duration of use (months) in patients who newly initiated drugs for UI, frequency & OAB in May 2013 (GMS)

Figure 8 details the percentages of GMS patients who continued drug treatment for longer than 6 months after commencing treatment in May 2013. [7] As is evident from Figure 8, persistence rates for longer than 6 months are highest with mirabegron (42%) and lowest with flavoxate (3%).

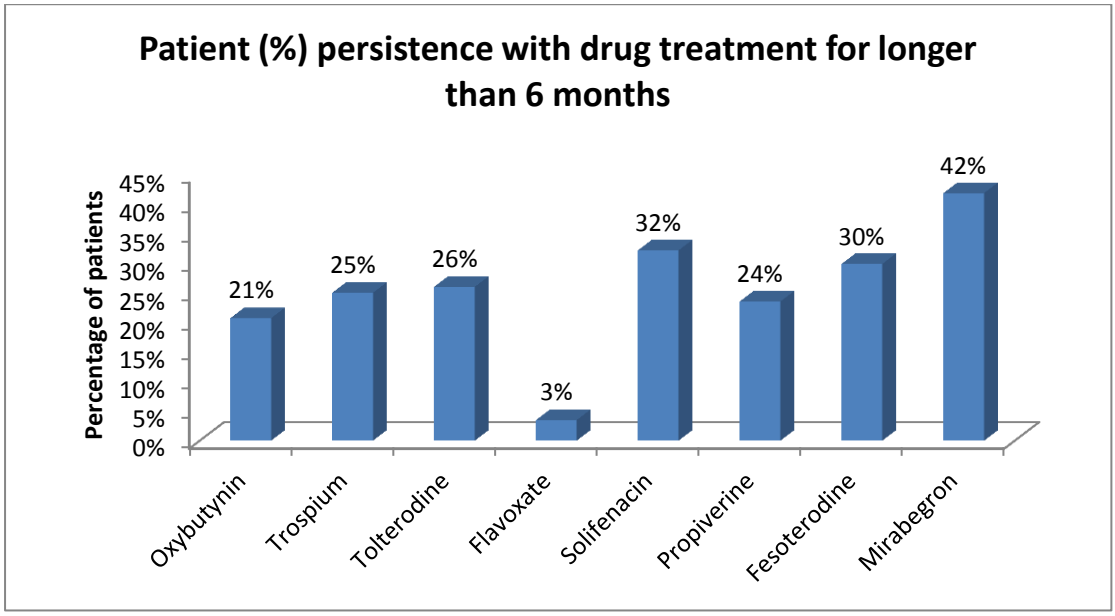

Figure 8. Percentage of patients (GMS) continuing drug treatment for longer than 6 months after initiation.

Figure 9 illustrates the proportion of patients who subsequently received a different drug from this therapeutic class within the 12 months following their initial therapy. Among patients commenced on antimuscarinic drugs who later changed drug, the most common drug therapy to which they switched was mirabegron, except in the case of patients taking flavoxate, who preferentially switched to fesoterodine.[7] There was no apparent favoured antimuscarinic in terms of those switching from mirabegron to another drug for UI, frequency or OAB. [7]

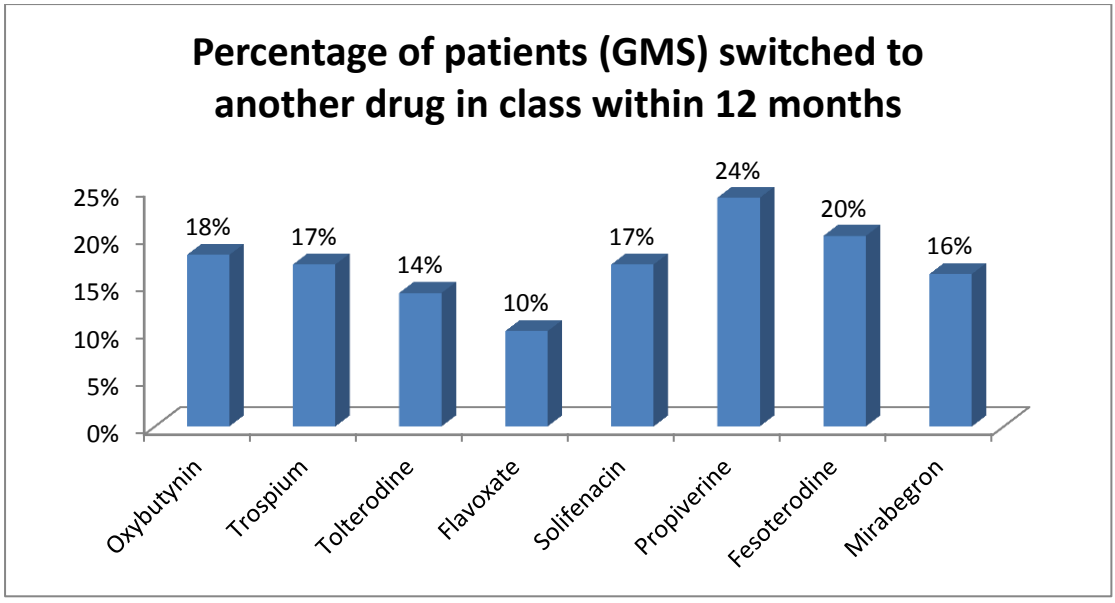

Figure 9. Percentage of patients (GMS) switched to another drug for UI, frequency or OAB within 12 months of starting named drug.

5.5.4 Co-prescribing of potentially interacting drugs

As tolterodine has been associated with possible QT prolongation (see Section 5.2.2), an analysis was performed to determine the prevalence of co-prescribing of drugs known to prolong the QT-interval alongside drugs used for UI, frequency or OAB. Pharmacy claims from July 2013-June2014 were searched to identify incidences of a QT-prolonging drug appearing on the same claim as one for the drugs presently under review. The QT-prolonging drugs included in the analysis were:

- Class IA anti-arrhythmics, i.e. lidocaine, flecainide, quinidine
- Class III antiarrhythmics, i.e. amiodarone, dronedarone, sotalol
- Antipsychotics, i.e. pimozide, haloperidol
- Tricyclic antidepressants, i.e. amitriptyline, clomipramine, dosulepin, doxepin, imipramine, lofepramine, nortriptyline, trimipramine
- Quinolone, i.e. moxifloxacin
- Anti-malarials, i.e. halofantrine, quinine
- Antihistamines, i.e. atemizole, mizolastine
- Atypical antipsychotics, i.e. amisulpiride, sertindole

Overall, 5% of all GMS claims for tolterodine (IR/ER) were associated with the dispensing of a drug known to prolong the QT-interval during the same claim episode. This translated to 6% of tolterodine-receiving patients. Analysis of dispensing claims for oxybutynin (all preparations), fesoterodine and solifenacin found similar overall rates of co-prescribing of drugs known to prolong the QT interval (6%, 5% and 5% of claims, respectively).

Summary – Prescribing trends

Market share

- ✓ Tolterodine, solifenacin and fesoterodine command the greatest shares of the Irish market. The market share of mirabegron is rapidly increasing.

Preferred drug(s): Tolterodine, solifenacin, fesoterodine.

Duration of use

- ✓ Patient persistence with drug therapy for longer than 6 months is highest for mirabegron, solifenacin, fesoterodine and tolterodine, respectively.
- ✓ Less than 25% of Irish patients started on oxybutynin (oral), trospium, flavoxate and propiverine continued on treatment after 6 months.

Preferred drug(s): Mirabegron, solifenacin, fesoterodine, tolterodine

6. Summary

The balance of evidence suggests that there are few clinically meaningful differences between the antimuscarinics in terms of efficacy in the management of symptoms of UI, frequency and OAB. There are a limited number of head-to-head RCTs comparing these drugs and where such RCTs exist, the differences in treatment outcomes between the drugs, though statistically significant, may not be clinically important. While a number of meta-analyses have identified statistically significant differences in efficacy between these drugs,[13, 15, 16, 17] in many cases the differences were modest. International clinical guidelines support this position.[4, 37-39] The AUA suggests that mirabegron appears to be as clinically effective as the antimuscarinics in treating the primary symptoms of UI, frequency and OAB.[4] Clinical efficacy data for mirabegron remains limited as yet limited to placebo-controlled RCTs (Appendix 1). Mirabegron was not included in the systematic reviews and meta-analysis of drugs for UI, frequency and OAB considered for this evaluation.

There is evidence supporting better tolerability of ER and once daily preparations over IR antimuscarinic preparations which require multiple daily doses, though studies have found little difference in discontinuation rates between antimuscarinics. An ER or once-daily antimuscarinic may be preferable to an IR preparation in terms of tolerability, and the available evidence suggests that mirabegron is well tolerated, though its long-term side effect profile is yet unknown.[38] In general, persistence with antimuscarinic treatment for UI, frequency and OAB is poor. A recent systematic review of antimuscarinic drugs found persistence rates ranging between 12% and 39% at 12 months, and between 8% and 15% at 18 months.[24] Owing to mirabegron entering the market in May 2013, long-term Irish pharmacy claims data (longer than 12 months) are not yet available for analysis as part of this evaluation. However, analysis of available Irish claims data by the MMP suggest higher persistence rates (≥25%) for patients prescribed mirabegron, solifenacin, fesoterodine and tolterodine after six months compared to the other drugs under review.[7] As discussed in section 5.5.3, however, the data are limited and it may not be possible to derive meaningful differences between the drugs in terms of persistence with treatment. Adverse effects may play a role in patients discontinuing therapy, but other factors such as perceived treatment failure and 'learning to get by' are also likely factors.

There are significant differences in the associated cost across this group of drugs. Three antimuscarinics (fesoterodine, propiverine and solifenacin) and mirabegron currently remain under patent protection; the four remaining antimuscarinics are available as generic preparations, though not all formulations (e.g. ER/XL) are available in generic form. At the time of publication (October 2014), none of these drugs had undergone reference pricing. The MMP analysis of Irish pharmacy claims data determined that of these drugs, fesoterodine and solifenacin are the most expensive drugs per prescription dispensed on the GMS scheme, both amounting to an estimated mean ingredient cost of €39.00 per dispensing.[7] This is considerably more per prescription than the cost of trospium, tolterodine ER and flavoxate. In June 2014, fesoterodine and solifenacin accounted for 21% and 29% of total expenditure on drugs for UI, frequency and OAB, respectively, on the GMS.[7]

Of the drugs included in this review, solifenacin and tolterodine held the largest GMS market share in June 2014, approximately 23% and 27% respectively, based on the number of claims for that period.[7] Oxybutynin and fesoterodine held approximately 15% and 17% of the GMS market share, respectively, while flavoxate, propiverine and trospium combined held approximately 5% of the market share. These figures are broadly consistent with claims data from the previous 11 months. In June 2014 mirabegron held approximately 14% of GMS market share based on the number of claims,[7] though this figure is likely to have increased since that time based on the rapidly increasing rate of mirabegron prescribing. Given that flavoxate, propiverine and trospium currently command so little market share, none of these drugs was considered for selection as the preferred drug for UI, frequency and OAB.

Based on the MMP's conclusion that there are few clinically important differences between the antimuscarinics in terms of clinical efficacy, and that the adverse effect profiles of the antimuscarinics in general are similar (with the exception of IR/ER oxybutynin, which evidence suggests may be more poorly tolerated), ER tolterodine has been selected as the preferred drug for UI and OAB. This selection has been made primarily on the basis of cost and national prescribing trends, which show tolterodine ER as one of the more commonly prescribed drugs for UI/OAB, with relatively high rates (≥25%) of treatment persistence after

6 months. The selection is in line with the recommendations of international clinical guidelines, which generally recommend an antimuscarinic as first line pharmacological treatment of UI, frequency and OAB, with consideration given to adverse effects, patient preference and cost.[37-40] Generic tolterodine ER is the least expensive of the market leaders. Since July 2014, the HPRA has deemed tolterodine ER products as interchangeable.[41] The MMP recognises that a single antimuscarinic may not suit every patient with UI, frequency or OAB. Where ER tolterodine is not tolerated or is ineffective, a trial of a second antimuscarinic or an alternative formulation such as transdermal oxybutynin, as is suggested in some clinical guidelines,[2, 38] is worthwhile. Similarly, the MMP recognises that mirabegron represents a good treatment alternative where tolterodine ER or other antimuscarinics are ineffective or poorly tolerated, but as yet, the data are too limited to support its selection as the preferred drug for UI, frequency and OAB, particularly given the wealth of information and clinical experience that is available for antimuscarinics.

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53. Herschorn S *et al.* A Phase III, Randomized, Double-blind, Parallel-group, Placebo-controlled, Multicentre Study to Assess the Efficacy and Safety of the b3-Adrenoceptor Agonist, Mirabegron, in Patients with Symptoms of Overactive Bladder. *Urology* 2013; 82: 313-320.

Appendix 1. Pivotal Clinical Trials

Table 2 details some of the pivotal RCTs for fesoterodine, solifenacin and tolterodine. Pivotal RCTs of generic drugs under review are not included in Table 2. With the exception of flavoxate, all were included in the meta-analyses discussed in Section 5.

Table 2. Pivotal clinical trials

Trial	Drug and comparator	Design	Results
Fesoterodine			
Fesoterodine 8 mg vs. tolterodine ER for the treatment of OAB: a head-to-head, randomised, placebo-controlled trial. ***Herschorn S et al, 2010.***[42]	Fesoterodine 8 mg* vs. tolterodine ER 4 mg and placebo. *Following 1-week lead in at 4 mg daily.	12-week, randomized, double-blind, placebo-controlled, head-to-head vs. tolterodine ER. (n=1,712)	Fesoterodine 8 mg was statistically superior to ER tolterodine 4mg & placebo in reducing: • Urge urinary incontinence (UUI) episodes per 24 h after 12 weeks (-1.72, -1.61, -1.46 respectively). • Urgency episodes per 24h (-3.5, -3.1 and -2.0, respectively).
Fesoterodine 8 mg vs. tolterodine ER 4 mg for the treatment of OAB: a head-to-head randomised, placebo-controlled trial. ***Kaplan P et al, 2011.***[43]	Following 1-week lead in at 4 mg daily, patients were randomised to receive fesoterodine 8 mg vs. tolterodine ER 4 mg and placebo.	12-week, randomized, double-blind, placebo-controlled, head-to-head vs. tolterodine ER. (n=2,411)	Fesoterodine 8 mg was statistically superior to tolterodine ER 4mg in decreasing UUI episodes per 24 h, number of micturitions per 24 h and urgency episodes per 24 h after 12 wks. • Mean reduction in UUI episodes per 24 was -1.95, -1.74 and -1.62 for fesoterodine 8

			mg, tolterodine 4 mg ER and placebo, respectively.
Randomized, double-blind, placebo-controlled study of flexible-dose fesoterodine in subjects with overactive bladder. ***Dmochowski RR et al, 2010.***[44]	Fesoterodine 4 mg vs. 8 mg vs. placebo.	12-wk, double-blind, placebo controlled, flexible-dose, multicentre study (n=883).	At week 12, compared to placebo, fesoterodine significantly decreased: • Mean micturitions per 24 h (-2.9 vs. -2.1 respectively); • UUI episodes per 24 h (-1.2 and -1.5, respectively). • Urgency episodes per 24 h (-4.0 vs. -3.0, respectively).
Long-term safety, tolerability and efficacy of fesoterodine treatment in subjects with overactive bladder symptoms. ***Van Kerrebroeck et al, 2010.***[45]	Fesoterodine 4 mg and 8 mg	Up to 2.7 year open label, Flexible dose extension of phase III Study (n=417). Due to an administrative error, only 417 of the 998 patients who partook in the phase III RCT were enrolled.	Significant improvement for all bladder diary variables per 24 h after 2 years (UUI episodes, urgency episodes, micturitions, mean voiding volume). 39% of participants discontinued fesoterodine before or at the primary 24-month study visit. The main reasons for discontinuation were adverse events, withdrawal of consent and insufficient clinical response.
Efficacy of Fesoterodine 8 mg compared to Fesoterodine 4 mg in reducing urgency urinary incontinence (UUI) in subjects with OAB after 12 weeks of treatment. ***Chapple et al, 2014.***[46]	Fesoterodine 4 mg vs. Fesoterodine 8 mg and placebo	12-week, randomised, double-blind, placebo-controlled, parallel-group multinational trial (n=2012).	Fesoterodine 8 mg was statistically superior to fesoterodine 4 mg after 12 weeks in reducing: • Mean number of UUI episodes per 24 h (-3.1 vs. -2.9, respectively).

			• Mean micturitions per 24 h (-3.0 vs. -2.5, respectively). • Urgency episodes per 24 h (-5.0 vs. -4.2, respectively).
Solifenacin			
STAR ***Chapple et al, 2005.*** [47]	Solifenacin 5 mg (optional increase to 10 mg after 4 weeks) vs. ER tolterodine 4 mg	12-week, randomised, double-blind, double dummy, parallel group, flexible dosing, phase IIIb non-inferiority trial (n=1,177).	Solifenacin 5/10 mg was non-inferior ER tolterodine 4 mg with respect to reduction in micturition frequency: (-2.45 vs. -2.24 micturition episodes per 24 h, respectively. • Urgency episodes per 24 h: -2.85 vs. -2.42 respectively. • UUI episodes per 24 h: -1.42 vs. -0.83, respectively. • Incontinence episodes per 24 h: -1.60 vs. -1.11, respectively. 74% of solifenacin-treated patients vs. 67% of ER tolterodine-treated patients experienced a ≥50% reduction in incontinence episodes by study end.
SUNRISE ***Cordoza et al, 2008.*** [48]	Solifenacin 5 mg (with optional increase to 10 mg at week 8) vs. placebo	16-week randomised, double-blind, placebo-controlled rising double dose phase III trial (n=865).	Solifenacin 5/10 mg was significantly more effective than placebo in reducing the mean number of episodes of severe urgency ± incontinence per 24 h from (−2.6 vs. −1.8). Also: • Mean reduction in micturitions per 24 h (-2.1

			vs. -1.3, respectively); • Mean reduction in incontinence episodes per 24 h: -1.7 vs. -1.4, respectively. • Mean reduction in urgency episodes per 24 h: -1.7 vs. -1.3, respectively.
VENUS ***Karram et al, 2009.*** [49]	Solifenacin 5 mg (optional increase to 10 mg at week 4) vs. placebo	12-week randomised, double-blind, placebo controlled, flexible dosing, phase IIIb trial (n=739).	Solifenacin was statistically superior to placebo in reducing: • Mean number of urgency episodes per 24 h: -3.91 vs. -2.73, respectively. • Number of incontinence episodes per 24 h: -2.10 vs -1.24, respectively; • Micturition frequency: -2.67 vs. -1.94, respectively. • 58% vs. 42% of incontinent patients respectively reported no episodes of incontinence at the end of the study. • Median warning time was increased with solifenacin compared to placebo.
VIBRANT ***Vardy et al, 2009.*** [50]	Solifenacin 5 mg (optional increase to 10 mg at week 4) vs. placebo	12-week, randomised, double-blind, placebo-controlled, flexible dosing, phase IV study (n=768).	Significant change from baseline on the OAB-q Symptom Bother scale • 9.4 points difference between solifenacin and

			placebo. Also: • Daily urgency episodes (-3.05 vs. -1.84 respectively) • Incontinence episodes (-1.85 vs. 1.24, respectively) • Frequency (-2.23 vs. -1.36, respectively)
Mirabegron			
Efficacy and Tolerability of Mirabegron, a Beta$_3$-Adrenoceptor Agonist, in Patients with Overactive Bladder: Results from a Randomised European–Australian Phase 3 Trial ***Khullar et al, 2013.***[51]	Following a 2-week single-blind, placebo run-in period, patients were randomised (1:1:1) to receive either mirabegron 50 mg, mirabegron 100 mg, tolterodine ER 4 mg or placebo once daily	12-week multicentre randomised double-blind, parallel-group placebo- and tolterodine-controlled phase 3 trial (1,978).	Mirabegron 50 mg and 100 mg groups demonstrated statistically significant improvements vs. placebo after 12 weeks: • Number of incontinence episodes per 24 h: -1.57, -1.46, -1.17, respectively; • Mean number of micturitions per 24 h: -1.93, -1.77 and -1.34 respectively.
Randomized Phase III Trial of Mirabegron in Patients with Overactive Bladder. ***Nitter VW et al, 2013.***[52]	Following a 2-week single-blind, placebo run-in period, patients were randomised (1:1:1) to receive either mirabegron 50 mg, mirabegron 100 mg, tolterodine ER 4 mg or placebo once daily	12-week multicentre randomised double-blind, parallel-group placebo- and tolterodine-controlled phase 3 trial (n=1,329).	Mirabegron 50 mg and 100 mg groups demonstrated statistically significant improvements vs. placebo after 12 weeks: • Number of incontinence episodes per 24 h: -1.47, -1.63 and -1.13 respectively;

			• Mean number of micturitions per 24 h: -1.66, -1.75 and -1.05, respectively. • Urgency incontinence episodes per 24 h: -1.32, -1.45, -10.89, respectively. • Discontinuations due to adverse effects: 4.1%, 4.4% and 3.7%, respectively.
Phase III, Randomised, Double-blind, Parallel-group, Placebo-controlled, Multicentre Study to Assess the Efficacy and Safety of the b3 Adrenoceptor Agonist, Mirabegron, in Patients With Symptoms of Overactive Bladder. ***Herschron et al, 2013.***[53]	Following a 2-week, single-blind, placebo run-in period, patients were randomised (1:1:1) to receive mirabegron 25 mg, 50 mg, or placebo once daily.	12-week randomised, parallel group, placebo-controlled, double-blind, multicentre, multinational study (n=1,306).	Mirabegron 25 mg and 50 mg groups demonstrated statistically significant improvements vs. placebo after 12 weeks: • Mean number of incontinence episodes: -1.36, -1.38, & -0.96, respectively; • Mean number of micturitions per 24 h: -1.65, -1.60, and -1.18, respectively. • Proportion of responders with 50% reduction in incontinence episodes: 72.8%, 70% and 59.2%, respectively.

Appendix 2. Prescribing Tips and Practice Points

Drugs for Urgency Incontinence, Frequency and Overactive Bladder Syndrome

Preferred Drugs
THE RIGHT CHOICE, RIGHT NOW.
MEDICINES MANAGEMENT PROGRAMME

Background

Urinary incontinence (UI) is the complaint of any involuntary loss of urine. UI can have a significant detrimental impact on the physical, psychological and social wellbeing of a person. In general, UI is approximately twice as common in women as in men, and is more common in older than younger persons. There are three main subtypes of UI:

- **Stress urinary incontinence**: involuntary leakage on effort or exertion, or on sneezing or coughing.
- **Urgency incontinence**: involuntary leakage accompanied by, or immediately preceded by, a sudden compelling desire to pass urine which is difficult to defer (urgency).
- **Mixed urinary incontinence**: involuntary leakage associated with both urgency and also physical stress (exertion, effort, sneezing, or coughing). Mixed UI may be stress or urge dominant.
- **Urinary frequency** usually denotes ≥ 8 micturitions per day during waking hours, though may vary depending on fluid intake, hours of sleep etc.

Overactive bladder (OAB) syndrome is defined as urgency, usually with increased frequency and nocturia, which may occur with or without urgency Incontinence. Troublesome **lower urinary tract symptoms (LUTS)** occur in up to 30% of men over the age of 65 years, and are categorised into voiding, storage or post-micturition symptoms.

Supervised bladder training, pelvic floor exercises, advice on fluid and caffeine intake, and lifestyle advice may all positively impact UI, OAB and LUTS. Pharmacological treatment may also help to improve the symptoms. Antimuscarinics and the beta$_3$ agonist mirabegron are the available drug treatment options for UI, frequency and OAB.

The Preferred Drug for UI, frequency & OAB is TOLTERODINE ER (extended-release).

Tolterodine ER

Dose

Adults (≥18 years) including the elderly: **4 mg once daily**

Where there is significant renal impairment (GFR ≤30 ml/min) or hepatic impairment, reduce the dose to 2 mg daily. Swallow whole with or without food.

The need for continuing antimuscarinic drug therapy should be reviewed every 4–6 weeks until symptoms stabilise, and then every 6–12 months thereafter.

Cautions & Contraindications

- Urinary retention or significant bladder outflow obstruction at risk of urinary retention
- Uncontrolled narrow angle ('closed angle') glaucoma
- Myasthenia Gravis
- Ulcerative colitis, toxic megacolon and gastrointestinal obstructive disorders, e.g. pyloric stenosis
- Risk factors for QT interval prolongation, e.g. congenital QT prolongation, electrolyte disturbances (hypokalaemia, hypomagnesaemia, hypocalcaemia), bradycardia or pre-existing cardiac disease (e.g. cardiomyopathy, arrhythmia, congestive heart failure)
- Concomitant administration with drugs known to prolong the QT interval, e.g. anti-arrhythmic drugs (e.g. amiodarone, sotalol)

Practice Points - Urinary Incontinence, Frequency and Overactive Bladder Syndrome

Preferred Drugs
THE RIGHT CHOICE, RIGHT NOW
MEDICINES MANAGEMENT PROGRAMME

Tips for Treating UI, Frequency and OAB

Categorise: Treat UI on the basis of category, i.e. where there is mixed UI, treat towards the predominant symptom (see categories overleaf) . The use of a bladder diary (or urinary frequency volume chart in men with LUTS) to record symptoms helps in the diagnosis and classification of UI/OAB and can be used to measure improvement on treatment.

Considerations: When starting drug treatment, always take into account factors such as:

- **Patient** – age, frailty, pre-existing contraindications/cautions to drug treatment.
- **Concomitant medications –** check for pharmacodynamic and pharmacokinetic drug interactions.
- **Risk of adverse effects** – some patients may be at greater risk due to age, pre-existing conditions etc.

Discuss with the patient:

- **Expectations of treatment** – set realistic targets. Remember, antimuscarinics and mirabegron treat only the symptoms of UI, frequency and OAB; they are not curative. The benefits of drug treatment may not be seen until 4 weeks after commencing drug treatment .
- The **likelihood of some adverse effects.** Adverse effects such as dry mouth and/or constipation are quite common with tolterodine and antimuscarinics and may be an indication that the drug is beginning to exert an effect. However, some patients may find these adverse effects intolerable.

Monitor for effect:

- Where there is **no/inadequate improvement** in symptoms after at least 4 weeks of treatment, or where **adverse effects are intolerable**, consider switching to an alternative antimuscarinic or mirabegron.
- Review the need for continued treatment every 4-6 weeks until symptoms stabilise and every 6-12 months thereafter (more frequently in elderly patients ≥ 75 years).

The preferred drug for UI, frequency and OAB is **Tolterodine ER**

Refer **women** with UI who have the following symptoms for specialist review:

- Microscopic haematuria (in women ≥ 50 years) or visible haematuria
- Recurrent or persistent UTI in women ≥ 40 years
- Suspected malignant mass of the urinary tract
- Visible symptomatic or palpable bladder after voiding

Refer **men** with LUTS for specialist review if they have:

- Recurrent/persistent UTI
- Urinary retention
- Suspected renal impairment
- Suspected urological cancer

Lifestyle considerations

Caffeine – reducing intake may improve symptoms of urgency and frequency. Suggest limiting caffeine intake.
Fluid intake – while the evidence for fluid restriction is conflicting, it is generally agreed that daily urine output should not be < 1,500 ml and should not exceed 3,000 ml.
Weight – In women, obesity appears to confer a 4-fold increase in the risk of UI. Encourage overweight patients with UI/OAB to lose weight (at least 5%).
Physical exercise – moderate physical exercise is associated with lower rates of UI in middle-aged and older women.