Mirabegron: A Novel Treatment for Overactive Bladder

Timmeda Campbell, PharmD Candidate

Overactive bladder (OAB) is a prominent syndrome that reportedly affects approximately 17% of women and 16% of men in the United States. However, these data likely underestimate the true prevalence of OAB because of underreporting due to patient embarrassment, lack of clinical data, and various definitions of OAB. OAB syndrome is defined by the International Continence Society as the occurrence of urinary urgency usually accompanied by frequency and nocturia with or without urgency urinary incontinence (UUI) in the absence of a known pathologic condition. Although OAB can affect people of all ages, the prevalence increases as the population ages and is anticipated to rise with the aging of the baby boomer generation. People with OAB report symptoms to be bothersome and such symptoms have a significant effect on activities of daily living, quality of life affecting social relationships, and self-esteem leading to embarrassment, anxiety, and depression. OAB is also associated with falls and debilitating injuries which can lead to fractures which increase morbidity, probability of death, and a substantial financial burden.

Currently, antimuscarinics are the first-line drug therapy for OAB in combination with behavioral interventions. Antimuscarinics act by inhibiting the action of acetylcholine at muscarinic cholinergic receptors blocking actions of the parasympathetic nervous system which relaxes the bladder smooth muscle smooth reducing urinary urgency. These agents including oxybutynin, tolterodine, fesoterodine solifenacin, darifenacin, have proved to be the very effective in suppressing premature detrusor contractions, enhancing bladder storage, and relieving UUI symptoms and complications. In general, antimuscarinics are efficacious and well tolerated treatments that improve the health-related quality of life in patients affected by OAB. To date, no significant differences in efficacy have been observed between agents in this class. The most prominent anticholinergic effects of these drugs is xerostomia and constipation. However, many patients are unable to tolerate the associated adverse effects due to their lack of selectivity for the bladder. The discontinuation rate of antimuscarinics within the first 30 days of the first prescription period has been reported as high as 43-83%.

**Editor’s Summary: Mirabegron (Myrbetriq®)**

**Description & Indication**
- β3-adrenergic agonist that works in the human detrusor muscle; activation of the receptors stimulate norepinephrine release and detrusor relaxation
- Approved for treatment of symptomatic OAB

**Dosing**
- 25-50 mg once daily; dose NTE 25 mg/day in those with severe renal impairment (CrCL 15-30 mL/min)

**Efficacy**
- 25-50 mg once daily (approved doses) effective in reducing number of micturitions/24 h, incontinence episodes, and urgency episodes compared with placebo

**Safety**
- Generally well-tolerated with adverse effects in trials occurring at a rate similar to placebo; less anticholinergic AEs relative to tolterodine; minor effect on BP/HR.
Because current drug treatments have significant adverse effects that limit their use, advances in pharmacologic therapies for OAB with different mechanism of actions are being targeted. Mirabegron (Myrbetriq®) is a new drug approved by the FDA in June of 2012 indicated for the treatment of OAB with symptoms of UUI, urgency, and urinary frequency. Mirabegron is the first-in-class \( \beta_3 \)-adrenergic agonist marketed as an alternative to antimuscarinics. The objective of this article is to provide a review of mirabegron’s mechanism of action, pharmacokinetic and pharmacodynamics profile, clinical trial data, and adverse reactions in populations with OAB.

### Pharmacology

OAB occurs when the detrusor muscle in the bladder involuntarily contracts suddenly during urine storage or filling phase of micturition which sometimes lead to UUI. Recently, the discovery of \( \beta_1 \), \( \beta_2 \), and \( \beta_3 \)-adrenergic receptors, in the human detrusor muscle and urothelium led to the discovery of the role of these receptors in the function of normal and neurogenic bladders. Activation of beta-adrenergic receptors from the release of norepinephrine from the sympathetic nerves of the bladder causes detrusor relaxation. Specifically, the \( \beta_3 \)-adrenergic receptor is thought to predominantly mediate bladder smooth muscle relaxation through the activation of adenylyl cyclase to form cyclic adenosine monophosphate (cAMP). Mirabegron selectively agonizes \( \beta_3 \)-adrenergic receptors by activating adenylyl cyclase which increase cAMP. This results in the relaxation of detrusor smooth muscle of the bladder to decrease the frequency of involuntary contractions during the filling phase without inhibiting voluntary bladder contractions during micturition. Ultimately, mirabegron exerts neural control by prolonging the duration of bladder storage instead of targeting the neural control of the voiding phase by blocking muscarinic receptors.

### Pharmacokinetics/Pharmacodynamics

Following oral administration, mirabegron achieves maximum concentrations a few hours after administration (Table 1). Steady state concentrations are achieved after 7 days of once daily dosing of mirabegron. A greater than dose proportional increase in \( C_{\text{max}} \) and AUC is demonstrated after multiple-dose administration of mirabegron. Although mirabegron can be taken safely with or without food with negligible effects on efficacy, the relative bioavailability is affected by food. Low fat meals tend to decrease bioavailability of mirabegron relative to high fat meals, possibly owing to mirabegron’s lipophilic nature. Hepatic metabolism of mirabegron is achieved through multiple pathways of phase I and phase II reactions, involving dealkylation, oxidation, direct glucoronidation, and amide hydrolysis. Mirabegron is the main pharmacological active component at the \( \beta_3 \)-adrenergic receptors. Cytochrome P450 2D6 (CYP2D6) and CYP3A4 isoenzymes play a partial role in the oxidative metabolism of mirabegron in combination with butyrylcholinesterase, uridine diphosphoglucuronosyltransferases (UGT), and possibly alcohol dehydrogenase. Renal elimination of mirabegron is achieved through active tubular secretion and glomerular filtration. Urinary unchanged mirabegron elimination is dose-dependent.

Due to polymorphisms related to CYP2D6, the bioavailability of mirabegron in poor metabolizers is higher with a mean \( C_{\text{max}} \) and AUC increase of 16% and 17%, respectively, compared to extensive metabolizers. The mean urinary fraction of mirabegron is 15.4% in poor metabolizers and 11.7% in extensive metabolizers. In addition to hepatic isoenzyme polymorphisms, the existence of a single nucleotide polymorphism (SNP) in the \( \beta_3 \)-adrenergic receptor of the bladder can alter variability of mirabegron’s action. However, the influence of this polymorphism in relation to mirabegron’s clinical effect in patients with OAB is unknown.

The \( C_{\text{max}} \) and AUC of mirabegron are similar in young and older subjects. However, women exhibit a \( C_{\text{max}} \) and AUC approximately 40% higher than men. After compensating for weight differences, the bioavailability of mirabegron is 20-30% higher in females compared to males. However, no dose adjustments are necessary when treating either gender. No data have been published to date on pharmacokinetics of mirabegron in pediatric patients. The pharmacokinetics of mirabegron is comparable between Caucasians and African Americans. Cross studies comparison showed exposure to be greater in Japanese subjects.
than in North Americans. Although, when $C_{\text{max}}$ and AUC were normalized for dose and body weight, the difference was smaller. $C_{\text{max}}$ and AUC can be affected in patients with hepatic and renal impairment (Table 2).

**CLINICAL EFFICACY**

Clinical data from four pivotal trials have determined the most appropriate dosing, efficacy and tolerability of mirabegron in patients with OAB compared to placebo.16,17,18,20

The BLOSSOM trial, a phase 2a proof-of-concept study, was conducted to determine the efficacy and tolerance of mirabegron at two doses (100 mg twice daily and 150 mg twice daily) in subjects with OAB in comparison to placebo and tolterodine (4 mg four times daily).16 This study was a randomized, double-blind, parallel-group trial that enrolled 260 patients, evenly divided into four groups (placebo, mirabegron 100 mg twice daily, mirabegron 150 mg twice daily, and tolterodine 4 mg four times daily). The primary endpoint was the change in mean number of micturitions per 24 hours. The study included OAB patients with symptoms for ≥ 3 months, at least three recorded episodes of severe urgency, and an average frequency of > 8 voiding episodes in a 24 hour period recorded in a diary 3 days prior to enrollment into the study. The secondary endpoints were the mean volume of urine voided per micturition, mean number of incontinence episodes, mean number of nocturia episodes, and UUI episodes in 24 hour periods. The efficacy data was evaluated based on the information collected in patient micturition diaries, which were completed three days prior to each study visit. Both mirabegron groups showed statistically significant improvement of the primary endpoint, mean urinary frequency per 24 hours, compared to the placebo. Mirabegron groups had a mean difference of 1 micturition per 24 hour compared to placebo, although the mean number of micturitions per 24 hours in each group was not reported. The relative reduction in mean micturition frequency was 17% and 18% at 100 mg and 150 mg doses of mirabegron, compared to 9% for placebo and 11% for tolterodine. Overall, treatment with mirabegron was also statistically superior to placebo with respect to mean volume per micturition, mean number of incontinence episodes, and urgency episodes in a 24 hour period. In both mirabegron groups, the mean volume voided was increased in a dose-dependent manner; this

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of pharmacokinetic profile of mirabegron.14</th>
</tr>
</thead>
</table>
| **Absorption** | . Oral bioavailability: 29-35%  
. Effects of food: (1) $C_{\text{max}}$ decreased from 45-75%; (2) AUC decreased from 17-51%  
. $T_{\text{max}}$: 3.5 hours |
| **Distribution** | . $V_d$: 1670 L (IV)  
. Protein binding: 71% bound to plasma protein with affinity for albumin and α-1 acid glycoprotein  
. Distributes to erythrocytes |
| **Metabolism** | . Hepatic: CYP2D6 and CYP3A4 (limited), butyrylcholinesterase, UGT, alcohol dehydrogenase (possibly) |
| **Excretion** | . Total body clearance: 57 L/hr  
. Half-life ($t_{1/2}$): 50 hours  
. Renal Clearance: 13 L/hr  
. Renal elimination: 6-12% unchanged  
. Urine excretion: 55%  
. Fecal excretion: 34% |

| Table 2 | Changes in mirabegron pharmacokinetics in patients with hepatic and renal impairment.14 |
|---|---|---|
| **Impairment** | **Classification** | **Increase in $C_{\text{max}}$** | **Increase in AUC** |
| **Hepatic** | None | Reference | Reference |
| Mild (Child Pugh Class A) | 9% | 19% |
| Moderate (Child Pugh Class B) | 175% | 65% |
| Severe (Child Pugh Class C) | Not studied | Not studied |
| **Renal** | None | Reference | Reference |
| Mild (CrCl > 60 mL/min) | 6% | 31% |
| Moderate (CrCl 30-60 mL/min) | 23% | 66% |
| Severe (CrCl 15-30 mL/min) | 92% | 118% |
| ESRD (CrCl <15 mL/min) | Not studied | Not studied |
finding was statistically significant in the 150 mg mirabegron group. Urgency and nocturia episodes also were reduced significantly with mirabegron, although the finding was only statistically in the 100 mg group compared to placebo and not the 150 mg mirabegron group.16

The dose-ranging, phase 2b study (DRAGON trial) assessed the efficacy of mirabegron once daily in patients with OAB.17 This 12-week, multicenter, double-blind, parallel-group, placebo and active-controlled trial used similar inclusion criteria to the BLOSSOM trial and included 919 patients randomly assigned to placebo or mirabegron once daily at a dose of 25, 50, 100, or 200 mg. The primary outcome of this trial was also to determine dose-dependent reductions in the mean number of micturitions per 24 hours. Secondary outcomes were the same as in the aforementioned BLOSSOM trial. All efficacy data was accessed by patient recorded micturition diaries. The difference in the primary efficacy outcome was statistically significant between mirabegron and placebo, ranging from 1.9 to 2.2 micturitions/24h, against placebo with 1.4 micturitions/24h (Table 3). Mirabegron also caused an increase in mean volume voided per micturition and decreased all other secondary parameters compared to placebo.

The European-Australia phase III trial studied the efficacy and tolerability data for mirabegron in patients in Europe and Australia.18 The method design for inclusion criteria was identical to the aforementioned phase 2 trials. However, patients (n=1978) were randomly assigned to receive placebo, a once daily dose of mirabegron 50 mg or mirabegron 100 mg, or tolterodine slow-release 4 mg once daily for 12 weeks. The co-primary endpoints were the change from baseline to final visit in the mean number of incontinence episodes and micturitions in 24 hours. Efficacy data were collected through patient micturition diaries. At the final visit, both mirabegron groups demonstrated statistically significant improvements from baseline compared to placebo in the number of urgency incontinence and micturitions per 24 hours. In contrast, tolterodine produced a non-significant decrease in episodes of incontinence (-1.27) and micturitions (-1.58) in a 24 h period from baseline.19

The North-American phase III trial studied the efficacy and safety of mirabegron in patients with OAB in the United States and Canada.20 This trial replicated the study design and inclusion criteria of the European-Australian phase III trial. A total of 1328 subjects were studied and randomly assigned to three groups: mirabegron 50 mg, mirabegron 100 mg, or placebo. Mirabegron 50 mg and 100 mg caused a statistically significant greater reduction in the primary co-endpoints of incontinence episodes and number of micturitions in 24 hours compared to placebo at the final 12-week visit. This significant decrease in the primary co-endpoints between mirabegron groups and placebo was found as early as 4 weeks. Secondary endpoints also improved more in the mirabegron study groups compared to placebo.

### Adverse Effects

The incidence of adverse effects was similar across the treatment groups in both phase 3 trials. The incidence of any adverse event in the North American trial was 50.1%, 51.6%, and 46.9% for placebo, mirabegron 50 mg, and mirabegron 100 mg.20 The European-Australian trial reported the incidence of any adverse event as 43.4%, 42.8%, 40.1%, and 46.7% in the placebo, mirabegron 50 mg, mirabegron 100 mg, and tolterodine treatment groups, respectively (Table 4).18 The most common adverse effects, occurring in ≥ 3% of mirabegron treated patients in clinical trials and with a greater incidence than placebo were hypertension, urinary tract infection, nasopharyngitis, headache, and dry mouth.14

Mirabegron has not been shown to affect urodynamics in patients with OAB.14 The mean maximum flow rate and mean detrusor pressure at maximum flow rate effects of mirabegron was studied in patients with lower urinary tract symptoms (LUTS) or bladder outlet obstruction (BOO) and no adverse effects were discovered.14 However, risks or mirabegron should be assessed in patients with clinically significant BOO and/or LUTS. Post-marketing of urinary retention has been reported in patients with BOO and in patients taking antimuscarinic medications for the treatment of OAB in patients taking mirabegron.14 Due to the risk of urinary tract infections found in clinical trials, mirabegron should be used with caution in patients with urinary retention with BOO and taking antimuscarinics for the treatment of OAB.14 Slight increases in heart rate and blood pressure have been noted with mirabegron use. This effect is thought to be associated with mirabegron possibly acting at β3-adrenoreceptors on myocardium and skeletal muscles.13 Mirabegron was shown to increase heart rate on ECG in a dose dependent manner. Mean increase from baseline in heart rate for the 50 mg, 100 mg, and 200 mg dose groups compared to placebo were 6.7 beat per minute (bpm), 11 bpm, and 17 bpm, respectively.14 Clinical efficacy and safety studies...
### Table 3: Summary of mirabegron clinical efficacy data.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>M 25</th>
<th>M 50</th>
<th>M 100</th>
<th>M 150</th>
<th>M 200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micturitions/24 h (primary)</td>
<td>-1.4</td>
<td>-1.9</td>
<td>7.3</td>
<td>15.3</td>
<td>35.6</td>
<td>55.3</td>
</tr>
<tr>
<td>Volume voided per micturition/24 h (mL)</td>
<td>-0.5</td>
<td>-0.5</td>
<td>-0.5</td>
<td>-0.5</td>
<td>-0.5</td>
<td>-0.5</td>
</tr>
<tr>
<td>Incontinence episodes</td>
<td>-0.4</td>
<td>-0.4</td>
<td>-0.4</td>
<td>-1.3</td>
<td>-1.3</td>
<td>-2.3</td>
</tr>
<tr>
<td>Urgency episodes (grade ≥ 3)</td>
<td>-1.1</td>
<td>-1.1</td>
<td>-1.1</td>
<td>-1.1</td>
<td>-1.1</td>
<td>-1.1</td>
</tr>
<tr>
<td>Co-primary endpoints at final visit</td>
<td>-1.17</td>
<td>-1.17</td>
<td>-1.17</td>
<td>-1.17</td>
<td>-1.17</td>
<td>-1.17</td>
</tr>
<tr>
<td>Volume voided/micturition (mL) at final visit</td>
<td>12.3 (1.99)</td>
<td>24.2 (2.01)</td>
<td>25.6 (2.00)</td>
<td>25.6 (2.00)</td>
<td>25.6 (2.00)</td>
<td>25.6 (2.00)</td>
</tr>
<tr>
<td>Number of micturitions/24 h</td>
<td>3.4 (0.110)</td>
<td>3.4 (0.111)</td>
<td>3.4 (0.111)</td>
<td>3.4 (0.111)</td>
<td>3.4 (0.111)</td>
<td>3.4 (0.111)</td>
</tr>
<tr>
<td>Number of incontinence episodes</td>
<td>1.1 (0.119)</td>
<td>1.1 (0.119)</td>
<td>1.1 (0.119)</td>
<td>1.1 (0.119)</td>
<td>1.1 (0.119)</td>
<td>1.1 (0.119)</td>
</tr>
<tr>
<td>Number of micturitions/24 h at Day 4</td>
<td>-0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Number of micturitions/24 h at Week 4</td>
<td>-0.10</td>
<td>0.10</td>
<td>0.10</td>
<td>0.10</td>
<td>0.10</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Effects on diastolic blood pressure were also shown to be dose-dependent. Upon discontinuation, systolic and diastolic blood pressure increases are reversible. Mirabegron does not appear to affect intraocular pressure. Since mirabegron increase blood pressure, it should be monitored in hypertensive patients taking mirabegron. However, mirabegron is not recommended in patients with severe uncontrolled hypertension, defined as a systolic blood pressure ≥ 180 mm Hg or diastolic blood pressure ≥ 110 mm Hg.

The most frequent adverse effects that led to discontinuation in clinical trials for the approved doses of mirabegron 25 mg or 50 mg were nausea, headache, hypertension, diarrhea, constipation, dizziness, and tachycardia (Table 5). Atrial fibrillation (0.2%) and prostate cancer (0.1%) were reported as serious adverse events by more than one patient at a rate greater than placebo but the rate was not found to be significant between mirabegron and placebo treated patients.

Other adverse reactions that were reported <1% includes palpitations, glaucoma, gastrointestinal disorders (dyspepsia, gastritis, abdominal distention), infections (sinusitis, rhinitis), increased liver function tests, bladder pain, nephrolithiasis, vaginal infections/pruritus, and mild skin reactions (urticarial, rash, lip edema).

### Drug Interactions

Since mirabegron is a moderate substrate of CPY2D6, competitive inhibition can occur with concomitant use with other drugs that are metabolized by CYP2D6. Therefore, appropriate monitoring is necessary when these drugs are co-administered with mirabegron due to the possible increase in systemic exposure of either drug which can lead to adverse effects. Some of these drugs include (but are not limited to) desipramine, metoprolol, propafenone, thioridazine, flecainide.

Mirabegron increases the Cmax (1.01 to 1.3 ng/mL [29% increase]) and AUC (16.7 to 19.3 ng·h/mL [27% increase]).
increase) of digoxin when given in combination. Since digoxin is a narrow therapeutic drug, careful monitoring of serum digoxin levels and digoxin titration is recommended when taken in conjunction with mirabegron.

The systemic exposure of warfarin is also increased when administered with mirabegron with an approximate increase in Cmax of 4% and AUC by 9% after multiple dose of mirabegron. However, no effect on INR or prothrombin time was found after a single dose administration of 25 mg of mirabegron. More extensive data are needed to determine the effects of mirabegron on the pharmacodynamic profile of warfarin. Drug studies investigating the pharmacokinetic effects of both mirabegron and co-administered drugs were conducted with ketoconazole, rifampin, solifenacin, tamsulosin, and oral contraceptives. These studies concluded that no dose adjustments are necessary when these drugs are taken with mirabegron.

The study participants in the clinical trials which investigated the safety and efficacy of mirabegron were homogenous; thus, mirabegron’s use in special populations should be reviewed upon initiation (Table 6).

**Dosing Recommendations**

The FDA approved strengths of mirabegron are 25 or 50 mg. The initial recommended dose of mirabegron is 25 mg once daily with or without food. Efficacy of the 25 mg dose should be seen within 8 weeks. An increase in dosage to 50 mg once daily is optional based on patient-specific tolerability and effectiveness.

Mirabegron doses should not exceed 25 mg in patients with severe renal impairment (CrCl 15-30 ml/min) or moderate hepatic impairment (Child-Pugh Class B). Dosing in patients with ESRD (CrCl < 15 ml/min) and severe hepatic impairment (Child-Pugh Class C) is not recommended.

**Cost Comparison**

Mirabegron was recently FDA approved for OAB and is only available as the brand, Myrbetriq®. Thus, the relative cost of mirabegron is expected to be higher in contrast to the standard of care with antimuscarinics. Table 7 summarizes the cost, using cash prices (non-insurance), of a once daily, 30-day supply of Myrbetriq.
betriq® and other antimuscarinic drugs at the lowest available strength on the market for the treatment of OAB.

CONCLUSIONS

Mirabegron is the first β3-adrenergic agonist approved by the FDA for the treatment of OAB. Unlike, antimuscarinics, it causes relaxation of the detrusor smooth muscle in the bladder resulting in a decrease in involuntary contractions and urinary frequency without causing anticholinergic side effects. On the other hand, mirabegron can slightly increase blood pressure and heart rate and should be used with caution in patients with hypertension. Additional comparative trials between mirabegron and specific antimuscarinics are necessary to determine the relative superiority or inferiority in efficacy and tolerability in OAB patients. However, mirabegron is a viable option as an alternative in OAB patients who cannot tolerate antimuscarinic therapy.

REFERENCES


Table 6  | Considerations for mirabegron use in special populations.14

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Special Considerations</th>
</tr>
</thead>
</table>
| Pregnancy          | · Pregnancy Category C: mirabegron has not been adequately studied in pregnant women therefore benefits should outweigh potential risks to the patient and fetus upon initiation  
· Based on animal data, mirabegron is predicted to have a low probability of increasing the risk of fetal development at recommended doses. |
| Nursing Mothers    | · Mirabegron is predicted to be excreted in human breast milk; no studies have been conducted to assess the impact of mirabegron on breast-fed children and therefore a decision to discontinue the drug or breastfeeding should be taken into account. |
| Renal Impairment   | · Mirabegron is not recommended in patients with ESRD (CrCl <15 ml/min).  
· Dose adjustments are necessary for patients with severe renal impairment (CrCl 15-30 ml/min). See Dosing Recommendations. |
| Hepatic Impairment | · Mirabegron is not recommended in patients with severe disease (Child-Pugh Class C).  
· Dose adjustments are necessary in patients with moderate disease (Child-Pugh Class B). |

Table 7  | Cost comparison of once-daily, 30-day supply of mirabegron and common alternative agents at lowest available strength.

<table>
<thead>
<tr>
<th>Product</th>
<th>UCH</th>
<th>Walgreens</th>
<th>Costco</th>
<th>King Soopers</th>
<th>Average cost/month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirabegron (Myrbetriq®) 25mg</td>
<td>$230.18</td>
<td>$256.99</td>
<td>n/a</td>
<td>$235.69</td>
<td>$235.69</td>
</tr>
<tr>
<td>Oxybutynin XL 5 mg⁷</td>
<td>$93.78</td>
<td>$89.99</td>
<td>$42.84</td>
<td>$76.69</td>
<td>$75.83</td>
</tr>
<tr>
<td>Tolterodine (Detrol LA®) 2 mg</td>
<td>$188.93</td>
<td>$235.99</td>
<td>$198.19</td>
<td>$202.19</td>
<td>$206.33</td>
</tr>
<tr>
<td>Trospium XR 60 mg⁷</td>
<td>$207.10</td>
<td>$209.99</td>
<td>$217.39</td>
<td>$180.89</td>
<td>$203.84</td>
</tr>
<tr>
<td>Darifenacin (Enablex®) 7.5 mg</td>
<td>$166.09</td>
<td>$205.99</td>
<td>$175.49</td>
<td>$168.29</td>
<td>$178.97</td>
</tr>
<tr>
<td>Solifenacin (Vesicare®) 5 mg</td>
<td>$206.05</td>
<td>$229.99</td>
<td>$228.79</td>
<td>$221.09</td>
<td>$221.48</td>
</tr>
</tbody>
</table>

All prices are cash prices without insurance.  
⁷Costco cash price was unavailable. Patient price was estimated to be >$200. Average was calculated without Costco price.  
⁸Generic medication price used.

Risks of NSAIDs and NSAID Use in High-Risk Patients

Jason Medeiros, PharmD Candidate

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are associated with over 100,000 hospitalizations and 16,500 deaths in the US per year.1 Despite this, NSAIDs are widely used in the treatment of inflammatory pain and musculoskeletal disorders, with over 100 million prescriptions written yearly, and an estimated $2 billion spent on over-the-counter NSAIDs.2 Some studies have suggested a minor risk (9 patients per 100,000 per year) of NSAID-induced hepatotoxicity.3 Studies have also implicated NSAIDs in raising systolic blood pressure by 4 to 6 mm Hg in hypertensive patients.4 Case reports have linked NSAIDs to CNS and dermatologic complications.5,6 However, the most clinically meaningful adverse effects of the NSAIDs are gastrointestinal, cardiovascular, and renal complications. This article will review risk factors for patients at high risk for gastrointestinal, cardiovascular, and renal complications, and how that risk can be mitigated.

GASTROINTESTINAL COMPLICATIONS

NSAIDs damage the GI tract by two major mechanisms—first, by direct irritation of the gastric mucosa (mainly associated with more acidic NSAIDs such as aspirin), and second, by means of inhibition of prostaglandin synthesis.7 Prostaglandins are products of COX enzymes 1 and 2, which are inhibited by NSAIDs. Prostaglandins are major mediators of inflammation but also promote thickening of, and the blood flow to, the protective mucus layer on the lining of the GI tract. Furthermore, prostaglandins stimulate bicarbonate secretion to buffer the acidic pH in the stomach. These beneficial effects are primarily conferred by prostaglandins produced via COX-1 and are abated by NSAID-mediated COX inhibition, predisposing the patient to ulceration. Even “enteric coated” or parenteral NSAIDs can still lead to ulceration if systemic absorption of NSAIDs is sufficient, due to the systemic effects of prostaglandin inhibition.8 For example, topical diclofenac (Voltaren® gel, Flector® patch, Pennsaid® lotion), which has very little systemic absorption, does not appear to have significant GI adverse effects beyond dyspepsia, nausea, or constipa-
tion. These effects were reported in 1.4% of 967 patients vs. 1.6% of 851 patients on placebo (p = 0.47, not significant) in one trial.\(^9\)

Between 10% and 30% of patients on chronic NSAID therapy may develop ulcer disease.\(^10\) Moreover, 2-4% of long-term NSAID users develop complicated ulcer disease (GI bleeding or perforation).\(^11\) A large meta-analysis showed an overall hazard ratio of 2.74 (95% CI 2.54-2.97) for adverse GI effects related to NSAID use.\(^12\) The hazard ratio was even higher for specific risk populations, notably adults aged 60 or greater (HR 5.52; 95% CI 4.63-6.60), patients with a prior history of GI events (HR 4.76; 95% CI 4.05-5.59), and patients taking concomitant corticosteroids (HR 1.83; 95% CI 1.20-2.78). These data indicate an approximate 2-6 fold increase in risk for GI complications associated with NSAIDs for certain risk groups and an approximate 3-fold increase in risk for all persons. A retrospective cohort study of over 100,000 Tennessee Medicaid patients aged 65 and older found a 13-fold increased risk (95% CI 6.3-25.7) of hemorrhagic peptic ulcer disease in patients using NSAIDs while on concurrent anticoagulant therapy.\(^13\) High dose NSAID therapy (e.g., ibuprofen ≥ 3600 mg/day, naproxen ≥ 1500 mg/day) was shown to have an 8-fold increased risk of peptic ulcer disease (95% CI 4.4-14.8).\(^14\) Low-dose aspirin has also been shown to increase the risk of GI bleeding.\(^15\)

Practice guidelines for the prevention of GI complications from NSAID therapy have incorporated many of the risk factors implicated in the literature into a risk stratification algorithm.\(^16\) A patient is classified as high, moderate, or low risk based upon the number of risk factors present. However, a prior history of any complicated GI ulcer automatically places a patient at high risk. The risk factors and patient risk stratification are summarized in Table 1 below. H. pylori infection is not included in the table as a risk factor, but evidence suggests that eradicating the infection does reduce a patient’s ulcer risk.\(^17\) This table also omits cardiovascular disease, which was shown to be associated with an increased risk (HR 1.84; p = 0.027) of NSAID-induced GI complications.\(^18\)

Several strategies help prevent GI complications or mitigate the risks of NSAID therapy. For all patients taking NSAIDs, regardless of risk, the lowest effective dose necessary should be used. For patients at moderate or high risk for GI complications, NSAID therapy should include adjunctive therapy with an acid suppressing agent, such as misoprostol or a proton pump inhibitor (PPI).\(^16\) For patients at high risk for NSAID-induced GI complications, NSAIDs should be avoided, if possible.\(^16\)

Although PPIs and misoprostol have comparable efficacy in preventing GI bleeding complications, PPIs are most commonly used, largely because of misoprostol’s adverse effect profile and more complex regimen.\(^19\) Misoprostol is commonly associated with intolerable diarrhea and cramping, whereas PPIs are not. However, PPIs are not entirely benign themselves, and recent data suggest an associated increased risk for pneumonia and Clostridium difficile infection.\(^20,21\) Alternative acid-suppressing medications, notably H\(_2\) receptor antagonists, have also been studied as potential alternative agents to PPIs. The data suggest that H\(_2\) receptor antagonists do reduce the risk of NSAID-induced ulcers, but only at high doses (famotidine 40 mg twice daily being the typical regimen studied).\(^22\) Importantly, H\(_2\) antagonists lose their ability to increase the pH over time.\(^23\)

Although some data suggest that COX-2 selective NSAIDs (e.g., celecoxib) have lower GI risk than non-selective agents, as a result of preserving COX-1’s function,\(^11\) other data suggest the risk of GI complications is no different than non-selective NSAIDs. Although COX-2 specific inhibitors reduce endoscopically-detected ulcerations, recent data suggest that COX-2 inhibitors do not actually reduce clinically-relevant GI risk. A study of 6,219 NSAID patients showed a 39% decreased risk of GI complications using COX-2 inhibitors versus nonselective NSAIDs, however the difference was not significant (95% CI 0.34-1.09).\(^24\) Similar to celecoxib, other NSAIDs that are considered COX-2 preferential, such as meloxicam, etodolac, and nabumetone, are thought to have lower GI risk profiles.\(^25\) Some research has shown meloxicam to be as-

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**Table 1 | Risk stratification for NSAID-induced GI complications.\(^16\)**

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Moderate Risk (1 to 2 risk factors)</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>- No risk factors present</td>
<td>- Age &gt; 65 years(^a)</td>
<td>- History of previously complicated ulcer (especially recent)</td>
</tr>
<tr>
<td>- High dose NSAID therapy</td>
<td>- High dose NSAID therapy</td>
<td>- More than 2 moderate risk factors</td>
</tr>
<tr>
<td>- Previous uncomplicated ulcer</td>
<td>- Previous uncomplicated ulcer</td>
<td></td>
</tr>
<tr>
<td>- Concurrent use of aspirin (including low-dose), anticoagulants, or corticosteroids</td>
<td>- Concurrent use of aspirin (including low-dose), anticoagulants, or corticosteroids</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)The age group found to be at high risk for GI complications in the studies was age > 60
associated with less GI bleeding compared to ibuprofen, diclofenac, piroxicam, or indomethacin (0.08% on meloxicam vs 0.50% on other NSAIDs; P = 0.007). This study also showed an overall reduction in adverse GI effects (1.80% vs 3.20%; P = 0.003). Additionally, a meta-analysis of nabumetone versus comparator NSAIDs showed a risk of 0.03% of GI perforations, bleeds, and ulcers (95% CI 0.0-0.08) compared to 1.4% (95% CI 0.5-2.4) on other NSAIDs. It is worth noting that the difference in COX-2 selectivity between “COX-2 inhibitors” (i.e., celecoxib) and “COX-2 preferential agents” (e.g., meloxicam) is very modest and may not be of clinical significance.

Although celecoxib in combination with a PPI or misoprostol is recommended by national guidelines for use in high risk patients, if an NSAID is needed, caution must be exercised given the risk of GI complications still exists with COX-2 selective NSAIDs. For all patients at high risk for GI complications, alternatives to NSAIDs should be used if possible, such as tramadol, acetaminophen, topical analgesics, and opioids.

### Cardiovascular Complications

The mechanism of NSAID cardiotoxicity is not fully understood, but is thought to be related to an imbalance between prostacyclin and thromboxane A2 (both mediators generated from COX enzymes) leading to an increase in thrombotic events. Additionally, this same proposed mechanism is attributed to accelerated atherosclerosis, vasoconstriction and increased blood pressure. Selective COX-2 inhibitors in particular have been implicated in causing cardiotoxicity. As a result of post-marketing studies finding cardiotoxicity, the COX-2 selective NSAID rofecoxib (Vioxx®) was pulled from the market. Similarly, celecoxib, despite its allegedly lower GI risk, was also suggested to increase the risk of a composite endpoint of CV death, MI, stroke, or heart failure. However, the increased CV risk is not limited to COX-2 selective NSAIDs.

A large meta-analysis showed an increased risk of cardiovascular events with several different NSAIDs, including COX-2 selective and non-selective NSAIDs. Patients had a significantly higher incidence of MI using rofecoxib (HR 2.12, 95% CI 1.26-3.56). Similarly, stroke risk was significantly increased with diclofenac (HR 2.86; 95% CI 1.09-8.36). Ibuprofen was also associated with a large increase in stroke risk that was not quite statistically significant (HR 3.36; 95% CI 1.00-11.6). Naproxen had a nonsignificant 76% increased risk of stroke (HR 1.76; 95% CI 0.91-3.33). Risk of CV death was significantly increased by 298% for patients on diclofenac (HR 3.98; 95% CI 1.48-12.7). Lastly, celecoxib was associated with a 50% increased risk of all-cause mortality but this was not significant (HR 1.5; 95% CI 0.96-2.54). A composite outcome for overall CV risk showed overall risk increases for ibuprofen (HR 2.26; 95% CI 1.11-4.89) which was statistically significant. This composite analysis also suggested that naproxen might actually be less harmful than other NSAIDs in terms of overall cardiovascular events (HR 1.22; 95% CI 0.78-1.93) as it carried the lowest risk of the drugs studied and was not significantly increased.

Of the NSAIDs, only aspirin has no increased risk of CV events and instead conveys protective CV properties. However, other NSAIDs can negate aspirin’s positive effects, by preventing aspirin from irreversibly inhibiting platelet function. For patients taking aspirin for primary or secondary prevention, aspirin should be dosed at least two hours before the other NSAID, to prevent the drug interaction and allow aspirin’s irreversible antiplatelet effect. Recommendations for NSAID treatment based on a patient’s GI and CV risks are summarized below in Table 2.

### Renal Complications

Acute renal failure has also been linked with NSAID use. A case-control study of over 120,000 elderly patients diagnosed with acute kidney injury demonstrated that patients who had used NSAIDs within the last 30 days were at nearly twice the risk (95% CI 1.61-2.60) for acute kidney injury compared to patients who had not taken NSAIDs in the past 30 days.

### Table 2 | NSAID therapy recommendations based on risk.

<table>
<thead>
<tr>
<th>Low GI risk</th>
<th>Moderate GI risk</th>
<th>High GI risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low CV risk</td>
<td>NSAID alone&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NSAID + PPI or misoprostol</td>
</tr>
<tr>
<td>High CV risk&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Use alternative therapy (preferred); Reserve naproxen + PPI or misoprostol as last line</td>
<td>Avoid NSAID therapy, use alternative</td>
</tr>
</tbody>
</table>

<sup>a</sup>Least ulcerogenic at lowest effective dose.
<sup>b</sup>Defined as requiring low-dose aspirin.
The risk of renal failure was no different with non-selective or COX-2 selective NSAIDs. The mechanism of renal toxicity, like the mechanism of GI toxicity, is linked to the inhibition of prostaglandin formation. Prostaglandins act as vasodilators in the glomerular afferent arteriole, maintaining blood flow into the nephron. Inhibition of prostaglandin synthesis via COX inhibition decreases this vasodilatory effect, reducing blood flow to the kidney and therefore reducing GFR. The risk of renal failure is greater in persons whose renal function is more dependent upon prostaglandins, such as those with altered fluid volume as a result of heart failure, liver disease, or diuretic use. NSAIDs are not strongly linked to chronic kidney disease (CKD); however, excessive doses of NSAIDs over an extended period of time, particularly in elderly patients, may exacerbate declining renal function.

For patients with chronic kidney disease, the benefits of NSAID therapy must be weighed against the risk of renal decline, and the smallest effective dose should be used for the shortest possible duration. However, in the absence of CKD or risk factors for acute kidney injury (e.g., CHF, hypertension, advanced age, or reduced intravascular volume), NSAIDs at lower therapeutic doses (e.g., ibuprofen 200-800 mg/day) do not seem to pose a large renal risk.

## Conclusion

While NSAIDs represent an efficacious and cost-effective means of managing many types of musculoskeletal and inflammatory pain, they pose significant risks, including GI bleeding, cardiovascular events, and renal complications. Patients found to have 1 or 2 risk factors for GI bleeding complications should use a PPI concurrently when NSAID therapy is needed. Patients with more than 2 risk factor or a history of complicated GI ulcers should ideally use alternatives to NSAIDs; a PPI with a COX-2 selective NSAID is considered a last line agent because of the GI bleeding risks. Patients on low-dose aspirin for CV protection are considered high risk for CV events, thus, alternatives to NSAIDs should be used; naproxen with a PPI is considered a last line agent because of the CV risks. Given renal function can decline with NSAID therapy, careful evaluation of the risks and benefits of NSAID therapy in patients with renal impairment is necessary. In all cases, the lowest NSAID dose necessary for the shortest amount of time should be used.

### References

19. Graham DY, et al. Ulcer prevention in long-term users of


