



## **Indiana Medicaid Therapeutics Committee** **Therapeutic Class Review Summary**

### **Therapeutic Class:**

Urinary Tract Antispasmodic Agents

### **Overview:**

Urinary tract antispasmodic agents are used to treat overactive bladder, urinary urgency, and urinary incontinence in ambulatory populations. Overactive bladder (OAB) syndrome is a clinical condition characterized by chronic urinary symptoms, including increased frequency of micturition and increased urge incontinence. The symptoms of OAB are thought to result from involuntary contractions of the detrusor muscle during bladder filling. Human bladder tissue contains M<sub>2</sub> and M<sub>3</sub> muscarinic receptors. M<sub>3</sub> receptors have been identified as the primary mediator of detrusor contraction in response to cholinergic activation. The M<sub>2</sub> receptors are greater in density (~80%), but their role has not yet been fully evaluated.

The urinary tract antispasmodic agents include antimuscarinic anticholinergics – oral, transdermal, and topical oxybutynin chloride, tolterodine tartrate, trospium, solifenacin succinate, darifenacin hydrobromide, fesoterodine fumarate – and flavoxate. Several studies have demonstrated the efficacy of oxybutynin in the treatment of overactive bladder with oxybutynin achieving more than 50% relief of symptoms. The side effect profile with oxybutynin represents typical antimuscarinic properties, with the most common adverse event being dry mouth. Controlled-release oxybutynin (dosed once daily) appears to be as efficacious as immediate release oxybutynin, with the primary benefit being a decrease in anticholinergic side effects compared to the immediate release formulation. The occurrence of dry mouth decreased by approximately 35-40% with the controlled release product. In February 2003, a transdermal patch delivering 3.9 mg/day of oxybutynin was introduced. Tolerability of the patch is comparable to controlled release oxybutynin with the exception of application site reactions such as erythema, rash and/or itching. In January 2009, oxybutynin topical gel was approved by the FDA. The tolerability of the gel is similar to the transdermal patch with dry mouth and application site reactions being the most common adverse events. Tolterodine has more selectivity than oxybutynin for the muscarinic receptors in the bladder smooth muscle. Tolterodine has

demonstrated equivalent efficacy to oxybutynin in reducing symptoms related to OAB with fewer adverse effects. A comparison of controlled release tolterodine (dose once daily) to immediate release tolterodine (dose twice daily) demonstrated equivalent efficacy with a lower incidence of dry mouth with the extended release product. When controlled release tolterodine was compared to controlled release oxybutynin, the results showed equal efficacy and slightly fewer side effects than the controlled release oxybutynin. Trospium is available as an immediate-release tablet dosed twice daily and an extended-release tablet dosed once daily. Trospium appears to have efficacy equivalent to oxybutynin and tolterodine with possibly fewer adverse events. Solifenacin, darifenacin, and fesoterodine are the newest antimuscarinics. Darifenacin is classified as an M<sub>3</sub> selective receptor antagonist; both solifenacin and darifenacin have demonstrated efficacy in the treatment of OAB. Fesoterodine, the most recently approved antimuscarinic, has also been proven efficacious in the treatment of OAB. A study comparing solifenacin to tolterodine ER was published in September 2005. In the primary efficacy analysis (change in mean number of micturitions per 24 hours), solifenacin demonstrated non-inferiority to tolterodine ER. In the analysis of several secondary efficacy endpoints, solifenacin demonstrated statistical significance over tolterodine ER. However, solifenacin had a higher incidence of dry mouth and constipation; p-values were not reported. More large, randomized, well-designed head-to-head comparisons are needed to determine the comparative adverse event profiles of oxybutynin, tolterodine, trospium, solifenacin, darifenacin, and fesoterodine.

Flavoxate hydrochloride counteracts smooth muscle spasms of the urinary tract and has been used for urge incontinence. Flavoxate has a weak affinity for the muscarinic receptor and therefore has a lower incidence in the typical adverse events associated with anticholinergic drugs such as oxybutynin and tolterodine. However, there is no clinical evidence that flavoxate offers effective treatment for OAB.

<b>Generic Name</b>	<b>Trade Name</b>	<b>Manufacturer</b>	<b>Generic Available</b>
Fesoterodine	Toviaz™	Pfizer	N
Flavoxate	Urispas®	Ortho-McNeil, various	Y
Oxybutynin	Ditropan®	Ortho-McNeil, various	Y
	Ditropan XL®	Ortho-McNeil, various	Y
	Gelnique™	Watson Pharmaceuticals	N
	Oxytrol™	Watson Pharma	N
Tolterodine	Detrol®	Pfizer	N
	Detrol® LA		

<b>Generic Name</b>	<b>Trade Name</b>	<b>Manufacturer</b>	<b>Generic Available</b>
Trospium	Sanctura®	Indevus	Y
	Sanctura XR™	Pharmaceuticals	N
Solifenacin	Vesicare®	GlaxoSmithKline	N
Darifenacin	Enablex®	Novartis	N

**Summary:**

Selection of a preferred agent should be based upon clinical efficacy, side effect profile, generic availability, and total cost impact to the health care system.