BlueCross BlueShield of Kansas City

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Overactive Bladder (OAB) Step Therapy Program

Policy Number: 5.01.556
Origination: 07/2013
Last Review: 11/2014
Next Review: 11/2015

Policy

BCBSKC will provide coverage for brand name Overactive Bladder agents when the following criteria are met. The brand name OAB agents affected are:

- Detrol® (tolterodine tablets)
- Detrol LA® (tolterodine extended-release capsules)
- Ditropan® (oxybutynin tablets, syrup)
- Ditropan XL® (oxybutynin extended-release tablets)
- Enablex® (darifenacin extended-release tablets)
- Gelnique™ (oxybutynin 3% and 10% gel)
- Oxytrol® (oxybutynin transdermal system)
- Sanctura® (trospium tablets)
- Sanctura XR (trospium extended-release capsules)
- Toviaz™ (fesoterodine fumarate extended-release tablets)
- Vesicare® (solifenacin tablets)
- Myrbetriq™ (mirabegron extended-release tablets)

When Policy Topic is covered:

This step therapy program was developed to encourage the use of a generic agent prior to a brand name agent. If the step therapy rule is not met for a brand name agent, coverage will be determined by prior authorization criteria.

Step 1: oxybutynin IR, oxybutynin XL, trospium, tolterodine, trospium XR
Step 2: Detrol, Detrol LA, Ditropan, Ditropan XL, Enablex, Gelnique, Oxytrol, Sanctura, Sanctura XR, Toviaz, Vesicare, Myrbetriq

CRITERIA

1. If the patient has tried a Step 1 agent, approve a Step 2 agent.

2. If the patient cannot swallow or has difficulty swallowing tablets or capsules, authorization for Gelnique, or Oxytrol may be given.

When Policy Topic is not covered:

The use of oral OAB agents is considered **investigational** for all other indications.

Considerations

The oral OAB medications require prior authorization through the Clinical Pharmacy Department.

This Blue Cross and Blue Shield of Kansas City policy Statement was developed using available resources such as, but not limited to: Hayes Medical Technology Directory, Food and Drug Administration (FDA) approvals, Facts and Comparisons, National specialty guidelines, Local medical policies of other health plans, Medicare (CMS), Local providers.

Description of Procedure or Service

The mainstay of drug therapy in the treatment of overactive bladder (OAB) are anticholinergic agents that target muscarinic receptors (i.e., antimuscarinics).[1] Oxybutynin, Detrol/LA, Toviaz, trospium, Sanctura XR, Vesicare, and Enablex are all antimuscarinics indicated for the treatment of OAB with symptoms of urge urinary incontinence, urgency, and frequency.[2-13] Oxybutynin immediate-release (IR) and oxybutynin extended-release (XL) are the only two agents in this class indicated in children (≥ 5 and ≥ 6 years, respectively).[2-3] Oxybutynin XL carries an additional indication in children for the treatment of OAB associated with a neurological condition.[3] All of the agents in this class have been shown to have a stabilizing effect on the detrusor muscle, increase bladder capacity, decrease the frequency of involuntary detrusor contractions, and delay the initial urge to void.[1]

Myrbetriq is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency.[21] It increases the bladder capacity by activating the beta-3 receptor, which relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle.

Rationale

All of the agents in the antimuscarinic class target the muscarinic receptors on the bladder (M_3 and M_2), but they are not exclusively selective for the bladder.[14] Other muscarinic receptor subtypes located throughout the body are also targeted to varying degrees. As a result, all of these agents are potentially associated with anticholinergic adverse effects (AEs) such as dry mouth (M_1 and M_3 on the salivary gland), blurred vision (M_3 and M_5 on the ciliary muscle), constipation (M_2 and M_3 which regulate gastric motility), and central nervous system (CNS) effects such as dizziness, somnolence, and impaired cognitive function (postsynaptic cortical M_1). Of the agents in this class, Enablex is the most selective for the M_3 receptor while having a lower affinity for the other muscarinic receptor subtypes. The benefit of this pharmacologic difference is questionable, however, as the overall incidence of CNS/cognitive, cardiac, and visual AEs reported in placebo- and active- controlled trials is low with all the agents in this class.[2-13] Oxybutynin, Detrol/LA, Toviaz, Vesicare, and Enablex are all tertiary amines. Trospium is a quaternary amine and, therefore, theoretically, does not enter the CNS to the same extent as a tertiary amine.[15] The clinical significance of this difference is questionable, however, as the overall incidence of CNS-related AEs reported in placebo-and active- controlled trials is low with all the agents in this class.[2-13] When treating OAB, the Fourth International Continence Society Incontinence Evaluation and Treatment Recommendations do not differentiate within this therapeutic class and instead refer to pharmacologic treatment in terms of antimuscarinic agents.[16]

Overall, in placebo-controlled trials, the incidence of dyspepsia, blurred vision, urinary retention, and tachycardia appears to be low and comparable across all agents.[2-13] The incidence of dizziness is comparable among all the agents with the exception of oxybutynin IR. Oxybutynin XL 10 mg/day is associated with a similar incidence of somnolence to Oxytrol, Gelnique (3% and 10%), Detrol, Detrol LA, Toviaz, trospium, Vesicare, and Enablex and a similar incidence of dry mouth to Detrol, Detrol LA, Toviaz, trospium, Vesicare 10 mg/day, and Enablex.

Table 1. Incidence (%) of Select Adverse Effects Reported in Placebo-Controlled Trials With the Antimuscarinic Agents.[2-13]

AE	Oxy IR[^]	Oxy XL		Oxytrol[*]	Gelnique 10%[€]	Gelnique 3%[€]	Detrol	
		5-30 mg/day	10 mg/day				IR[#]	LA[α]
Dry mouth	71%	61%	29%	7%	7.5%	12.1%	35%	23%
Constipation	13%	13%	7%	3%	--	--	7%	6%
Blurred vision	9%	8%	1%	3%	--	<2%	2%	1%

Dyspepsia	7%	7%	5%	--	--	--	4%	3%
Urinary retention	< 5%	< 5%	--	--	--	--	--	--
Tachycardia	< 5%	--	--	--	--	--	--	--
Dizziness	16%	6%	4%	--	2.8%	--	5%	2%
Somnolence	13%	12%	2%	< 2%	2.1%	--	3%	3%
Application site pruritus/ erythema	n/a	n/a	n/a	15%/7%	5.4%[£]	14.2%[£]	n/a	n/a

Table 1 (continued). Incidence (%) of Select Adverse Effects Reported in Placebo-Controlled Trials with the Antimuscarinic Agents.[2-13]

AE	Toviaz		Sanctura		Vesicare		Enablex	
	4 mg	8 mg	IR[§]	XR∞	5 mg/day	10 mg/day	7.5 mg/day	15 mg/day
Dry mouth	18.8%	34.6%	20%	11%	11%	28%	20%	35%
Constipation	4.2%	6.0%	10%	9%	5%	13%	15%	21%
Blurred vision	--	--	< 1%	--	4%	5%	< 2%	< 2%
Dyspepsia	1.6%	2.3%	1%	1%	1%	4%	3%	8%
Urinary retention	1.1%	1.4%	1%	--	0%	1%	--	--
Tachycardia	--	--	< 1%	< 2%	--	--	--	--
Dizziness	--	--	--	--	2%	2%	1%	2%
Somnolence	--	--	--	--	--	--	--	--
Application site pruritus/ erythema	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

AE – adverse effect; IR – immediate release; XL – extended release; LA – long-acting; [^] 5-20 mg/day; [*] 3.9 mg/day; [€] Patients using the 10% gel received 100 mg of oxybutynin and those using the 3% gel received 56-84 mg/day of oxybutynin; [#] 2 mg twice daily; [α] 4 mg once daily; [§] 20 mg twice daily; ∞ 60 mg daily; [£] Incidence reported for the gel includes all patients who experienced any application site reaction; n/a – not applicable.

Studies with extended-release formulations (i.e., oxybutynin XL, Oxytrol, Gelnique, and Detrol LA) as well as the more recently developed agents (i.e., trospium, Vesicare, and Enablex) have shown that AEs are typically mild to moderate, generally tolerable, and seldom lead to withdrawal of therapy.[14] A review article that analyzed data from randomized, controlled trials in order to evaluate tolerability differences among the antimuscarinics concluded that all of the agents except for oxybutynin IR were found to be well tolerated and only oxybutynin IR and Oxytrol were associated with excess withdrawals due to AEs.[17]

The most commonly observed AEs in patients taking Myrbetriq in pivotal studies and a long-term safety study were hypertension, nasopharyngitis, headache, and urinary tract infection.[21]

Greater functional decline may be noted in patients with existing dementia using cholinesterase inhibitors in combination with antimuscarinics.[18] The Beers criteria for potentially inappropriate medication use in older adults (updated in 2012) indicate that antimuscarinics for urinary incontinence have strong anticholinergic effects and should therefore be avoided in older adults with dementia and cognitive impairment due to adverse CNS effects.[19] This list also notes that oral antimuscarinics for urinary incontinence can worsen chronic constipation and use should be avoided in older adults with chronic constipation unless there are no alternatives.

The goal of therapy in the treatment of OAB is the reduction or resolution of symptoms without the emergence of significant AEs.[20] An alternative antimuscarinic may be prescribed if symptoms do not improve or if there are intolerable AEs in hopes that another agent may have a better suited efficacy/tolerability profile for that patient. It may be difficult to discern whether a therapeutic failure/withdrawal of therapy was due to lack of efficacy or due to tolerability issues, or both as intolerability may actually interfere with any potential efficacy.

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Billing Coding/Physician Documentation Information

N/A The OAB medications are considered a pharmacy benefit.

Additional Policy Key Words

Policy Number**:** 5.01.556

Related Topics

N/A

Policy Implementation/Update Information

08/2013 New Policy titled Overactive Bladder Step Therapy Program
11/2014 No policy changes made