OVERACTIVE BLADDER MEDICATIONS, NON-PREFERRED BRANDS:

- DETROL® (tolterodine tartrate) oral tablet
- DETROL LA® (tolterodine tartrate ER) oral capsule
- DITROPA XL® (oxybutynin chloride ER) oral tablet
- ENABLEX® (darifenacin ER) oral tablet
- GELNIQUE® (oxybutynin chloride) transdermal gel
- TOVIAZ® (fesoterodine fumarate ER) oral tablet

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member’s specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms “experimental” and “investigational” are considered to be interchangeable.

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Description:

Overactive bladder (OAB) occurs when bladder muscle contractions are not controlled. When these muscle contractions happen too often or cannot be controlled, symptoms of overactive bladder, such as urinary frequency, urgency, and incontinence (leakage) occur.

The urinary bladder contains nerves, muscles, and connective tissue. The most important muscle in the bladder is the detrusor muscle. In normal circumstances, the bladder stretches as it fills with urine. When the volume in the
OVERACTIVE BLADDER MEDICATIONS, NON-PREFERRED BRANDS (cont.)

bladder reaches approximately 300 mL, the stretch in the wall of the bladder triggers a nerve response to initiate urination. This reaction results in loosening of the sphincter in the neck of the bladder that connects the bladder to the urethra and contraction of the detrusor muscle to begin urination. This response is under voluntary control and can be overridden by the individual to prevent urination if it is not the right time or place. An overactive bladder can result from dysfunction of the nerves or muscles in the bladder, most commonly the detrusor muscle. In OAB, the detrusor can contract inappropriately regardless of how much urine is stored in the bladder, resulting in a condition known as detrusor overactivity or hyperactive detrusor.

All medications for OAB are effective for reducing incontinence episodes and urinary frequency and all medications for OAB have an adequate track record for safety. No medication for OAB has been shown to be safer or more effective overall than any other.

There are many generically available oral antimuscarinic/anticholinergic medications for the treatment of OAB, formulated as immediate- and extended-release products.

Antimuscarinic/anticholinergic medications are associated with several adverse effects including dry mouth, dry eyes, blurry vision, urinary retention, constipation and somnolence. The safety profiles of antimuscarinic/ anticholinergic medications are similar overall, but may differ slightly based on route of administration.

Mirabegron (Myrbetriq), a beta-3 adrenergic agonist, offers an option for patients unable to tolerate antimuscarinic/anticholinergic adverse effects. Over-the-counter (OTC) oxybutynin transdermal patches provide a non-oral dosing option.

Guidelines recommend behavioral therapies (such as bladder training, bladder control strategies, pelvic floor muscle training, and fluid management) as first-line treatment for OAB, either alone or in combination with oral antimuscarinics or beta-3-AR agonists.

Definitions:

Drug related events:

Ineffective / failure
Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

Adverse Drug Event: Allergic reaction / Hypersensitivity / Intolerance
Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is
documented in medical record. A significant adverse drug event is when an individual's outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals' body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

**Allergic reaction / hypersensitivity** – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

**Intolerance** – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

**Contraindication**
Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer’s labelled recommendation and is considered investigational or experimental

**Non-adherence**
Individual does not follow prescribe regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record

**Precertification:**

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

This Pharmacy Coverage Guideline does not apply to FEP or other states’ Blues Plans.

Information about medications that require precertification is available at [www.azblue.com/pharmacy](http://www.azblue.com/pharmacy).

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.
OVERACTIVE BLADDER MEDICATIONS, NON-PREFERRED BRANDS (cont.)

Criteria:

See “Resources” section for FDA-approved dosage.

- Precertification for Overactive Bladder Medications, non-preferred brands Detrol, Detrol LA, Ditropan XL, Enablex, Gelnique, and Toviaz requires completion of the specific request form in its entirety. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. Incomplete forms will be returned.

- FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of non-preferred brands Detrol, Detrol LA, Ditropan XL, Enablex, Gelnique, and Toviaz is considered medically necessary when ALL of the following criteria are met:

  1. Medical record documentation of ONE of the following:
     - **For Detrol, Detrol LA, Enablex, Gelnique, and Toviaz:**
       - Individual is 18 years of age or older with a confirmed diagnosis of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency
     
     - **For Ditropan XL either** of the following:
       - Individual is 6 years of age or older with a confirmed diagnosis of symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida)
       
     - Individual is 18 years of age or older with a confirmed diagnosis of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency

  2. Unable to use **ALL** of following generic agents for OAB due to **either** all generics failed to control symptoms, all generics caused a significant intolerant reaction or **all generics caused a hypersensitivity reaction that was due to an ingredient that has been identified:**
     - Darifenacin ER
     - Flavoxate
     - Oxybutynin IR
     - Oxybutynin ER
     - Tolterodine IR
     - Tolterodine ER
     - Trospium IR
     - Trospium ER

  3. Unable to use **BOTH** Myrbetric (mirabegron) and VESIcare (solifenacin) for OAB due to **either** failed to control symptoms, experienced a significant intolerant reaction, experienced a hypersensitivity reaction or has a contraindication

  4. Absence of **ALL** of the following contraindications:
     - Urinary retention
     - Gastric retention
     - Uncontrolled narrow-angle glaucoma
OVERACTIVE BLADDER MEDICATIONS, NON-PREFERRED BRANDS (cont.)

- Hypersensitivity to any component of the product

5. Absence of **ALL** of the following exclusions:
   - **For Detrol LA:**
     - Severe hepatic impairment (Child-Pugh Class C)
     - Woman who is breast feeding an infant or child
     - Creatinine Clearance < 10 mL/min
   - **For Detrol:**
     - Woman who is breast feeding an infant or child
   - **For Enablex and Toviaz:**
     - Severe hepatic impairment (Child-Pugh Class C)

- **Continuation of coverage (renewal request):** Non-preferred Overactive Bladder Medication is considered **medically necessary** with documentation of **ALL** of the following:
  1. The individual has benefited from therapy but remains at high risk
  2. The condition has not progressed or worsened while on therapy
  3. Individual has not developed any contraindications or other exclusions to its continued use

- Overactive Bladder Medications, non-preferred brands Detrol, Detrol LA, Ditropan XL, Enablex, Gelnique, and Toviaz for all other indications not previously listed is considered **experimental or investigational** based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

**Resources:**

OVERACTIVE BLADDER MEDICATIONS, NON-PREFERRED BRANDS (cont.)


FDA-approved indication and dosage:

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<th>Indication</th>
<th>Recommended Dose</th>
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<td>DETROL tablets are indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.</td>
<td>The initial recommended dose of DETROL tablets is 2 mg twice daily. The dose may be lowered to 1 mg twice daily based on individual response and tolerability. For patients with significantly reduced hepatic or renal function or who are currently taking drugs that are potent inhibitors of CYP3A4, the recommended dose of DETROL is 1 mg twice daily.</td>
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| DETROL LA is an antimuscarinic indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. | 4 mg capsules taken orally once daily with water and swallowed whole.  
2 mg capsules taken orally once daily with water and swallowed whole in the presence of:  
- mild to moderate hepatic impairment (Child-Pugh class A or B)  
- severe renal impairment [Creatinine Clearance (CCr) 10-30 mL/min]  
- drugs that are potent CYP3A4 inhibitors  
DETROL LA is not recommended for use in patients with CCr <10 mL/min  
DETROL LA is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C) |
| DITROPA XL is a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. DITROPA XL is also indicated for the treatment of pediatric patients aged 6 years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida). | DITROPA XL must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed.  
DITROPA XL may be administered with or without food.  
**Adults:** Start with 5 mg or 10 mg, once daily at approximately the same time every day. Dose should not exceed 30 mg per day.  
**Pediatric patients (6 years of age or older):** Start with 5 mg, once daily at approximately the same time every day. Dose should not exceed 20 mg per day. |
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| ENABLEX is a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency. | The recommended starting dose of ENABLEX is 7.5 mg once daily. Based upon individual response, the dose may be increased to 15 mg once daily, as early as two weeks after starting therapy. ENABLEX should be taken once daily with water. ENABLEX may be taken with or without food, and should be swallowed whole and not chewed, divided or crushed. For patients with moderate hepatic impairment (Child-Pugh B) or when co-administered with potent CYP3A4 inhibitors (for example, ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin and nefazadone), the daily dose of ENABLEX should not exceed 7.5 mg. ENABLEX is not recommended for use in patients with severe hepatic impairment (Child-Pugh C). |
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| GELNIQUE 3% and 10% is a muscarinic receptor antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. | For GELNIQUE 3% gel:  
- Apply three pumps of GELNIQUE 3% (84 mg) once daily to clean and dry, intact skin on the abdomen, or upper arms/shoulders, or thighs.  
- Application site may be rotated if necessary.  
- GELNIQUE 3% is for topical application only and should not be ingested.  
For GELNIQUE 10% gel:  
- Apply contents of one sachet of GELNIQUE once daily to dry, intact skin on the abdomen, upper arms/shoulders, or thighs.  
- Rotate application sites, avoiding use of the same site on consecutive days.  
- GELNIQUE 10% is for topical application only and should not be ingested. |
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| TOVIAZ is a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. | The recommended starting dose of TOVIAZ is 4 mg once daily. Based upon individual response and tolerability, the dose may be increased to 8 mg daily.  
The daily dose of TOVIAZ should not exceed 4 mg in the following populations:  
- Patients with severe renal impairment (CLCR <30 mL/min)  
- Patients taking potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, and clarithromycin  
TOVIAZ is not recommended for use in patients with severe hepatic impairment (Child-Pugh C).  
TOVIAZ should be taken with liquid and swallowed whole. TOVIAZ can be administered with or without food, and should not be chewed, divided, or crushed. |