

# **OXYBUTYNIN- oxybutynin tablet, film coated, extended release**

## **NCS HealthCare of KY, LLC dba Vanguard Labs**

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### **HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS safely and effectively. See full prescribing information for OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS.**

### **OXYBUTYNIN CHLORIDE extended-release tablets, for oral use**

**Initial U.S. Approval: 1975**

### **INDICATIONS AND USAGE**

- Oxybutynin chloride is a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. (1)
- Oxybutynin chloride extended-release tablets are 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). (1)

### **DOSAGE AND ADMINISTRATION**

Oxybutynin chloride extended-release tablets must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed. Oxybutynin chloride extended-release tablets may be administered with or without food. (2)

- **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. (2.1)
- **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. (2.2)

### **DOSAGE FORMS AND STRENGTHS**

Extended-release tablets 5 mg, 10 mg and 15 mg (3) (3)

### **CONTRAINDICATIONS**

- Urinary retention (4)
- Gastric Retention (4)
- Uncontrolled narrow angle glaucoma (4)
- Known hypersensitivity to oxybutynin chloride or any component of oxybutynin chloride extended-release tablets (4)

### **WARNINGS AND PRECAUTIONS**

- **Angioedema:** Angioedema has been reported with oxybutynin. If symptoms of angioedema occur, discontinue oxybutynin chloride extended-release tablets immediately and initiate appropriate therapy. (5.1)
- **Central Nervous System (CNS) effects:** CNS effects have been reported with oxybutynin. If patient experiences anticholinergic CNS effects, consider dose adjustment or discontinuation of oxybutynin chloride extended-release tablets. (5.2)
- **Use with caution due to aggravation of symptoms:**
  - Pre-existing dementia in patients treated with cholinesterase inhibitors (5.2),
  - Parkinson's disease (5.2),
  - Myasthenia gravis (5.3), and
  - Decreased gastrointestinal motility in patients with autonomic neuropathy. (5.4)
- **Urinary Retention:** Use with caution in patients with clinically significant bladder outflow obstruction because of the risk of urinary retention (5.5)
- **Gastrointestinal Adverse Reactions:** Use with caution in patients with gastrointestinal obstructive disorders or decreased intestinal motility due to risk of gastric retention. Use with caution in patients with gastroesophageal reflux or in patients concurrently taking drugs that can exacerbate esophagitis. (5.6)

### **ADVERSE REACTIONS**

The most common (incidence  $\geq 5\%$ ) adverse reactions were dry mouth, constipation, diarrhea, headache,

somnolence and dizziness. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Zydus Pharmaceuticals USA Inc. at 1-877-993-8779 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

-----**DRUG INTERACTIONS**-----

- Co-administration with other anticholinergic drugs may increase the frequency and/or severity of anticholinergic-like effects. (7)
- Co-administration with strong cytochrome P450 (CYP) 3A4 inhibitors (e.g., ketoconazole) increases the systemic exposure of oxybutynin. (7)

-----**USE IN SPECIFIC POPULATIONS**-----

- Pediatric Use: Oxybutynin chloride extended-release tablets are not recommended in pediatric patients who cannot swallow the tablet whole without chewing, dividing or crushing, or in children under the age of 6 years. (8.4)
- Renal or Hepatic Impairment: There have been no studies conducted in patients with renal or hepatic impairment. (8.6, 8.7)

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 3/2024**

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**FULL PRESCRIBING INFORMATION: CONTENTS\***

**1 INDICATIONS AND USAGE**

**2 DOSAGE AND ADMINISTRATION**

2.1 Adults

2.2 Pediatric Patients Aged 6 Years of Age and Older

**3 DOSAGE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

**5 WARNINGS AND PRECAUTIONS**

5.1 Angioedema

5.2 Central Nervous System Effects

5.3 Worsening of Symptoms of Myasthenia Gravis

5.4 Worsening of Symptoms of Decreased Gastrointestinal Motility in Patients with Autonomic Neuropathy

5.5 Urinary Retention

5.6 Gastrointestinal Adverse Reactions

**6 ADVERSE REACTIONS**

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

**7 DRUG INTERACTIONS**

**8 USE IN SPECIFIC POPULATIONS**

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Renal Impairment

8.7 Hepatic Impairment

**10 OVERDOSAGE**

**11 DESCRIPTION**

**12 CLINICAL PHARMACOLOGY**

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

### **13 NONCLINICAL TOXICOLOGY**

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

### **14 CLINICAL STUDIES**

### **16 HOW SUPPLIED/STORAGE AND HANDLING**

### **17 PATIENT COUNSELING INFORMATION**

\* Sections or subsections omitted from the full prescribing information are not listed.

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

Oxybutynin chloride extended-release tablets are a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

Oxybutynin chloride extended release tablets are 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).

### **2 DOSAGE AND ADMINISTRATION**

Oxybutynin chloride extended release tablets must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed.

Oxybutynin chloride extended release tablets may be administered with or without food.

#### **2.1 Adults**

The recommended starting dose of oxybutynin chloride extended-release tablet is 5 mg or 10 mg once daily at approximately the same time each day. Dosage may be adjusted in 5 mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 30 mg/day). In general, dosage adjustment may proceed at approximately weekly intervals.

#### **2.2 Pediatric Patients Aged 6 Years of Age and Older**

The recommended starting dose of oxybutynin chloride extended-release tablets are 5 mg once daily at approximately the same time each day. Dosage may be adjusted in 5 mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 20 mg/day).

### **3 DOSAGE FORMS AND STRENGTHS**

Oxybutynin chloride extended-release tablets, USP are available as 5 mg, 10 mg and 15

mg tablets for oral use:

Oxybutynin chloride extended-release tablets USP, 5 mg are white to off-white, round, beveled-edged, biconvex, coated-tablets debossed on one side with "255" and plain on other side.

Oxybutynin chloride extended-release tablets USP, 10 mg are white to off-white, round, beveled-edged, biconvex, coated-tablets debossed on one side with "256" and plain on other side.

Oxybutynin chloride extended-release tablets USP, 15 mg are white to off-white, round, beveled-edged, biconvex, coated-tablets debossed on one side with "257" and plain on other side.

## **4 CONTRAINDICATIONS**

Oxybutynin chloride extended release tablets are contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma.

Oxybutynin chloride extended release tablets are also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product. There have been reports of hypersensitivity reactions, including anaphylaxis and angioedema.

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Angioedema**

Angioedema of the face, lips, tongue and/or larynx has been reported with oxybutynin. In some cases, angioedema occurred after the first dose. Angioedema associated with upper airway swelling may be life-threatening. If involvement of the tongue, hypopharynx, or larynx occurs, oxybutynin should be promptly discontinued and appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided.

### **5.2 Central Nervous System Effects**

Oxybutynin is associated with anticholinergic central nervous system (CNS) effects [see *Adverse Reactions (6)*]. A variety of CNS anticholinergic effects have been reported, including hallucinations, agitation, confusion and somnolence. Patients should be monitored for signs of anticholinergic CNS effects, particularly in the first few months after beginning treatment or increasing the dose. Advise patients not to drive or operate heavy machinery until they know how Oxybutynin chloride extended-release tablets affects them. If a patient experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered.

Oxybutynin chloride extended-release tablets should be used with caution in patients with preexisting dementia treated with cholinesterase inhibitors due to the risk of aggravation of symptoms.

Oxybutynin chloride extended-release tablets should be used with caution in patients

with Parkinson's disease due to the risk of aggravation of symptoms.

### **5.3 Worsening of Symptoms of Myasthenia Gravis**

Oxybutynin chloride extended-release tablets should be used with caution in patients with myasthenia gravis due to the risk of aggravation of symptoms.

### **5.4 Worsening of Symptoms of Decreased Gastrointestinal Motility in Patients with Autonomic Neuropathy**

Oxybutynin chloride extended-release tablets should be used with caution in patients with autonomic neuropathy due to the risk of aggravation of symptoms of decreased gastrointestinal motility.

### **5.5 Urinary Retention**

Oxybutynin chloride extended-release tablets should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention [see *Contraindications (4)*].

### **5.6 Gastrointestinal Adverse Reactions**

Oxybutynin chloride extended-release tablets should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention [see *Contraindications (4)*].

Oxybutynin chloride extended-release tablets, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis and intestinal atony.

Oxybutynin chloride extended-release tablets should be used with caution in patients who have gastroesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis.

As with any other nondeformable material, caution should be used when administering oxybutynin chloride extended-release tablets to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs in nondeformable controlled-release formulations.

## **6 ADVERSE REACTIONS**

### **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety and efficacy of oxybutynin chloride extended-release tablets (5 to 30 mg/day) was evaluated in 774 adult subjects who participated in five double-blind, controlled clinical trials. In four of the five studies, Oxybutynin chloride extended-release tablets (5 to 20 mg/day in 199 subjects) was an active comparator. Adverse reactions

reported by  $\geq 1\%$  of subjects are shown in Table 1.

**Table 1 Adverse Drug Reactions Reported by  $\geq 1\%$  of Oxybutynin Chloride Extended-Release Tablets-treated Adult Subjects in Five Double-blind, Controlled Clinical Trials of Oxybutynin Chloride Extended-Release Tablets**

| <b>System/Organ Class<br/>Preferred Term</b>               | <b>Oxybutynin<br/>Chloride<br/>Extended-Release<br/>Tablets<br/>5 to 30 mg/day<br/>n = 774<br/>%</b> | <b>Oxybutynin<br/>Chloride<br/>Immediate-<br/>Release<br/>Tablets<br/>5 to 20 mg/day<br/>n = 199<br/>%</b> |
|--|--|--|
| <b>Psychiatric Disorders</b>                               |  |  |
| Insomnia   | 3  | 5.5  |
| <b>Nervous System Disorders</b>                            |  |  |
| Headache   | 7.5  | 8  |
| Somnolence   | 5.6  | 14.1   |
| Dizziness  | 5  | 16.6   |
| Dysgeusia  | 1.6  | 1.5  |
| <b>Eye Disorders</b>                                       |  |  |
| Vision blurred   | 4.3  | 9.6  |
| Dry eye  | 3.1  | 2.5  |
| <b>Respiratory, Thoracic and Mediastinal<br/>Disorders</b> |  |  |
| Cough  | 1.9  | 3  |
| Oropharyngeal pain   | 1.9  | 1.5  |
| Dry throat   | 1.7  | 2.5  |
| Nasal dryness  | 1.7  | 4.5  |
| <b>Gastrointestinal Disorders</b>                          |  |  |
| Dry mouth  | 34.9   | 72.4   |
| Constipation   | 8.7  | 15.1   |
| Diarrhea   | 7.9  | 6.5  |
| Dyspepsia  | 4.5  | 6  |
| Nausea   | 4.5  | 11.6   |
| Abdominal pain   | 1.6  | 2  |
| Vomiting   | 1.3  | 1.5  |
| Flatulence   | 1.2  | 2.5  |
| Gastro-esophageal reflux disease                           | 1  | 0.5  |
| <b>Skin and Subcutaneous Tissue Disorders</b>              |  |  |
| Dry skin   | 1.8  | 2.5  |
| Pruritus   | 1.3  | 1.5  |
| <b>Renal and Urinary Disorders</b>                         |  |  |
| Dysuria  | 1.9  | 2  |
| Urinary hesitation   | 1.9  | 8.5  |
| Urinary retention  | 1.2  | 3  |

## General Disorders and Administration

### Site Conditions

|         |     |   |
|---------|-----|---|
| Fatigue | 2.6 | 3 |
|---------|-----|---|

### Investigations

|                                    |     |     |
|------------------------------------|-----|-----|
| Residual urine volume <sup>2</sup> | 2.3 | 3.5 |
|------------------------------------|-----|-----|

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<sup>2</sup> The bundled term residual urine volume consists of the preferred terms residual urine volume and residual urine volume increased.

The discontinuation rate due to adverse reactions was 4.4% with oxybutynin chloride extended-release tablets compared to 0% with oxybutynin chloride immediate-release tablets. The most frequent adverse reaction causing discontinuation of study medication was dry mouth (0.7% ).

The following adverse reactions were reported by <1% of oxybutynin chloride-treated patients and at a higher incidence than placebo in clinical trials: *Metabolism and Nutrition Disorders*: anorexia, fluid retention; *Vascular disorders*: hot flush; *Respiratory, thoracic and mediastinal disorders*: dysphonia; *Gastrointestinal Disorders*: dysphagia, frequent bowel movements; *General disorders and administration site conditions*: chest discomfort, thirst.

## 6.2 Postmarketing Experience

The following additional adverse reactions have been reported from worldwide postmarketing experience with oxybutynin chloride extended-release tablets. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Infections and Infestations*: Urinary tract infection; *Psychiatric Disorders*: psychotic disorder, agitation, confusional state, hallucinations, memory impairment, abnormal behavior; *Nervous System Disorders*: convulsions; *Eye Disorders*: glaucoma; *Respiratory, Thoracic and Mediastinal Disorders*: nasal congestion; *Cardiac Disorders*: arrhythmia, tachycardia, QT interval prolongation; *Vascular Disorders*: flushing, hypertension; *Skin and Subcutaneous Tissue Disorders*: rash; *Renal and Urinary Disorders*: impotence; *General Disorders and Administration Site Conditions*: hypersensitivity reactions, including angioedema with airway obstruction, urticaria, and face edema; anaphylactic reactions requiring hospitalization for emergency treatment; *Injury, poisoning and procedural complications*: fall.

Additional adverse events reported with some other oxybutynin chloride formulations include: cycloplegia, mydriasis, and suppression of lactation. In one reported case, concomitant use of oxybutynin with carbamazepine and dantrolene was associated with adverse events of vomiting, drowsiness, confusion, unsteadiness, slurred speech and nystagmus, suggestive of carbamazepine toxicity.

## 7 DRUG INTERACTIONS

The concomitant use of oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other

anticholinergic-like effects may increase the frequency and/or severity of such effects.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index. Anticholinergic agents may also antagonize the effects of prokinetic agents, such as metoclopramide.

Mean oxybutynin plasma concentrations were approximately 2 fold higher when oxybutynin chloride extended-release tablets were administered with ketoconazole, a potent CYP3A4 inhibitor. Other inhibitors of the cytochrome P450 3A4 enzyme system, such as antimycotic agents (e.g., itraconazole and miconazole) or macrolide antibiotics (e.g., erythromycin and clarithromycin), may alter oxybutynin mean pharmacokinetic parameters (i.e., C<sub>max</sub> and AUC). The clinical relevance of such potential interactions is not known. Caution should be used when such drugs are co-administered.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### ***Risk Summary***

There are no adequate data on oxybutynin chloride extended-release tablets use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

### **8.2 Lactation**

#### ***Risk Summary***

There are no data on the presence of oxybutynin in human milk, the effects on the breastfed infant, or the effects of oxybutynin chloride on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for oxybutynin chloride extended-release tablets and any potential adverse effects on the breastfed child from oxybutynin chloride extended-release tablets or from the underlying maternal condition.

### **8.4 Pediatric Use**

The safety and efficacy of oxybutynin chloride extended-release tablets were studied in 60 children in a 24 week, open-label, non-randomized trial. Patients were aged 6 to 15 years, all had symptoms of detrusor overactivity in association with a neurological condition (e.g., spina bifida), all used clean intermittent catheterization, and all were current users of oxybutynin chloride extended-release tablets. Study results demonstrated that administration of oxybutynin chloride extended-release tablets 5 to 20 mg/day was associated with an increase from baseline in mean urine volume per catheterization from 108 mL to 136 mL, an increase from baseline in mean urine volume after morning awakening from 148 mL to 189 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 34% to 51%.



Urodynamic results were consistent with clinical results. Administration of oxybutynin chloride extended-release tablets resulted in an increase from baseline in mean maximum cystometric capacity from 185 mL to 254 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 44 cm H<sub>2</sub>O to 33 cm H<sub>2</sub>O, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H<sub>2</sub>O) from 60% to 28%.

The pharmacokinetics of oxybutynin chloride in these patients were consistent with those reported for adults [see *Clinical Pharmacology* (12.3)].

Oxybutynin chloride extended-release tablets are not recommended in pediatric patients who cannot swallow the tablet whole without chewing, dividing, or crushing, or in children under the age of 6.

### **8.5 Geriatric Use**

The rate and severity of anticholinergic effects reported by patients less than 65 years old and those 65 years and older were similar. The pharmacokinetics of oxybutynin chloride extended-release tablets were similar in all patients studied (up to 78 years of age).

### **8.6 Renal Impairment**

There were no studies conducted with oxybutynin chloride extended-release tablets in patients with renal impairment.

### **8.7 Hepatic Impairment**

There were no studies conducted with oxybutynin chloride extended-release tablets in patients with hepatic impairment.

## **10 OVERDOSAGE**

The continuous release of oxybutynin from oxybutynin chloride extended-release tablets should be considered in the treatment of overdosage. Patients should be monitored for at least 24 hours. Treatment should be symptomatic and supportive. A cathartic may be administered.

Overdosage with oxybutynin chloride has been associated with anticholinergic effects including central nervous system excitation, flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention.

Ingestion of 100 mg oxybutynin chloride in association with alcohol has been reported in a 13 year old boy who experienced memory loss, and a 34 year old woman who developed stupor, followed by disorientation and agitation on awakening, dilated pupils, dry skin, cardiac arrhythmia, and retention of urine. Both patients fully recovered with symptomatic treatment.

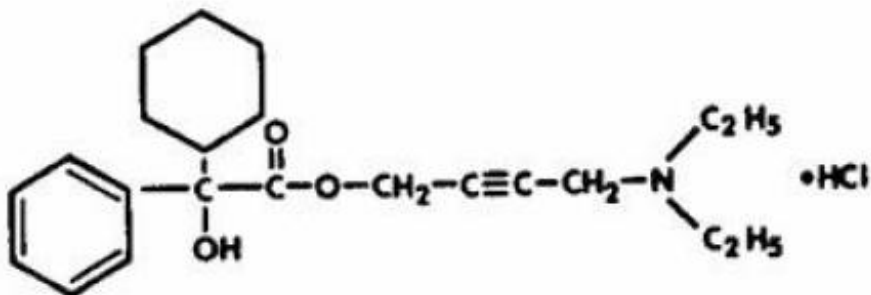
## **11 DESCRIPTION**

Oxybutynin chloride extended-release tablets are an antispasmodic, muscarinic antagonist. Each oxybutynin chloride extended-release tablets contains 5 mg, 10 mg, or

15 mg of oxybutynin chloride USP, formulated as a once-a-day controlled-release tablet for oral administration. Oxybutynin chloride is administered as a racemate of R-and S-enantiomers.

Chemically, oxybutynin chloride is d,l (racemic) 4-diethylamino-2-butynyl phenylcyclohexylglycolate hydrochloride. The empirical formula of oxybutynin chloride is  $C_{22}H_{31}NO_3 \cdot HCl$ .

Its structural formula is:



Oxybutynin chloride, USP is a white crystalline, practically odorless powder with a molecular weight of 393.95. It is freely soluble in water and in alcohol, very soluble in methanol and in chloroform, soluble in acetone, slightly soluble in ether and very slightly soluble in hexane.

Oxybutynin chloride extended-release tablet, USP also contains the following inactive ingredients: alginic acid, hydrogenated castor oil, hypromellose, lactose monohydrate, magnesium stearate, methacrylic acid copolymer dispersion, microcrystalline cellulose, povidone, talc and triethyl citrate.

The product complies the USP Dissolution Test 8

### **System Components and Performance**

Oxybutynin chloride extended-release tablet uses an enteric coated hydrophilic hydrogel matrix to deliver oxybutynin chloride at controlled rate over approximately 24 hours by diffusion mechanism. The system comprises of a core, which contains the drug, rate controlling hydrogel and other excipients. The core is surrounded by a partially or complete pH dependent membrane. Hence, when the drug reaches the acidic medium, in stomach minimal drug release will occur and when it reaches an environment of pH 5.5 and above, the outer membrane will be dissolved exposing the inner core. This inner core will partially hydrate to form a gel layer and the drug release will occur via diffusion mechanism from a gel layer and subsequently through gel erosion.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

Oxybutynin relaxes bladder smooth muscle. Oxybutynin chloride exerts a direct

antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (antinicotinic effects).

Antimuscarinic activity resides predominantly in the R-isomer. A metabolite, desethyloxybutynin, has pharmacological activity similar to that of oxybutynin in *in vitro* studies.

## 12.2 Pharmacodynamics

In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that oxybutynin increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void.

## 12.3 Pharmacokinetics

### Absorption

Following the first dose of oxybutynin chloride extended-release tablets, oxybutynin plasma concentrations rise for 4 to 6 hours; thereafter steady concentrations are maintained for up to 24 hours, minimizing fluctuations between peak and trough concentrations associated with oxybutynin.

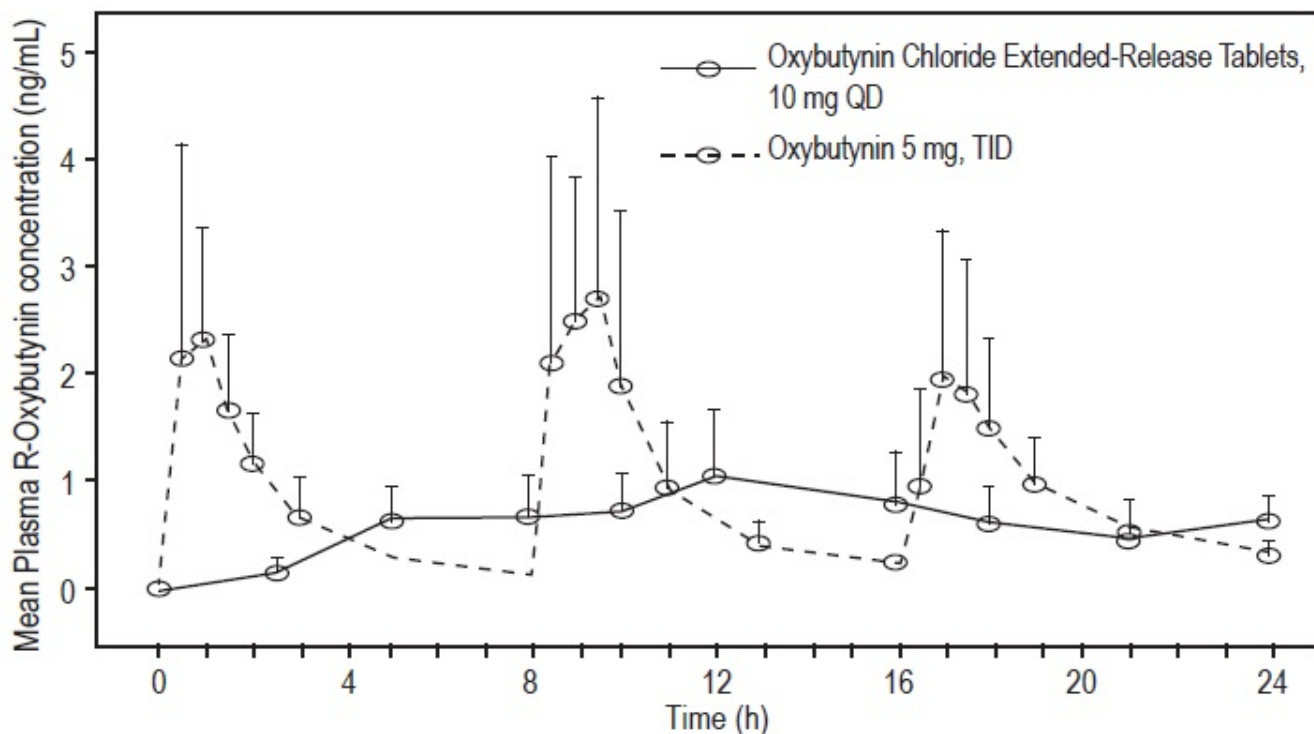
The relative bioavailabilities of R- and S-oxybutynin from oxybutynin chloride extended-release tablets are 156% and 187%, respectively, compared with oxybutynin. The mean pharmacokinetic parameters for R- and S-oxybutynin are summarized in Table 2. The plasma concentration-time profiles for R- and S-oxybutynin are similar in shape; Figure 1 shows the profile for R-oxybutynin.

**Table 2 Mean (SD) R- and S-Oxybutynin Pharmacokinetic Parameters Following a Single Dose of Oxybutynin Chloride Extended-Release Tablets 10 mg (n=43)**

| <b>Parameters (units)</b>          | <b>R-Oxybutynin</b> | <b>S-Oxybutynin</b> |
|------------------------------------|---------------------|---------------------|
| C <sub>max</sub> (ng/mL)           | 1 (0.6)             | 1.8 (1)             |
| T <sub>max</sub> (h)               | 12.7 (5.4)          | 11.8 (5.3)          |
| t <sub>1/2</sub> (h)               | 13.2 (6.2)          | 12.4 (6.1)          |
| AUC <sub>(0 to 48)</sub> (ng•h/mL) | 18.4 (10.3)         | 34.2 (16.9)         |
| AUC <sub>inf</sub> (ng•h/mL)       | 21.3 (12.2)         | 39.5 (21.2)         |

### Figure 1

**Mean R-oxybutynin plasma concentrations following a single dose of oxybutynin chloride extended-release tablets 10 mg and oxybutynin 5 mg administered every 8 hours (n=23 for each treatment).**



Steady state oxybutynin plasma concentrations are achieved by Day 3 of repeated oxybutynin chloride extended-release dosing, with no observed drug accumulation or change in oxybutynin and desethyloxybutynin pharmacokinetic parameters.

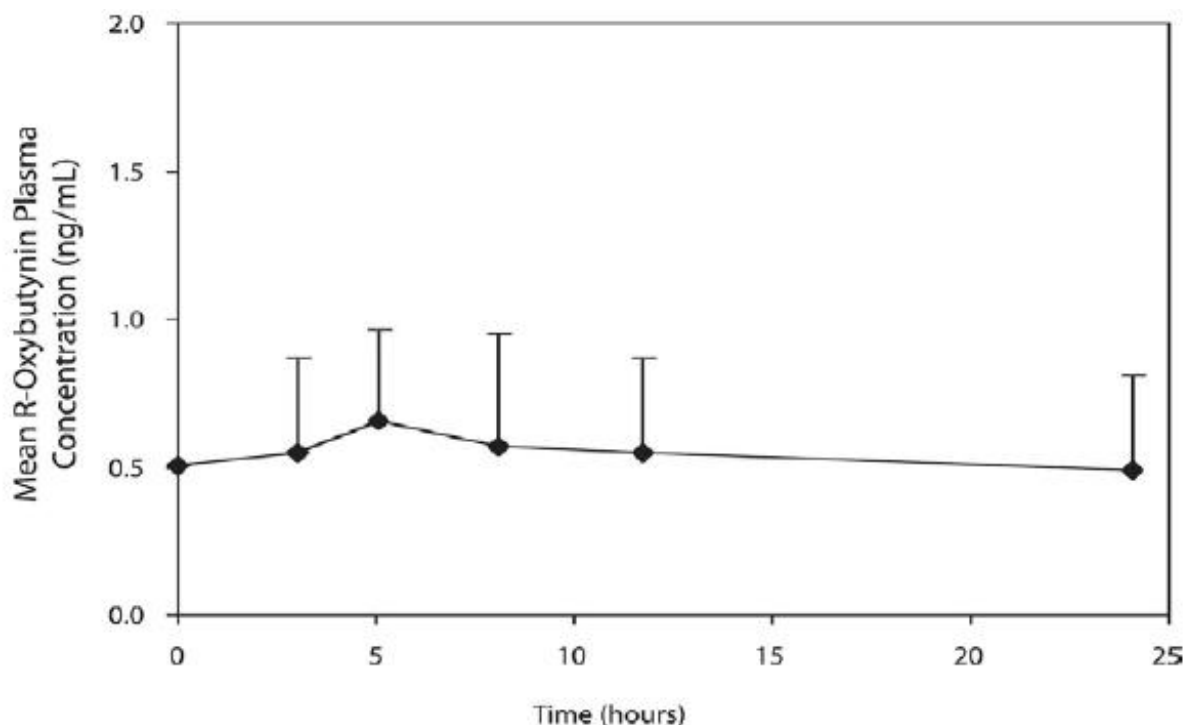
Oxybutynin chloride extended-release tablets steady state pharmacokinetics were studied in 19 children aged 5 to 15 years with detrusor overactivity associated with a neurological condition (e.g., spina bifida). The children were on oxybutynin chloride extended-release tablets total daily dose ranging from 5 to 20 mg (0.10 to 0.77 mg/kg). Sparse sampling technique was used to obtain serum samples. When all available data are normalized to an equivalent of 5 mg per day of oxybutynin chloride extended-release tablets, the mean pharmacokinetic parameters derived for R- and S-oxybutynin and R- and S-desethyloxybutynin are summarized in Table 3. The plasma-time concentration profiles for R- and S-oxybutynin are similar in shape; Figure 2 shows the profile for R-oxybutynin when all available data are normalized to an equivalent of 5 mg per day.

**Table 3 Mean  $\pm$  SD R- and S-Oxybutynin and R- and S-Desethyloxybutynin Pharmacokinetic Parameters in Children Aged 5 to 15 Following Administration of 5 to 20 mg Oxybutynin Chloride Extended-Release Tablets Once Daily (n=19), All Available Data Normalized to an Equivalent of Oxybutynin Chloride Extended-Release Tablets 5 mg Once Daily**

|                   | <b>R-Oxybutynin</b> | <b>S-Oxybutynin</b> | <b>R-Desethyloxybutynin</b> | <b>S-Desethyloxybutynin</b> |
|-------------------|---------------------|---------------------|-----------------------------|-----------------------------|
| $C_{max}$ (ng/mL) | 0.7 $\pm$ 0.4       | 1.3 $\pm$ 0.8       | 7.8 $\pm$ 3.7               | 4.2 $\pm$ 2.3               |
| $T_{max}$ (h)     | 5                   | 5                   | 5                           | 5                           |
| AUC (ng•h/mL)     | 12.8 $\pm$ 7        | 23.7 $\pm$ 14.4     | 125.1 $\pm$ 66.7            | 73.6 $\pm$ 47.7             |

**Figure 2**

**Mean steady state ( $\pm$  SD) R-oxybutynin plasma concentrations following administration of 5 to 20 mg oxybutynin chloride extended-release tablets once daily in children aged 5 to 15. Plot represents all available data normalized to an equivalent of oxybutynin chloride extended-release tablets 5 mg once daily.**



### *Food Effects*

The rate and extent of absorption and metabolism of oxybutynin are similar under fed and fasted conditions.

### *Distribution*

Oxybutynin is widely distributed in body tissues following systemic absorption. The volume of distribution is 193 L after intravenous administration of 5 mg oxybutynin chloride. Both enantiomers of oxybutynin are highly bound (>99%) to plasma proteins. Both enantiomers of N-desethyloxybutynin are also highly bound (>97%) to plasma proteins. The major binding protein is alpha-1 acid glycoprotein.

### *Metabolism*

Oxybutynin is metabolized primarily by the cytochrome P450 enzyme systems, particularly CYP3A4 found mostly in the liver and gut wall. Its metabolic products include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and desethyloxybutynin, which is pharmacologically active. Following oxybutynin chloride extended-release tablets administration, plasma concentrations of R- and S-desethyloxybutynin are 73% and 92%, respectively, of concentrations observed with oxybutynin.

## Excretion

Oxybutynin is extensively metabolized by the liver, with less than 0.1% of the administered dose excreted unchanged in the urine. Also, less than 0.1% of the administered dose is excreted as the metabolite desethyloxybutynin.

## Dose Proportionality

Pharmacokinetic parameters of oxybutynin and desethyloxybutynin ( $C_{max}$  and AUC) following administration of 5 to 20 mg of oxybutynin chloride extended-release tablets are dose proportional.

## Use in Specific Populations

### *Pediatric*

The pharmacokinetics of oxybutynin chloride extended-release tablets were evaluated in 19 children aged 5 to 15 years with detrusor overactivity associated with a neurological condition (e.g., spina bifida). The pharmacokinetics of oxybutynin chloride extended-release tablets in these pediatric patients were consistent with those reported for adults (see Tables 2 and 3, and Figures 1 and 2 above).

### *Gender*

There are no significant differences in the pharmacokinetics of oxybutynin in healthy male and female volunteers following administration of oxybutynin chloride extended-release tablets .

### *Race*

Available data suggest that there are no significant differences in the pharmacokinetics of oxybutynin based on race in healthy volunteers following administration of oxybutynin chloride extended-release tablets .

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### ***Carcinogenesis***

A 24 month study in rats at dosages of oxybutynin chloride of 20, 80, and 160 mg/kg/day showed no evidence of carcinogenicity. These doses are approximately 6, 25, and 50 times the maximum human exposure, based on a human equivalent dose taking into account normalization of body surface area.

#### ***Mutagenesis***

Oxybutynin chloride showed no increase of mutagenic activity when tested in *Schizosaccharomyces pompholiciformis*, *Saccharomyces cerevisiae*, and *Salmonella typhimurium* test systems.

#### ***Impairment of Fertility***

No impairment of fertility was seen in rats at dosages up to 75 mg/kg/day (24 times the MRHD on a mg/m<sup>2</sup> basis) when administered for 2 weeks prior to mating in females and for 9 weeks prior to mating in males.

## 14 CLINICAL STUDIES

Oxybutynin chloride extended-release tablets were evaluated for the treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency in three controlled efficacy studies. The majority of patients were Caucasian (89%) and female (91.9%) with a mean age of 59 years (range, 18 to 98 years). Entry criteria required that patients have urge or mixed incontinence (with a predominance of urge) as evidenced by  $\geq 6$  urge incontinence episodes per week and  $\geq 10$  micturitions per day. Study 1 was a fixed-dose escalation design, whereas the other two studies used a dose-adjustment design in which each patient's final dose was adjusted to a balance between improvement of incontinence symptoms and tolerability of side effects. All three studies included patients known to be responsive to oxybutynin or other anticholinergic medications, and these patients were maintained on a final dose for up to 2 weeks.

The efficacy results for the three controlled trials are presented in the following Tables 4, 5, and 6 and Figures 3, 4, and 5.

**Table 4 Number of Urge Urinary Incontinence Episodes Per Week (Study 1)**

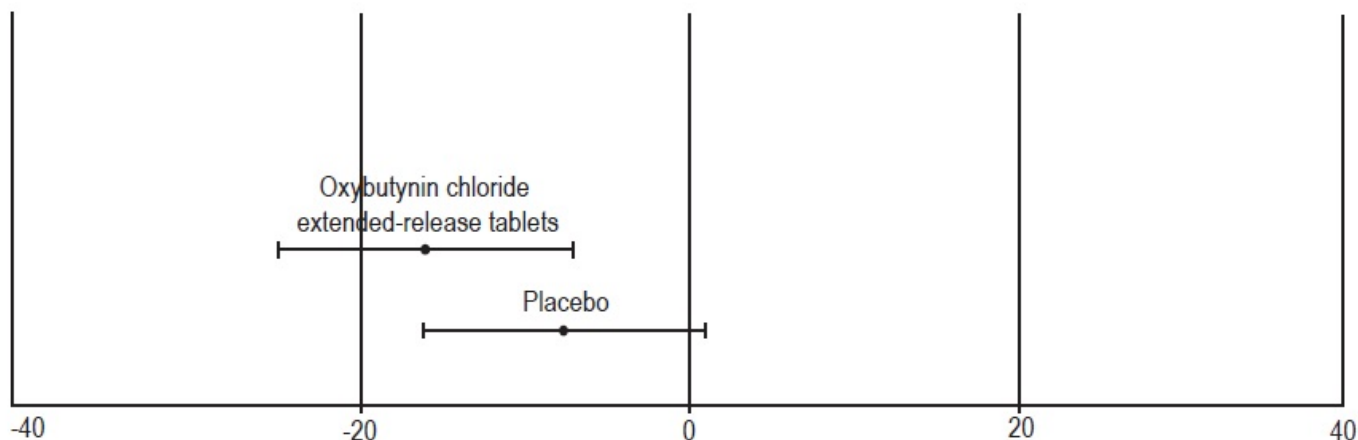
| <b>Study 1</b>   | <b>n</b> | <b>Oxybutynin Chloride<br/>Extended-Release<br/>Tablets</b> | <b>n</b> | <b>Placebo</b> |
|--|----------|---|----------|----------------|
| Mean Baseline  | 34       | 15.9  | 16       | 20.9           |
| Mean (SD) Change from<br>Baseline <sup>†</sup>   | 34       | -15.8 (8.9)   | 16       | -7.6 (8.6)     |
| 95% Confidence Interval<br>for Difference<br>(Oxybutynin chloride<br>extended-release Tablets<br>-Placebo) |          | (-13.6, -2.8)*  |          |                |

\* The difference between oxybutynin chloride extended-release tablets and placebo was statistically significant.

<sup>†</sup> Covariate adjusted mean with missing observations set to baseline values.

### Figure 3

**Mean Change ( $\pm$ SD) in Urge Urinary Incontinence Episodes Per Week from Baseline (Study 1)**



\*The difference between oxybutynin chloride extended-release tablets and placebo was statistically significant.

**Table 5 Number of Urge Urinary Incontinence Episodes Per Week (Study 2)**

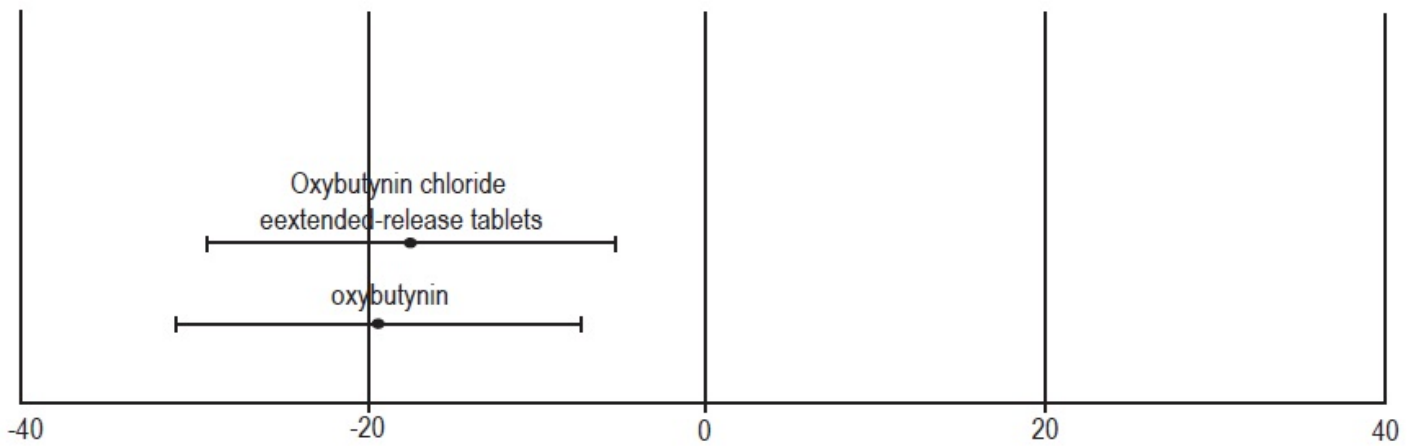
| <b>Study 2</b>   | <b>n</b> | <b>Oxybutynin Chloride Extended-Release Tablets</b> | <b>n</b> | <b>Oxybutynin</b> |
|--|----------|---|----------|-------------------|
| Mean Baseline  | 53       | 27.6  | 52       | 23.0              |
| Mean (SD) Change from Baseline <sup>†</sup>  | 53       | -17.6 (11.9)  | 52       | -19.4 (11.9)      |
| 95% Confidence Interval for Difference (Oxybutynin chloride extended-release tablets - oxybutynin) |          | (-2.8, 6.5)   |          |                   |

<sup>†</sup> Covariate adjusted mean with missing observations set to baseline values

**Figure 4**

**Mean Change ( $\pm$ SD) in Urge Urinary Incontinence Episodes Per Week from Baseline (Study 2)**





**Table 6 Number of Urge Urinary Incontinence Episodes Per Week (Study 3)**

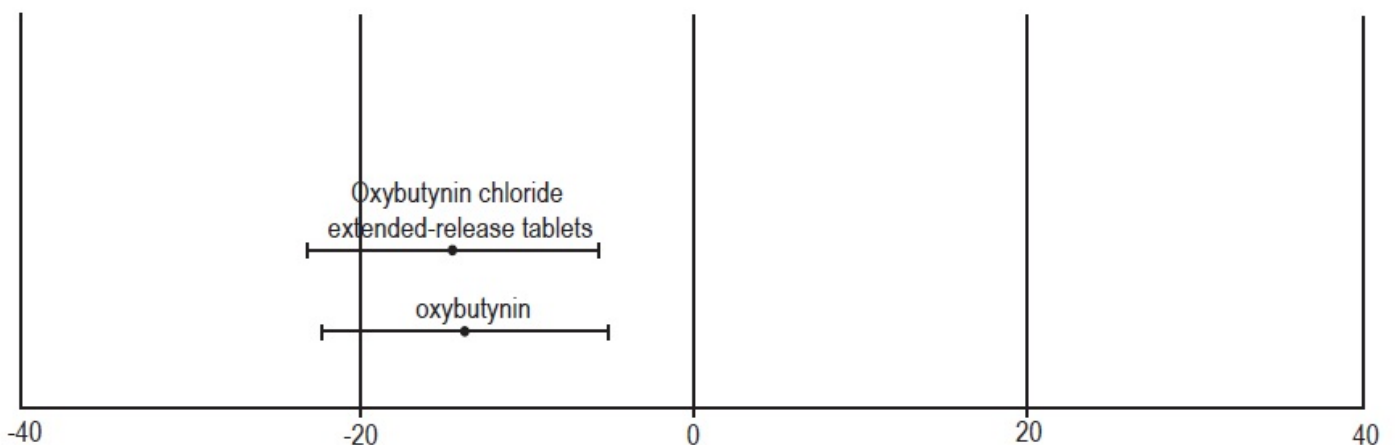
| Study 3  | n   | Oxybutynin Chloride Extended-Release Tablets | n   | Oxybutynin  |
|--|-----|--|-----|-------------|
| Mean Baseline  | 111 | 18.9   | 115 | 19.5        |
| Mean (SD) Change from Baseline <sup>†</sup>  | 111 | -14.5 (8.7)                                  | 115 | -13.8 (8.6) |
| 95% Confidence Interval for Difference (Oxybutynin chloride Extended-release tablets - oxybutynin) |     | (-3.0, 1.6)**                                |     |             |

\*\*The difference between oxybutynin chloride extended-release tablets and oxybutynin fulfilled the criteria for comparable efficacy.

<sup>†</sup> Convariate adjusted mean with missing observations set to baseline values

**Figure 5**

**Mean Change ( $\pm$ SD) in Urge Urinary Incontinence Episodes Per Week from Baseline (Study 3)**



\*\*The difference between oxybutynin chloride extended-release tablets and oxybutynin fulfilled the criteria for comparable efficacy.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

Oxybutynin Chloride Extended-release Tablets USP, 5 mg are white to off-white, round, beveled-edged, biconvex, coated-tablets debossed on one side with "255" and plain on other side and are supplied as follows:

NDC 0615-8219-39 in blistercards of 30 tablets

Oxybutynin Chloride Extended-release Tablets USP, 10 mg are white to off-white, round, beveled-edged, biconvex, coated-tablets debossed on one side with "256" and plain on other side and are supplied as follows:

Oxybutynin Chloride Extended-release Tablets USP, 15 mg are white to off-white, round, beveled-edged, biconvex, coated-tablets debossed on one side with "257" and plain on other side and are supplied as follows:

### **Storage**

Store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature].

Protect from moisture and humidity.

Keep out of reach of children.

## **17 PATIENT COUNSELING INFORMATION**

- Patients should be informed that oxybutynin may produce angioedema that could result in life threatening airway obstruction. Patients should be advised to promptly discontinue oxybutynin therapy and seek immediate medical attention if they experience swelling of the tongue, edema of the laryngopharynx, or difficulty breathing.
- Patients should be informed that anticholinergic (antimuscarinic) agents such as oxybutynin chloride extended-release tablets, may produce clinically significant adverse reactions related to anticholinergic activity such as:
  - Urinary retention and constipation
  - Heat prostration due to decreased sweating. Heat prostration can occur when anticholinergic medicines are administered in the presence of high environmental temperature.
    - Patients should be informed that anticholinergic medicines such as oxybutynin chloride extended-release tablets may produce drowsiness (somnolence), dizziness or blurred vision. Patients should be advised to exercise caution in decisions to engage in potentially dangerous activities until oxybutynin chloride extended-release tablets effects have been determined.
    - Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin chloride extended-release tablets.
    - Patients should be informed that oxybutynin chloride extended-release tablets should be swallowed whole with the aid of liquids. Patients should not chew, divide, or crush

tablets. The hydrated polymer system of the tablet is not rigid and is expected to be broken up by normal peristalsis in the GI tract. The biologically inert components of the tablet may occasionally remain intact during GI transit and will be eliminated in the feces as a soft, hydrated mass.

- Oxybutynin chloride extended-release tablets should be taken at approximately the same time each day.

**Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

Please address medical inquiries to, [MedicalAffairs@zydususa.com](mailto:MedicalAffairs@zydususa.com) or Tel.: 1-877-993-8779

**Manufactured by:**

**Zydus Lifesciences Ltd.**

Ahmedabad, India.

**Distributed by:**

**Zydus Pharmaceuticals (USA) Inc.**

Pennington, NJ 08534

2091952 Rev.: 01/23

**PACKAGE LABEL.PRINCIPAL DISPLAY PANEL**



VLI NDC 0615-8219-39  
Oxybutynin Chloride

ER Tabs USP  
5 mg

LOT 8219-

EXP

8219-AA-39 v02

QTY  
30

Mfg By Zydus

(NDC 68382-255-01)  
PKG BY VANGAIRD  
GLASGOW, KY 42141

See Boxed  
Statement  
on Reverse

Rx Only

(Zydus NDC 68382-255-01)  
Oxybutynin Chloride  
ER Tabs USP  
5 mg

Received: \_\_\_\_\_

|    |    |    |   |
|----|----|----|---|
| 31 | 24 | 16 | 8 |
| 30 | 23 | 15 | 7 |
| 29 | 22 | 14 | 6 |
| 28 | 21 | 13 | 5 |
| 27 | 20 | 12 | 4 |
| 26 | 19 | 11 | 3 |
| 25 | 18 | 10 | 2 |
| 24 | 17 | 9  | 1 |

Start Date \_\_\_\_\_ Start Time \_\_\_\_\_

STORE AT 20° - 25° C (68° - 77° F)  
(SEE USP CONTROLLED ROOM TEMPERATURE)  
Swallow tablets whole. Do not chew, divide  
or crush tablets.

Dispense in a tight container. Protect from  
moisture and humidity.

See package insert or label for dosage information  
**FOR INSTITUTIONAL USE ONLY**

|    |    |    |   |
|----|----|----|---|
| 16 | 8  |    |   |
| 30 | 23 | 15 | 7 |
| 29 | 22 | 14 | 6 |
| 28 | 21 | 13 | 5 |
| 27 | 20 | 12 | 4 |
| 26 | 19 | 11 | 3 |
| 25 | 18 | 10 | 2 |
| 24 | 17 | 9  | 1 |



The overall configuration of this package is a trademark of Omnicare, Inc.

Grid of 24 boxes, each containing:

- Manufacturer: Pkg by Vangard, Glasgow, KY 42141
- Product: Oxybutynin Chloride ER Tab USP 5 mg
- Lot: LOT 8219-
- Barcode
- NDC: 68382-255-01

# OXYBUTYNIN

oxybutynin tablet, film coated, extended release

## Product Information

|                                |                         |                           |                              |
|--------------------------------|-------------------------|---------------------------|------------------------------|
| <b>Product Type</b>            | HUMAN PRESCRIPTION DRUG | <b>Item Code (Source)</b> | NDC:0615-8219(NDC:68382-255) |
| <b>Route of Administration</b> | ORAL                    |                           |                              |

## Active Ingredient/Active Moiety

| Ingredient Name   | Basis of Strength   | Strength |
|---|---------------------|----------|
| OXYBUTYNIN CHLORIDE (UNII: L9F3D9RENQ) (OXYBUTYNIN - UNII:K9P6MC7092) | OXYBUTYNIN CHLORIDE | 5 mg     |

## Inactive Ingredients

| Ingredient Name                            | Strength |
|--|----------|
| ALGINIC ACID (UNII: 8C3Z4148WZ)            |          |
| HYDROGENATED CASTOR OIL (UNII: ZF94AP8MEY) |          |

|   |  |
|---|--|
| <b>HYPROMELLOSES</b> (UNII: 3NXW29V3WO)               |  |
| <b>LACTOSE MONOHYDRATE</b> (UNII: EWQ57Q8I5X)         |  |
| <b>MAGNESIUM STEARATE</b> (UNII: 70097M6I30)          |  |
| <b>METHACRYLIC ACID</b> (UNII: 1CS02G8656)            |  |
| <b>CELLULOSE, MICROCRYSTALLINE</b> (UNII: OP1R32D61U) |  |
| <b>POVIDONE</b> (UNII: FZ989GH94E)                    |  |
| <b>TALC</b> (UNII: 7SEV7J4R1U)                        |  |
| <b>TRIETHYL CITRATE</b> (UNII: 8Z96QXD6UM)            |  |

### Product Characteristics

|                 |                            |                     |          |
|-----------------|----------------------------|---------------------|----------|
| <b>Color</b>    | white (WHITE TO OFF-WHITE) | <b>Score</b>        | no score |
| <b>Shape</b>    | ROUND (ROUND)              | <b>Size</b>         | 7mm      |
| <b>Flavor</b>   |                            | <b>Imprint Code</b> | 255      |
| <b>Contains</b> |                            |                     |          |

### Packaging

| # | Item Code        | Package Description                                     | Marketing Start Date | Marketing End Date |
|---|------------------|---|----------------------|--------------------|
| 1 | NDC:0615-8219-39 | 30 in 1 BLISTER PACK; Type 0: Not a Combination Product | 01/25/2019           |                    |

### Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|--|----------------------|--------------------|
| ANDA               | ANDA202332                               | 08/10/2017           |                    |

**Labeler** - NCS HealthCare of KY, LLC dba Vangard Labs (050052943)

### Establishment

| Name                                       | Address | ID/FEI    | Business Operations |
|--|---------|-----------|---------------------|
| NCS HealthCare of KY, LLC dba Vangard Labs |         | 050052943 | repack(0615-8219)   |

Revised: 4/2024

NCS HealthCare of KY, LLC dba Vangard Labs