OXYBUTYNIN CHLORIDE—oxybutynin chloride tablet

OXYBUTYNIN CHLORIDE TABLETS USP

Rx Only

DESCRIPTION
Oxybutynin Chloride Tablets USP are very pale blue, round, biconvex, scored, debossed tablets containing 5 mg of oxybutynin chloride, USP. Chemically, oxybutynin chloride, USP is 1,4-dialkylamino-2-butynyl phenylcyclohexylglycolate hydrochloride. The structural formula appears below:

\[ \text{C}_{22}\text{H}_{30}\text{N}_{2}\text{O}_{4}\text{Cl} \]

Oxybutynin chloride, USP is a white crystalline solid. It is readily soluble in water and acids, but relatively insoluble in alcohols.

Oxybutynin Chloride Tablets USP also contain calcium stearate, microcrystalline cellulose, anhydrous lactose, sodium starch glycolate and FDC Blue No. 1. Administration Lake.

Oxybutynin Chloride Tablets USP are for oral administration.

Uses USP Dissolution Test 2.

Therapeutic Category: Antispasmodic, anticholinergic.

CLINICAL PHARMACOLOGY
Oxybutynin chloride exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Oxybutynin chloride has an anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (anticholinergic effects).

Oxybutynin chloride relieves bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that oxybutynin chloride increases bladder (vesical) capacity, diminishes the frequency of un inhibited contractions of the detrusor muscle, and delays the initial desire to void. Oxybutynin chloride thus decreases urgency and the frequency of both incontinent episodes and voluntary urinations.

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

Pharmacokinetics
Absorption
Following oral administration of oxybutynin chloride tablets, oxybutynin is rapidly absorbed achieving Cmax within an hour, following which plasma concentration decreases with an effective half-life of approximately 2 to 3 hours. The absolute bioavailability of oxybutynin is reported to be about 0% (range 1.6 to 10.9%) for the tablets. Wide interindividual variation in pharmacokinetic parameters is evident following oral administration of oxybutynin.

The mean pharmacokinetic parameters for R- and S-oxybutynin are summarized in Table 1. The plasma concentration-time profiles for R- and S-oxybutynin are similar in shape. Figure 1 shows the profile for R-oxybutynin.

Table 1: Mean (SD) R- and S-Oxybutynin Pharmacokinetic Parameters Following Three Doses of Oxybutynin Chloride 5 mg Administered Every 8 Hours (n = 23)

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>R-Oxybutynin</th>
<th>S-Oxybutynin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax  (hr)</td>
<td>3.4 (2.2)</td>
<td>3.5 (2.3)</td>
</tr>
<tr>
<td>T1/2  (hr)</td>
<td>8.0 (4.4)</td>
<td>7.5 (4.5)</td>
</tr>
<tr>
<td>AUC0-t (ng.h/mL)</td>
<td>22.6 (11.5)</td>
<td>24.3 (12.3)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>30.1 (17.5)</td>
<td>37.7 (18.7)</td>
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</table>

Figure 1: Mean R-Oxybutynin Plasma Concentrations Following Three Doses of Oxybutynin Chloride 5 mg Administered Every 8 Hours for 1 Day in 23 Healthy Adult Volumes

Oxybutynin chloride steady-state pharmacokinetics were also studied in 11 pediatric patients with detrusor overactivity associated with a neurogenic condition (e.g., spina bifida). These pediatric patients were on oxybutynin chloride tablets with total daily dose ranging from 7.5 mg to 15 mg (0.22 to 0.53 mg/kg). Overall, most patients (85%) were taking a total daily oxybutynin chloride dose between 10 mg and 15 mg. Sparse sampling technique was used to obtain within subjects. When all available data are normalized to an equivalent of 5 mg twice daily oxybutynin chloride, the mean pharmacokinetic parameters derived for R- and S-oxybutynin and R- and S-desethyloxybutynin are summarized in Table 2. The plasma-time concentration profiles for R- and S-oxybutynin are similar in shape. Figure 2 shows the profile for S-oxybutynin when all available data are normalized to an equivalent of 5 mg twice daily oxybutynin chloride.

Table 2: Mean ± SD R- and S-Oxybutynin Chloride Chloride and R- and S-Desethyloxybutynin Chloride Parameters in Children Aged 5 to 15 Following Administration of 7.5 mg to 15 mg Total Daily Oxybutynin Chloride Chloride Tablets (N = 15)

<table>
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Figure 2: Mean Steady-State (± SD) R-Oxybutynin Plasma Concentrations Following Administration of Total Daily Oxybutynin Chloride Chloride Tablet Dose of 7.5 mg to 15 mg (0.22 mg/kg to 0.53 mg/kg) in Children 5 to 15 Years of Age. – Plot Represents All Available Data Normalized to the Equivalency of Oxybutynin Chloride 5 mg BID or TID at Steady-State

Food Effects
Data in the literature suggests that oxybutynin solutions coadministered with food resulted in a slight delay in absorption and an increase in its bioavailability by 20% (± 18%).

Distribution
Oxybutynin is widely distributed in body tissues following systemic absorption. The volume of distribution is 10 L after intravenous administration of 5 mg oxybutynin chloride. Both enantiomers of oxybutynin are highly bound (~95%) to plasma protein. Both enantiomers of desethyloxybutynin are also highly bound (~97%) to plasma protein. The major limiting protein is alpha-1 acid glycoprotein.

Metabolism
Oxybutynin is metabolized primarily by the cytochrome P450 enzyme system, particularly CYP3A4 found mostly in the liver and gut wall. Its metabolite include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and desethyloxybutynin, which is pharmacologically active.

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

CLINICAL STUDIES
Oxybutynin chloride was well tolerated in patients administered the drug in controlled studies of 30 days’ duration and uncontrolled studies in which some of the patients received the drug for 2 years.

INDICATIONS AND USAGE
Oxybutynin Chloride Tablets USP are indicated for the relief of symptoms of bladder instability associated with voiding inpatients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dribbling).

CONTRAINDICATIONS
Oxybutynin chloride is contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

Oxybutynin chloride is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

WARNINGS
Angiomata 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.

PRECAUTIONS
Central Nervous System Effects
Oxybutynin is associated with anticholinergic central nervous system (CNS) effects (see ADVERSE REACTIONS). A variety of CNS anticholinergic effects have been reported, including hallucination, 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. If a patient experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered.

Oxybutynin chloride should be used with caution in patients with preexisting dementia treated with cholinesterase inhibitors due to the risk of antagonized symptoms.

General
Oxybutynin chloride should be used with caution in elderly patients with hepatic or renal impairment, and in patients with myasthenia gravis.

Oxybutynin chloride may aggravate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmia, heat stroke, hyperpyrexia, myasthenia gravis, and porphyria cutanea.

Urinary Retention
Oxybutynin chloride should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention (see CONTRAINDICATIONS).

Gastrointestinal Disorders
Oxybutynin chloride should be administered with caution to patients with gastroesophageal reflux disease because of the risk of gastroesophageal reflux (see CONTRAINDICATIONS).

Administration of oxybutynin chloride to patients with ulcerative colitis may suppress intestinal motility to the point of producing a paralytic ileus and precipitate or aggravate toxic megacolon, a serious complication of the disease.

Oxybutynin chloride, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as diverticulosis, and intestinal atony.

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

Information for Patients
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 edema of the tongue, hypopharynx, or larynx.

Patients should be informed that heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as oxybutynin chloride are administered in the presence of high environmental temperature.

Because anticholinergic agents such as oxybutynin may produce dry mouth, constipation, somnolence (drowsiness), and other anticholinergic-like effects, may increase the frequency and/or severity of such effects.

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 concurrently administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index.

Mean oxybutynin chloride plasma concentrations were approximately 3- to 4-fold higher when oxybutynin chloride was administered with lactulose, a potent CYP3A4 inhibitor.

Other inhibitors of the cytochrome P450 3A4 enzyme system, such as anticonvulsants (e.g., carbamazepine and phenytoin), macrolide antibiotics (e.g., erythromycin and clarithromycin), and other oxybutynin mean pharmacokinetic parameters (i.e., TVSSD and AUC). The clinical relevance of such potential interactions is not known. Caution should be used when such drugs are administered.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-month study in rats at doses of oxybutynin chloride of 20, 80, and 160 mg/kg/day showed no evidence of carcinogenicity. These doses are approximately 25, 50, and 100 times the maximum human exposure, based on surface area.

Oxybutynin chloride showed no increase of mutagenic activity when tested in Salmonella typhimurium, Escherichia coli, and Saccharomyces cerevisiae and Salmonella typhimurium reversion systems.

Reproduction studies using oxybutynin chloride in the hamster, rabbit, rat, and mouse have shown no evidence of impaired fertility. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when oxybutynin chloride is administered to a nursing woman.

Reproduction studies using oxybutynin chloride in the hamster, rabbit, rat, and mouse have shown no evidence of impaired fertility or harm to the animal fetus. The safety of oxybutynin chloride administered to women who are or may become pregnant has not been established. Therefore, oxybutynin chloride should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefit outweighs the possible hazard.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when oxybutynin chloride is administered to a nursing woman.

Pediatric Use

The safety and efficacy of oxybutynin chloride administration have been demonstrated for pediatric patients 5 years of age and older (see DOSAGE AND ADMINISTRATION).

The safety and efficacy of oxybutynin chloride studies involved young, elderly, and frail elderly volunteers. Aromatization 1980; 22 (7): 839-880.


TEVA PHARMACEUTICALS USA, INC.

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REMEMBER TO PACKAGE LABELS FOR DISTRIBUTORS

NDC NUMBER

Rev: D-9/2015

OXY-1

OVERDOSAGE

Overdosage with oxybutynin chloride has been associated with anticholinergic effects including central nervous system excitation (e.g., restlessness, tremor, irritability, convolution, delirium, hallucinations), flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention. Other symptoms may include hypertension or hypotension, respiratory failure, paralysis, and coma.

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 nystagmus, followed by disorientation and agitation on awakening, dilated pupils, dry skin, cardiac arrhythmia, and retention of urine. Both patients fully recovered with symptomatic treatment.

DOSAGE AND ADMINISTRATION

Adults

The usual dose is one 5 mg tablet two to three times a day. The maximum recommended dose is one 5 mg tablet four times a day. A lower starting dose of 2.5 mg two to three times a day is recommended for the frail elderly.

Pediatric Patients Over 5 Years of Age

The usual dose is one 5 mg tablet two times a day. The maximum recommended dose is one 5 mg tablets three times a day.

HOW SUPPLIED

Oxybutynin Chloride Tablets USP are available as follows: 5 mg – Very pale blue, round, biconvex, scored tablets. Distributed with PLIVA 464 on one side and scored on the other side. Available in bottles of 100 (NDC: 50111-456-01), 500 (NDC:50111-456-02), and 1000 (NDC: 50111-456-03) tablets.

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

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

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

REFERENCES

3. Olvecrona et al. Pharmacokinetics and Clinical Effects of Oxybutynin in Geriatric Patients. J.


5. TEVA PHARMACEUTICALS USA, INC.

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ADVERSE REACTIONS

The safety and efficacy of oxybutynin chloride was evaluated in a trial of 395 patients in three clinical trials. These patients were treated with oxybutynin chloride 5 to 20 mg/day for up to 6 weeks.

Table 3 lists the incidence of adverse events judged by investigators to be at least possibly related to treatment and reported by at least 5% of patients.

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Event</th>
<th>Oxybutynin Chloride (5 to 20 mg/day) (n = 199)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and Infections</td>
<td>Urinary tract infection</td>
<td>6.5%</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Insomnia</td>
<td>2.6%</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Nervousness</td>
<td>1.4%</td>
</tr>
<tr>
<td>Neurologic System Disorders</td>
<td>Dizziness</td>
<td>16.6%</td>
</tr>
<tr>
<td>Neurologic System Disorders</td>
<td>Nausea</td>
<td>14%</td>
</tr>
<tr>
<td>Neurologic System Disorders</td>
<td>Headache</td>
<td>6.5%</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>Blurred vision</td>
<td>9.6%</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Diarrhea</td>
<td>11%</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Dysphagia</td>
<td>8%</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>Urinary Retention</td>
<td>8%</td>
</tr>
</tbody>
</table>

The most common adverse events reported by patients receiving oxybutynin chloride 5 to 20 mg/day were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related.

In addition, the following adverse events were reported by 1% to 5% of patients receiving oxybutynin chloride (5 to 20 mg/day) in all studies. Infections and Infecctions; gastroenteritis; upper respiratory tract infection, bronchitis, cystitis, fungal infection; Menillicosis and Narcan Use Disorders: fluid-overload; Psychotropic Disorders: confusion, state; Nervous System Disorders: dysphagia, sinus bradycardia, Erythrocyte Disorders: anemia, platelets, hemorrhage; thrombocytopenia; Respiratory, Thoracic and Mediastinum Disorders: dyspnea, cough, pharyngitis, laryngitis; pain, dysphasia, cough, pharyngitis, laryngitis; pain, dryness, cough, pyrexia, sweating, dyspnea, cough, pharyngitis, laryngitis; pain, dryness; cough, pyrexia, sweating, dyspnea; crush injury, cardiac arrhythmia, vomiting; gastrointestinal disorders; increased blood glucose increased, blood pressure decreased; injury, poisoning, and Procedures Complication.

Postermarking Surveillance

Because posteriormarking adverse events 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. The following additional adverse events have been reported from worldwide posteriormarking experience with oxybutynin chloride: Psychiatric Disorders: suicidal ideation, drug-use, hallucinations, memory impairment. Nervous System Disorders: convulsions; Eye Disorders: cycloplegia, mydriasis; Gastrointestinal Disorders: dysphagia, acid reflux; Gastrointestinal Disorders: decrease gastrointestinal motility; Skin and Subcutaneous Tissue Disorders: dry skin, pruritus, Maculopapular and Connective Tissue Disorders: back pain, arthralgia, pain in extremity, flush, pain; Renal and Urinary Disorders: dysuria, pollakiuria; General Disorders and Administration Site Conditions: fatigue, edema peripheral, asthenia, pain, thirst, edema, increased blood pressure increased; blood glucose increased, blood pressure decreased; injury, poisoning, and Procedures Complication.

OVERDOSAGE

Treatment should be symptomatic and supportive. Activated charcoal as well as a cathartic may be administered.