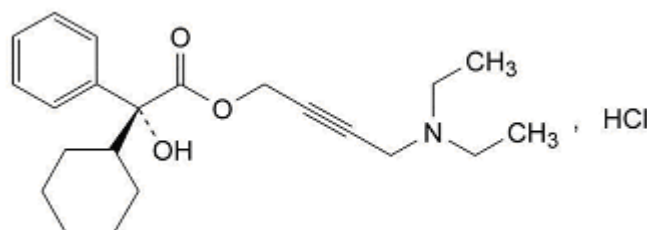


LYRINEL[®] XL Extended-Release Tablets

DATA SHEET

NAME OF THE MEDICINE

Oxybutynin hydrochloride



$C_{22}H_{31}NO_3 \cdot HCl$ MW 394.0
CAS-1508-65-2

DESCRIPTION

LYRINEL XL is available as an extended-release tablet for once daily oral administration containing 5, 10 or 15 mg oxybutynin hydrochloride. LYRINEL XL tablets contain the following inactive ingredients: cellulose acetate, hypromellose, lactose, magnesium stearate, polyethylene glycol, polyethylene oxide, synthetic iron oxides, sodium chloride, butylated hydroxytoluene and Opadry ink black WB NS-78-17715. The 5 mg tablet also contains Opadry light yellow YS-12871-A. The 10 mg tablet also contains Opadry pink YS-14518-A. The 15 mg tablet also contains Opadry grey YS-17506-A.

PHARMACOLOGY

Pharmacodynamics

Oxybutynin hydrochloride is a synthetic tertiary amine with direct spasmolytic and anticholinergic action on the smooth musculature of the detrusor muscle of the bladder. It increases bladder capacity, reduces the frequency of uninhibited detrusor contractions and delays the first urge to urinate. Thus, it decreases the symptoms of urinary incontinence due to either idiopathic detrusor instability or detrusor hyperreflexia.

Pharmacokinetics

The pharmacokinetics of LYRINEL XL were similar in all patients studied, irrespective of gender or age and are unaffected by food intake.

Absorption: Following the first dose of LYRINEL XL, oxybutynin plasma concentrations rise for 4 to 6 hours; thereafter, steady concentrations are maintained for up to 24 hours, thus minimising the fluctuations between peak and trough concentrations associated with oxybutynin immediate release formulations.

Distribution: Oxybutynin is widely distributed in body tissue following systemic absorption. The volume of distribution is 193 L after intravenous administration of 5 mg oxybutynin hydrochloride. Both enantiomers of oxybutynin are highly bound (>99%) 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 LYRINEL XL administration, plasma concentrations of R- and S-desethyloxybutynin are 73% and 92%, respectively, of concentrations observed with oxybutynin immediate release formulations.

Elimination: Oxybutynin is extensively metabolised 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.

CLINICAL TRIALS

LYRINEL XL was demonstrated to be effective for the treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency and frequency in three controlled studies and one open label study. The majority of patients were Caucasian (89.0%) 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 ≥ 6 urge incontinence episodes per week and ≥ 10 micturitions per day.

Study MR 9 was a 6 week forced dose escalation design, multicentre, randomised, double-blind, placebo and active controlled, parallel group study in 82 female patients. The results show that LYRINEL XL was significantly ($p=0.001$) more effective than placebo and was not different ($p=0.181$) from immediate release oxybutynin in reducing urge urinary incontinence episodes.

Studies MR 10 and MR 12 were 8 week randomised, multicentre, double blind, parallel group, dose titration studies, in 105 and 226 patients respectively. The results show that LYRINEL XL has similar efficacy to the immediate release oxybutynin comparator in reducing urge incontinence episodes, producing overall continence and decreasing voiding frequency. Overall, all dry mouth events tended to be reported by fewer patients using LYRINEL XL than with immediate release oxybutynin.

INDICATIONS

LYRINEL XL is indicated for the treatment of overactive bladder with symptoms of urinary incontinence, urgency and frequency.

CONTRAINDICATIONS

LYRINEL XL is contraindicated in patients with:

- known hypersensitivity to oxybutynin or any inactive ingredient used in this product (see **DESCRIPTION**);
- urinary retention
- gastric retention and other severe decreased gastrointestinal motility conditions
- uncontrolled narrow-angle glaucoma.

PRECAUTIONS

Use with caution in the following circumstances

Oxybutynin is associated with anticholinergic central nervous system (CNS) effects (see **ADVERSE REACTIONS**). 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.

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 has the potential to become 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.

Heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as oxybutynin hydrochloride are administered in the presence of high environmental temperature.

Because anticholinergic agents such as oxybutynin hydrochloride may produce drowsiness (somnolence) or blurred vision, patients should be advised to exercise caution.

LYRINEL XL should be given with caution in patients with the following conditions:

- hepatic or renal impairment;
- clinically significant bladder outflow obstruction because of the risk of urinary retention (see **Contraindications**);
- gastrointestinal obstructive and gastrointestinal motility disorders because of risk of gastric retention (see **Contraindications**);
- conditions such as ulcerative colitis due to the potential for decreased gastrointestinal motility;
- myasthenia gravis due to the risk of symptom aggravation;
- gastroesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis;
- pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic).
- pre-existing dementia treated with cholinesterase inhibitors due to the risk of aggravation of symptoms.

Carcinogenicity and mutagenicity

A 24-month study in rats at dosages of oxybutynin hydrochloride 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 surface area.

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

Effects on fertility

Reproduction studies with oxybutynin hydrochloride in the mouse, rat, hamster, and rabbit showed no evidence of impaired fertility.

Use in pregnancy

Category B1

Reproduction studies with oxybutynin hydrochloride in the mouse, rat, hamster, and rabbit showed no evidence of impaired fertility or harm to the animal foetus. The safety of LYRINEL XL administered to women who are or who may become pregnant has not been established. Consequently, risks and potential benefits should be considered before this drug is administered to pregnant patients.

Use in lactation

It is not known whether oxybutynin is excreted in human milk. Caution should be exercised if LYRINEL XL is administered to a nursing woman

Interactions with other medicines

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 (e.g., convulsions).

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 (e.g., digitalis).

Mean oxybutynin hydrochloride plasma concentrations were approximately 2 fold higher when oxybutynin was 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 increase oxybutynin mean pharmacokinetic parameters (i.e., C_{max} and AUC). The clinical relevance of such potential interactions is not known. Caution should be used when such drugs are co-administered.

Effects on Ability to Drive and Use Machines

No studies have been performed on the effect of LYRINEL XL on the ability to drive and use machines. Because anticholinergic agents such as oxybutynin may produce drowsiness or blurred vision, patients should be advised to exercise caution.

Instructions for the patient

LYRINEL XL must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

ADVERSE REACTIONS

The safety of LYRINEL XL was evaluated in 1030 subjects who participated in a total of six double-blind, controlled (i.e., placebo or active comparator) and open-label (i.e., no control group) clinical trials for the management of overactive bladder. Of the 1030 subjects who were treated with LYRINEL XL in the six clinical trials, 774 subjects participated in five double-blind, controlled clinical trials and 256 subjects participated in one open-label clinical trial.

The most common adverse reactions reported during clinical trials were dry mouth, constipation, diarrhoea, headache, somnolence and dizziness.

Adverse drug reactions (ADRs) reported by $\geq 1\%$ of LYRINEL XL-treated subjects in the five double-blind clinical trials are shown in Table 1.

Table 1. Adverse Drug Reactions Reported by ≥ 1% of LYRINEL XL-treated Subjects in Five Double-blind, Controlled Clinical Trials of LYRINEL XL

| System/Organ Class Preferred Term | LYRINEL XL 5 to 30 mg/day n = 774 % | Ditropan IR ¹ 5 to 20 mg/day n = 199 % | Detrol LA ² 4 mg/day n = 592 % | Placebo n = 33 % |
|---|--|--|--|------------------------|
| Psychiatric Disorders | | | | |
| Insomnia | 3.0 | 5.5 | 0.8 | 3.0 |
| Nervous System Disorders | | | | |
| Headache | 7.5 | 8.0 | 6.6 | 15.2 |
| Somnolence | 5.6 | 14.1 | 1.9 | 27.3 |
| Dizziness | 5.0 | 16.6 | 2.9 | 3.0 |
| Dysgeusia | 1.6 | 1.5 | 0.3 | 0 |
| Eye Disorders | | | | |
| Vision blurred | 4.3 | 9.6 | 1.5 | 33.3 |
| Dry eye | 3.1 | 2.5 | 1.4 | 0 |
| Respiratory, Thoracic and Mediastinal Disorders | | | | |
| Cough | 1.9 | 3.0 | 2.7 | 0 |
| Oropharyngeal pain | 1.9 | 1.5 | 1.5 | 0 |
| Dry throat | 1.7 | 2.5 | 0.2 | 0 |
| Nasal dryness | 1.7 | 4.5 | 1.0 | 0 |
| Gastrointestinal Disorders | | | | |
| Dry mouth | 34.9 | 72.4 | 24.8 | 42.4 |
| Constipation | 8.7 | 15.1 | 6.9 | 24.2 |
| Diarrhoea | 7.9 | 6.5 | 5.4 | 3.0 |
| Dyspepsia | 4.5 | 6.0 | 2.9 | 3.0 |
| Nausea | 4.5 | 11.6 | 1.5 | 12.1 |
| Abdominal pain | 1.6 | 2.0 | 1.2 | 3.0 |
| Vomiting | 1.3 | 1.5 | 2.7 | 0 |
| Flatulence | 1.2 | 2.5 | 0.7 | 6.1 |
| Gastroesophageal reflux disease | 1.0 | 0.5 | 0.3 | 0 |
| Skin and Subcutaneous Tissue Disorders | | | | |
| Dry skin | 1.8 | 2.5 | 0.5 | 3.0 |
| Pruritus | 1.3 | 1.5 | 0.7 | 0 |
| Renal and Urinary Disorders | | | | |
| Dysuria | 1.9 | 2.0 | 0.8 | 0 |
| Urinary hesitation | 1.9 | 8.5 | 0.3 | 0 |
| Urinary retention | 1.2 | 3.0 | 0.5 | 0 |
| General Disorders and Administration Site Conditions | | | | |
| Fatigue | 2.6 | 3.0 | 1.9 | 6.1 |
| Investigations | | | | |
| Residual urine volume ³ | 2.3 | 3.5 | 0.8 | 3.0 |

¹ IR = immediate release

² LA = long acting

³ The bundled term residual urine volume consists of the preferred terms residual urine volume and residual urine volume increased

Additional ADRs reported by < 1% of LYRINEL XL-treated subjects in the six double-blind, controlled and open-label clinical trials that are not reported in Table 1 are shown in Table 2.

Table 2. Adverse Drug Reactions Reported by < 1% of LYRINEL XL-treated Subjects in Six Double-blind, Controlled and Open-label Clinical Trials

| |
|--|
| System/Organ Class Preferred Term |
| Metabolism and Nutrition Disorders Anorexia, Fluid retention |
| Vascular Disorders Flushing, Hot flush |
| Respiratory, Thoracic and Mediastinal Disorders Dysphonia, Throat irritation |
| Gastrointestinal Disorders Abdominal discomfort, Dysphagia, Frequent bowel movements |
| Skin and Subcutaneous Tissue Disorders Rash |
| Renal and Urinary Disorders Residual urine |
| General Disorders and Administration Site Conditions Chest discomfort, Mucosal dryness, Thirst |

Postmarketing Data

Adverse drug reactions first identified during postmarketing experience with LYRINEL XL are included in Table 3. The frequencies are provided according to the following convention:

| | |
|-------------|--|
| Very common | ≥ 1/10 |
| Common | ≥ 1/100 to < 1/10 |
| Uncommon | ≥ 1/1,000 and < 1/100 |
| Rare | ≥ 1/10,000 and < 1/1,000 |
| Very Rare | < 1/10,000, including isolated reports |

Table 3. Adverse Drug Reactions Identified During Postmarketing Experience with LYRINEL XL by Frequency Category Estimated from Spontaneous Reporting Rates

| |
|--|
| Infections and Infestations <i>Very rare</i> Urinary tract infection |
| Immune System Disorders <i>Very rare</i> Hypersensitivity |
| Psychiatric Disorders <i>Rare</i> Hallucinations <i>Very rare</i> Agitation, Confusional state, Memory impairment, Psychotic disorder |
| Nervous System Disorders <i>Rare</i> Convulsions |
| Eye Disorders <i>Very rare</i> Glaucoma |
| Respiratory, Thoracic and Mediastinal Disorders <i>Very rare</i> Nasal congestion |
| Cardiac Disorders <i>Rare</i> Arrhythmia, Tachycardia |

| | |
|---|-----------------------|
| <i>Very rare</i> | Palpitations |
| Vascular Disorders | |
| <i>Very rare</i> | Hypertension |
| Skin and Subcutaneous Tissue Disorders | |
| <i>Very rare</i> | Angioedema, Urticaria |
| Renal and Urinary Disorders | |
| <i>Rare</i> | Impotence |
| Injury, Poisoning and Procedural Complications | |
| <i>Very rare</i> | Fall |

DOSAGE AND ADMINISTRATION

Adults

LYRINEL XL must be swallowed whole with the aid of liquids and must not be chewed, divided or crushed. LYRINEL XL may be administered with or without food.

Patients New to Oxybutynin: The recommended starting dose of LYRINEL XL is 5 mg once daily. Dosage may be adjusted in 5 mg increments to achieve a balance of efficacy and tolerability. In general, dosage adjustment may proceed at approximately weekly intervals.

Patients Currently Using Oxybutynin: Clinical judgement should be used when selecting the appropriate dose of LYRINEL XL, taking into account the current oxybutynin immediate-release dose.

In patients requiring a higher dose, 20 mg once daily is usually sufficient. A daily dose above 30 mg is not recommended.

Use in Children

The safety and efficacy of LYRINEL XL have not been established in patients under 18 years. The use of LYRINEL XL in children is not recommended.

OVERDOSAGE

Signs and Symptoms

The symptoms of overdosage progress from an intensification of the usual CNS disturbances (from restlessness and excitement to psychotic behaviour), circulatory changes (flushing, fall in blood pressure, circulatory failure etc.), respiratory failure, paralysis and coma.

Treatment

Treatment consists of appropriate measures:

- Immediate gastric lavage, or
- Physostigmine by slow intravenous injection

Adults: 0.5 to 2.0 mg I.V. slowly, repeated after 5 minutes if necessary, up to a maximum of 5 mg.

Children: 30 µg/kg i.v. slowly, repeated as necessary, up to a maximum of 2 mg.

Fever should be treated symptomatically with tepid sponging or ice packs.

In pronounced restlessness or excitation, diazepam 10 mg may be given by intravenous injection. Tachycardia may be treated with intravenous propranolol and urinary retention managed by bladder catheterisation.

In the event of progression of curare-like effects to paralysis of the respiratory muscles, mechanical ventilation will be required.

The continuous release of oxybutynin from LYRINEL XL should be considered when treating patients with overdose. Patients should be monitored for at least 24 hours.

PRESENTATION

LYRINEL XL oxybutynin hydrochloride extended-release tablets are:

- 5mg: round yellow tablet with "5 XL" printed on one side with black ink
- 10 mg: round pink with "10 XL" printed on one side with black ink
- 15 mg: round grey "15 XL" printed on one side with black ink.

LYRINEL XL tablets are supplied in HDPE bottles with a child resistant closure, containing silica gel desiccant, in pack sizes of 7, 14, 30, 60, 90 or 100 tablets.

Store below 25°C. Keep container tightly closed.

LYRINEL XL 5mg , 10mg and 15mg tablets are not currently marketed in New Zealand.

MEDICINE CLASSIFICATION

Prescription Medicine

STORAGE

Store below 25°C. Keep container tightly closed.

SHELF LIFE

3 years

SPONSOR

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