Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lyrinel XL ™15 mg prolonged release tablet.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged release tablet contains 15mg of oxybutynin hydrochloride.
For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablet.

Round grey coloured tablet printed with “15 XL" on one side in black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults and Elderly

For the symptomatic treatment of urge incontinence and/or increased urinary frequency associated with urgency as may occur in patients with unstable bladder.

Children over the age of 6 years

The symptomatic treatment of detrusor hyperreflexia secondary to a neurogenic condition.

4.2 Posology and method of administration

Dosage

Adults and Elderly

Starting dose: the recommended starting dose is one 5 mg tablet once daily.

Maintenance dose/dose adjustment: In order to achieve a maintenance dose giving an optimal balance of efficacy and tolerability, after at least one week on 5 mg daily, the dose may be increased to 10 mg once daily, with subsequent incremental increases or decreases of 5 mg/day. There should be an interval of at least one week between dose changes.

Maximum dose: in patients requiring a higher dose, the total daily dose should not exceed 20 mg.

For patients currently taking oxybutynin immediate release, clinical judgement should be exercised in selecting the appropriate dose of Lyrinel XL. The dosage should be adjusted to the minimum dose that achieves an optimal balance of efficacy and tolerability, taking into account the current immediate-release dose.

Children over the age of 6 years

Initial dose of 5 mg once a day increased in 5mg increments up to a maximum of 15 mg once a day.

Lyrinel XL is not recommended for use in children below age of 6 years, due to a lack of data on safety and efficacy *(see sections 5.1 and 5.2).*

Method of administration

Lyrinel XL must be swallowed whole with the aid of liquid, and must not be chewed, divided, or crushed.

Patients should be advised that the tablet membrane may pass through the gastrointestinal tract unchanged. This has no bearing on the efficacy of the product.

Lyrinel XL may be administered with or without food *(see section 5.2).*

4.3 Contraindications

- Hypersensitivity to oxybutynin or any of the excipients
- Narrow-angle glaucoma or shallow anterior chamber
- Myasthenia gravis
- Urinary retention
- Gastrointestinal obstructive disorder, paralytic ileus or intestinal atony
- Severe ulcerative colitis
- Toxic megacolon
- Urinary frequency and nocturia due to heart or renal failure
- Porphyria

4.4 Special warnings and precautions for use

Oxybutynin is associated with anticholinergic central nervous system (CNS) effects *(see section 4.8 Undesirable Effects).* 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 should be given with caution in patients with the following conditions:
- hepatic or renal impairment
- clinically significant bladder outflow obstruction since anticholinergic drugs may aggravate bladder outflow and cause retention *(see section 4.3)*
- gastrointestinal motility disorders *(see section 4.3)*
- gastroesophageal reflux and/or who are currently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis
- pre-existing dementia treated with cholinesterase inhibitors due to risk of aggravation of symptoms

Oxybutynin should be used with caution in the frail elderly who may be more sensitive to the effects of oxybutynin.

If urinary tract infection is present, an appropriate antibacterial therapy should be started.

Oxybutynin may aggravate the symptoms of hyperthyroidism, congestive heart failure, cardiac arrhythmia, tachycardia, hypertension and prostatic hypertrophy.

When oxybutynin is used in patients with fever or in high environmental temperatures, this can cause heat prostration, or heat stroke, due to decreased sweating.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Oxybutynin may lead to decreased salivary secretions, which could result in tooth caries, periodontisis, or oral candidiasis.

As oxybutynin may trigger angle-closure glaucoma, visual acuity and intraocular pressure should be monitored periodically during therapy. Patients should be advised to seek advice immediately if they are aware of a sudden loss of visual acuity.

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of oxybutynin with other anticholinergic medicinal products or drugs with anticholinergic activity, such as amantadine and other anticholinergic antiparkinsonian drugs (e.g. biperiden, levodopa), antihistamines, antipsychotics (e.g. phenothiazines, butyrophenones, clozapine), quinidine, tricyclic antidepressants, atropine and related compounds like atropinc antispasmodics, dipyridamole, may increase the frequency or severity of dry mouth, constipation and drowsiness.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. They may also antagonize the gastrointestinal prokinetic effects of metoclopramide and domperidone. However, the interaction between prokinetics and oxybutynin has not been established.

Sublingual nitrates may fail to dissolve under the tongue owing to dry mouth, resulting in reduced therapeutic effect.

Oxybutynin is metabolised by cytochrome P450 isoenzyme CYP3A4. Mean oxybutynin chloride concentrations were approximately 2 fold higher when Lyrinel **XL** was administered with ketoconazole, a potent CYP3A4 inhibitor. Other inhibitors of cytochrome P450 3A4 enzyme system, such as antimycotic agents (e.g. itraconazole and fluconazole) or macrolide antibiotics (e.g. erythromycin), may alter oxybutynin pharmacokinetics. The clinical relevance of such potential interaction is not known. Caution should be used when such drugs are co-administered.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data on the use of oxybutynin in pregnant women. Studies in animals have shown minor reproductive toxicity (see Section 5.3). Lyrinel XL should only be used during pregnancy if the expected benefit outweighs the risk.

Lactation
When oxybutynin is used during lactation, a small amount is excreted in the mother’s milk. Breast feeding while using oxybutynin is therefore not recommended.

4.7 Effects on ability to drive and use machines

As oxybutynin may produce drowsiness or blurred vision, patients should be cautioned regarding activities requiring mental alertness such as driving, operating machinery or performing hazardous work while taking this drug.

4.8 Undesirable effects

The table below reflects the data obtained with Lyrinel XL in clinical trials and from postmarketing experience. In clinical trials with Lyrinel XL (n=1006), adverse events were associated mainly with the anticholinergic actions of oxybutynin. Adverse events were generally dose related. As with other oxybutynin formulations, dry mouth was the most frequently reported adverse reaction. However, in clinical studies, dry mouth has been less frequently reported with Lyrinel XL than with oxybutynin immediate release formulations. For patients who required final doses of 5 or 10 mg of Lyrinel XL, the relative incidence of dry mouth that occurred at any dose level was 1.8 times lower compared with patients who required final doses > 10 mg.

	Very Common ≥1/10	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1000**	**Not Known***
Infections and infestations		urinary tract infection, cystitis, pharyngitis, nasopharyngitis, upper respiratory tract infection, bronchitis,, sinusitis,			
Blood and Lymphatic system disorders:				leukopenia, thrombocytopenia	
Immune System Disorders				hypersensitivity	
Metabolism & Nutrition Disorders			anorexia, dehydration, hyperglycaemia	appetite increased	
Psychiatric disorders		insomnia, depression nervousness, confusional state	anxiety, abnormal dreams		hallucinations, night terror, psychotic disorder, agitation, memory impairment
Nervous System Disorders		somnolence, headache, dizziness, dysgeusia	paraesthesia, vertigo	hypertonia, tremor, tinnitus	convulsions
Eye disorders		vision blurred, dry eye, keratoconjunctivitis sicca	conjunctivitis	diplopia, glaucoma, photophobia	
Cardiac disorders		palpitations		atrial arrhythmia, bradycardia, bundle branch block, nodal arrhythmia, supraventricular extrasystoles	arrhythmia tachycardia
Vascular disorders		hypertension	vasodilatation, migraine	hypotension, phlebitis,	flushing

				ecchymosis	
Respiratory, thoracic and mediastinal disorders		nasal dryness, mucosal dryness, cough,pharyngo-laryngeal pain, dry throat	rhinitis, hoarseness, epistaxis, dyspnoea	laryngitis, laryngeal oedema, respiratory disorder, sputum increased	
Gastrointestinal Disorders	dry mouth	constipation, diarrhoea, nausea, dyspepsia, abdominal pain, flatulence, gastroesophageal reflux disease loose stools, vomiting	dysphagia, mouth ulceration, abdominal distension, glossitis, stomatitis	faecal abnormality, oesophageal stenosis acquired, gastritis, gastroenterititis viral, hernia, rectal disorder, gastric atony, tongue disorder, tongue oedema	
Skin and subcutaneous tissue disorders		dry skin, pruritus	acne, urticaria, face oedema, alopecia, eczema, nail disorder, skin discolouration, anhidrosis	hair disorder, rash maculo-papular, granuloma, sweating increased, photosensitivity reaction	rash
Musculoskeletal and connective tissue disorders		pain in extremity, back pain, arthralgia	muscle cramps, myalgia	arthritis	
Renal and urinary disorders		micturition disorder, residual urine volume, urinary retention, dysuria, urinary hesitation	urinary frequency, urinary tract disorder, haematuria, nocturia, pyuria, micturition urgency	urinary incontinence, urine abnormal, urogenital disorder	impotence, erectile dysfunction
Reproductive system and breast disorders			breast pain, vaginitis	vulvovaginal disorder, uterine cervical disorder, genital discharge	
General disorders and administration site conditions		asthenia, oedema peripheral, fatigue, chest pain	pain, thirst, oedema	rigor, pyrexia, influenza like illness, malaise, pelvic pain	
Investigations		blood pressure increased	electrocardiogram abnormal, blood urea increased, blood creatinine increased	blood alkaline phosphatase increased, blood lactase deshydrogenase increased, blood aspartate, aminotransferase increased, blood alanine aminotransferase	

				increased	
Injury, poisoning and procedural complications					fall
*Cannot be estimated from the available clinical data.					

Undesirable effects noted with other oxybutynin hydrochloride formulations:
In addition, cyclopegia, mydriasis and suppression of lactation have been reported with the use of other oxybutynin hydrochloride formulations.

4.9 Overdose

The symptoms of overdose with oxybutynin 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.

Measures to be taken are:

1) administration of activated charcoal
2) 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.

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 in the treatment of overdose. Patients should be monitored for at least 24 hours.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: urinary antispasmodic, ATC code: G04B D04.

Mechanism of action: oxybutynin acts as a competitive antagonist of acetylcholine at post-ganglionic muscarinic receptors, resulting in relaxation of bladder smooth muscle.

Pharmacodynamic effects: in patients with overactive bladder, characterized by detrusor muscle instability or hyperreflexia, cystometric studies have demonstrated that oxybutynin increases maximum urinary bladder capacity and increases the volume to first detrusor contraction. Oxybutynin thus decreases urinary urgency and frequency of both incontinence episodes and voluntary urination.

Oxybutynin is a racemic (50:50) mixture of R- and S- isomers. Antimuscarinic activity resides predominantly in the R-isomer. The R-isomer of oxybutynin shows greater selectivity for the M_1 and M_3 muscarinic subtypes (predominant in bladder detrusor muscle and parotid gland) compared to the M_2 subtype (predominant in cardiac tissue). The active metabolite, N-desethyloxybutynin, has pharmacological activity on the human detrusor muscle that is similar to that of oxybutynin *in vitro* studies, but has a greater binding affinity for parotid tissue than oxybutynin. The free base form of oxybutynin is pharmacologically equivalent to oxybutynin hydrochloride.

Children over the age of 6 years: in children with detrusor hyperreflexia secondary to a neurogenic condition, oxybutynin, in combination with clean intermittent urinary catheterisation, has been shown in open uncontrolled studies to increase mean urine volume per catherisation, increase maximum cystometric capacity and decrease mean detrusor pressure at maximum cystometric capacity.

5.2 Pharmacokinetic properties

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

The relative bioavailabilities of R-oxybutynin and S-oxybutynin from Lyrinel XL are 156% and 187% respectively, compared with oxybutynin immediate release. After a 10 mg single dose of Lyrinel XL, the peak plasma concentrations of R-oxybutynin and Soxybutynin, achieved after 12.7±5.4 and 11.8±5.3 hours respectively, are 1.0±0.6 and 1.8±1.0 ng/ml, and the plasma concentration time profiles of both enantiomers are similar in shape. The elimination half-life is 13.2±10.3 hours for R-oxybutynin and 12.4±6.1 hours for S-oxybutynin.

Steady state oxybutynin plasma concentrations are achieved by Day 3 of repeated Lyrinel XL dosing, with no observed change in oxybutynin and desethyloxybutynin pharmacokinetic parameters over time.

Pharmacokinetic parameters of oxybutynin and desethyloxybutynin (Cmax and AUC) are dose proportional following administration of 5-20 mg of Lyrinel XL.

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

Limited data suggest that the pharmacokinetics of Lyrinel XL is similar in adults and children aged 8 years and above. The pharmacokinetics of Lyrinel XL have not been investigated in patients with renal or hepatic insufficiency.

Oxybutynin is extensively metabolised by the liver, primarily by the cytochrome P450 enzyme system, particularly CYP3A4 found mostly in the liver and gut wall. Absolute bioavailability of immediate release oxybutynin has been estimated to be 2-11%. Following intravenous administration of 5 mg oxybutynin, clearance and volume of distribution were estimated to be 26 L/h and 193 L, respectively. Less than 0.1% of the administered dose is excreted unchanged in the urine. Its metabolic products include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and desethyloxybutynin, which is pharmacologically active.

Following Lyrinel XL administration, area under the plasma concentration profiles of R- and Sdesethyloxybutynin are 73% and 92% respectively of those observed with oxybutynin immediate release formulations.

The binding of oxybutynin to plasma proteins is unknown.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on studies of acute toxicity, repeat dose toxicity, genotoxicity, carcinogenic potential and local toxicity. In a fertility study of subcutaneous oxybutynin injections in rats, female fertility was impaired while no effect was noted in male animals. In a rabbit embryotoxicity study, organ anomalies were observed in the presence of maternal toxicity at a dose of 0.4 mg/kg/day subcutaneously. The relevance to human safety is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylhydroxytoluene (E321)
Cellulose acetate
Hypromellose
Macrogol 3350
Magnesium stearate
Polyethylene oxide
Sodium chloride
Black iron oxide (E172)
Lactose anhydrous.

Film coat:
Black iron oxide (E172)
Hypromellose
Macrogol 400
Polysorbate 80
Titanium dioxide (E171)

Printing Ink:
Black iron oxide (E172)
Hypromellose
Propylene glycol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

18 months

6.4 Special precautions for storage

Keep the container tightly closed in order to protect from moisture. Do not store above 25^{o}C.

6.5 Nature and contents of container

High density polyethylene bottles with child resistant closure (polypropylene) and desiccant.

Pack sizes 3, 7, 10, 14, 30, 50, 60, 90 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Janssen-Cilag Limited
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High Wycombe
Buckinghamshire HP12 4EG
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0748/052/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 14 June 2005

10 DATE OF REVISION OF THE TEXT

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