Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lyrinel XL 5 mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lyrinel XL 5mg prolonged release tablets: Each prolonged release tablet contains 5 mg of oxybutynin hydrochloride.

Excipient: Each Lyrinel XL prolonged release tablet contains lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablet.

Product imported from Greece
Round yellow coloured tablet, approximately 7.5 mm in diameter, printed with “5 XL" on one side in black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults

Lyrinel XL is indicated in adults for the symptomatic treatment of urge incontinence and/or increased urinary frequency associated with urgency as may occur in patients with unstable bladder.

Paediatric population

Oxybutynin hydrochloride is indicated in children over 5 years of age for:
Urinary incontinence, urgency and frequency in unstable bladder conditions due to idiopathic overactive bladder or neurogenic bladder disorders (detrusor overactivity).
Nocturnal enuresis associated with detrusor overactivity, in conjunction with nondrug therapy, when other treatment has failed.

4.2 Posology and method of administration

Posology

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

Adults

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.

In case of a missed dose, the patient should wait and take the next dose at the regular time.

Elderly patients

No dosage adjustment is necessary in elderly patients.

Children over the age of 5 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 5 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 because the tablet is formulated to provide prolonged release.

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.

4.3 Contraindications

- Hypersensitivity to the active substance or to 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.

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 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.

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.

Paediatric population
Oxybutynin hydrochloride is not recommended for use in children below age 5 years due to insufficient data on safety and efficacy.

There is limited evidence supporting the use of Oxybutynin in children with monosymptomatic nocturnal enuresis (not related to detrusor overactivity).

In children over 5 years of age, Oxybutynin hydrochloride should be used with caution as they may be more sensitive to the effects of the product, particularly the CNS and psychiatric adverse reactions.

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.

Paediatric population

Interaction studies have only been performed in adults. It is not known whether the extent of interactions in the paediatric population is similar to that in adults.

4.6 Fertility, 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 is not recommended during pregnancy.

Breastfeeding
When oxybutynin is used during breastfeeding, a small amount is excreted in the mother's milk. The effect on newborns/infants is unknown. Lyrinel XL should not be used during breastfeeding.

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

4.7 Effects on ability to drive and use machines

Oxybutynin has minor influence on the ability to drive and use machines. Oxybutynin may produce drowsiness or blurred vision; therefore, 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

Summary of the safety profile
The most common adverse reactions reported during clinical trials by > 5% of patients were dry mouth, constipation, diarrhoea, headache, somnolence and dizziness.
Serious adverse reactions associated with oxybutynin include anticholinergic central nervous system effects (see section 4.4).

List of adverse reactions
The safety of Lyrinel XL was evaluated in five double-blind, controlled (i.e., placebo or active comparator) clinical trials for the management of overactive bladder, in which 759 adult subjects received doses ranging from 5 to 20 mg/day. Additionally, safety was evaluated in one open-label (i.e., active comparator) clinical trial, in which 60 paediatric subjects received doses of 10 or 15 mg/day, Table 1 below reflects the adverse drug reactions reported with Lyrinel XL in clinical trials in adults and from postmarketing experience. Adverse drug reactions reported in the paediatric clinical trial are shown in Table 2.

Table 1: Adverse drug reactions reported in clinical trials in adults and from postmarketing experience

	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			

Immune system disorders			Hypersensitivity		Anaphylactic reaction
Metabolism and nutrition disorders			anorexia, fluid retention		
Psychiatric disorders		insomnia,	Hallucinations, Confusional state, agitation, memory impairment		psychotic disorder,
Nervous system disorders		somnolence, headache, dizziness, dysgeusia	convulsions		
Eye disorders		vision blurred, dry eye	Glaucoma		
Cardiac disorders		palpitations		arrhythmia, tachycardia	
Vascular disorders				hypertension, flushing	
Respiratory, thoracic and mediastinal disorders		oropharyngeal pain, cough, nasal dryness, dry throat	dyspnonia, nasal congestion, throat irritation		
Gastro-intestinal disorders	Dry mouth	gastroesophageal reflux disease, abdominal pain, dyspepsia, constipation, diarrhoea, nausea, flatulence	dysphagia, abdominal discomfort, frequent bowel movements, vomiting		
Skin and subcutaneous tissue disorders		Dry skin, pruritus	urticaria, rash		angioedema
Renal and urinary disorders		dysuria, urinary hesitation	Urinary retention, residual urine		impotence
General disorders and administration site conditons		fatigue	chest discomfort, mucosal dryness, thirst		
Investigations		Residual urine volume+			
Injury, poisoning and procedural complications			Fall		

* Cannot be estimated from the available clinical data.
+ The bundles term residual urine volume consists of the preferred terms residual urine volume and residual urine volume increased.

Description of selected adverse reactions
The following postmarketing adverse reactions listed in Table 1 are from postmarketing reports only (not seen in clinical trials), with the frequency category estimated from clinical trial safety data comprising 759 patients: hallucinations, agitation, memory impairment, and convulsions. These estimates represent the upper limit of the 95% CI.

As with other oxybutynin formulations, dry mouth was the most frequently reported adverse drug 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.

Paediatric population
The safety of Lyrinel XL was evaluated in 60 paediatric subjects (age range 5 to 15 years; dose range 10-15 mg/day) who participated in an open-label, active control, three-arm clinical trial. Adverse drug reactions reported by Lyrinel XL-treated paediatric subjects in this clinical trial are shown in Table 2.

Table 2: Adverse drug reactions reported in clinical trials with paediatric subjects

	Very common ≥1/10	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1000**
Metabolism and nutrition disorders		Anorexia		
Psychiatric disorders		Insomnia		
Nervous system disorders		Headache		
Vascular disorders		Flushing		
Gastrointestinal disorders	Constipation	Diarrhoea		
Skin and subcutaneous tissue disorders		Rash, pruritus		

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

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

In pronounced restlessness or excitation, diazepam 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.

Paediatric population
An open-label study was conducted to evaluate the efficacy and safety of Lyrinel XL in children aged 6-15 years with detrusor hyperreflexia due to neurogenic conditions, all used clean intermittent catheterisation, and all were current uses of 10 or 15mg oxybutynin hydrochloride administered as Ditropan syrup, Ditropan tablets or Ditropan XL extended-release tablets.

The study results showed that there was an increase from baseline in mean urine volume per catheterisation, an increase from baseline in mean urine volume after morning awakening, from baseline in the mean percentage of catheterisations without a leaking episode, an increase from baseline in mean maximum cystometric capacity, a decrease from baseline in mean detrusor pressure at maximum cystometric pressure and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions as shown in the table below.

Change in Baseline to Week 24			
Parameter	n	Mean (SEM)	Range
Average volume per catheterization (mL)	109	25.5 (5.9)	-292 to 245
Volume of 1st catheterization after morning awakening (mL)	109	33.0 (8.3)	-223 to 450
Maximal bladder capacity (mL)*	105	75.4 (9.8)	-150 to 420
Detrusor pressure at maximal bladder capacity (cm H_2O)*	105	-9.2 (2.3)	-102 to 64
Intravesical pressure at maximal bladder capacity (cm H_2O)*	105	-7.5 (2.5)	-108 to 76
*Urodynamic studies			
At baseline, 66 of 116 (56.9%) patients had uninhibited detrusor contractions _ 15 cm H_2O. At Week 24, 30 of 105 (28.6%) patients had uninhibited contractions ≥ 15 cm H_2O. The percentage of catheterisations without a leaking accident increased from 36.0% at baseline to 55.5% at Week 24.			

5.2 Pharmacokinetic properties

Absorption
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 pharmacokinetic parameters (C_{max} and AUC) of oxybutynin and desethyloxybutynin are dose proportional following administration of 5-20 mg of Lyrinel XL. 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.

Absolute bioavailability of immediate release oxybutynin has been estimated to be 2-11%. 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 S-oxybutynin, 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 pharmacokinetics of Lyrinel XL are unaffected by food intake.

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

Metabolism and Excretion
Oxybutynin is extensively metabolised by the liver, primarily by the cytochrome P450 enzyme system, 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, area under the plasma concentration profiles of R- and S-desethyloxybutynin are 73% and 92% respectively of those observed with oxybutynin immediate release formulations.Following intravenous administration of 5 mg oxybutynin, clearance was estimated to be 26 L/h. Less than 0.1% of the administered dose is excreted unchanged in the urine. The elimination half-life is 13.2±10.3 hours for R-oxybutynin and 12.4±6.1 hours for S-oxybutynin.

Special Populations
Paediatric population
The steady-state pharmacokinetics of Lyrinel XL were evaluated in a limited number of children aged 6-15 years with detrusor overactivity associated with a neurological condition (e.g., spina bifida) receiving 10 or 15 mg total daily doses of Lyrinel XL. The pharmacokinetics of Lyrinel XL in these paediatric patients were consistent with those reported for adults. The table below summarizes maximum and average plasma concentrations for each of the four analytes, R- and S-Oxybutynin and R- and S-Desethyloxybutynin, by age group and total daily dose.

Mean (SD) Maximum and Average Concentrations (ng/mL) of R- and S-Oxybutynin and R and S-Desethyloxybutynin in Children Following Administration of 10 and 15 mg Lyrinel XL Once Daily				
	Age <10 yrs[a]		**Age >10 yrs[b]**	
Dose/Analyte	**C_{max}**	**C_{avg}**	**C_{max}**	**C_{avg}**
10 mg Dose				
R-Oxybutynin	1.39 (0.1)	0.91 (0.2)	1.37 (0.9)	1.06 (.08)
S-Oxybutynin	2.46 (0.5)	1.58 (0.5)	2.45 (1.7)	2.00 (1.5)
R-Desethyloxybutynin	15.4 (2.2)	8.74 (2.8)	13.2 (9.7)	9.48 6.8)
S-Desethyloxybutynin	6.81 (0.9)	4.38 (1.8)	8.05 (6.7)	6.70 (6.1)
15 mg Dose				
R-Oxybutynin	2.59 (1.4)	1.78 (0.8)	2.16 (2.0)	1.86 (2.0)
S-Oxybutynin	5.03 (3.2)	3.67 (2.1)	3.29 (2.7)	2.80 (2.7)
R-Desethyloxybutynin	23.0 (11.0)	16.2 (6.0)	27.8 (22)	20.8 (22)

S-Desethyloxybutynin	13.3 (7.9)	10.3 (6.1)	12.2 (6.8)	9.13 (7.5)
a – 10 mg: n=3; 15 mg: n=6 b – 10 mg: n=5; 15 mg: n=2				

5.3 Preclinical safety data

Non-clinical 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
Magnesium stearate
Polyethylene oxide
Sodium chloride
Black iron oxide (E172)
Ferric oxide yellow (E172)
Lactose anhydrous

Film coat:
Ferric oxide yellow (E172)
Hypromellose
Macrogol
Polysorbate
Titanium dioxide (E171)

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Keep the container tightly closed in order to protect from moisture. Do not store above 25°C.

6.5 Nature and contents of container

Bottles containing 30 tablets contained in an overlabelled outer carton.

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

Do not remove or swallow the sachet of granules in the bottle. This contains desiccant, which keeps the tablets dry.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA0465/295/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31st August 2012

10 DATE OF REVISION OF THE TEXT

August 2014