1. NAME OF THE MEDICINAL PRODUCT

Kentera 3.9 mg / 24 hours transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each transdermal patch contains 36 mg of oxybutynin. The area of the patch is 39 cm^2, releasing a nominal 3.9 mg of oxybutynin per 24 hours.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patch. The patch is a clear plastic with an adhesive backing, protected by a release liner that is to be removed prior to application.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in adult patients with unstable bladder.

4.2 Posology and method of administration

The patch should be applied to dry, intact skin on the abdomen, hip, or buttock immediately after removal from the protective sachet. A new application site should be selected with each new patch to avoid reapplication to the same site within 7 days.

The recommended dose is one 3.9 mg transdermal patch applied twice weekly (every 3 to 4 days).

Elderly population

Based on clinical trial experience no dose adjustment is considered necessary in this population. Nonetheless Kentera should be used with caution in elderly patients, who may be more sensitive to the effects of centrally acting anticholinergics and exhibit differences in pharmacokinetics (see section 4.4).

Paediatric population

The safety and efficacy of Kentera in the paediatric population has not been established. Kentera is not recommended for use in the paediatric population. Currently available data are described in section 4.8 but no recommendation on a posology can be made.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Kentera is contraindicated in patients with urinary retention, severe gastro-intestinal condition, myasthenia gravis or narrow-angle glaucoma and in patients who are at risk for these conditions.

4.4 Special warnings and precautions for use

Kentera should be used with caution in patients with hepatic or renal impairment. The use of Kentera in patients with hepatic impairment should be carefully monitored. Other causes of frequent urination

(heart failure or renal disease) should be assessed before treatment with Kentera. If urinary tract infection is present, an appropriate antibacterial therapy should be started.

Urinary retention: Anticholinergic products should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.

Kentera should be used with caution in elderly patients, who may be more sensitive to the effects of centrally acting anticholinergics and exhibit differences in pharmacokinetics.

In total 496 patients were exposed to Kentera in the randomised, double-blind, placebo-controlled 12-week and the 14-week safety extension studies. Of these 188 patients (38%) were 65 years of age and older and exhibited no overall differences in safety or effectiveness compared to younger patients. Thus based on current clinical evidence no need for dose adjustment in elderly patients is considered necessary.
Psychiatric and central nervous system (CNS) anticholinergic events like sleep disorders (e.g. insomnia) and cognitive disorders have been associated with oxybutynin use, especially in elderly patients. Caution should be exercised when oxybutynin is administrated concomitantly with other anticholinergic medicines (see also section 4.5). If a patient experiences such events, drug discontinuation should be considered.

Other psychiatric events implying an anticholinergic mechanism have been reported during post-marketing use (see section 4.8).

Oral administration of oxybutynin may warrant the following cautionary statements, but these events were not observed during clinical trials with Kentera:

Gastrointestinal disorders: Anticholinergic medicinal products may decrease gastrointestinal motility and should be used with caution in patients with gastrointestinal obstructive disorders because of the risk of gastric retention. Also in conditions such as ulcerative colitis, and intestinal atony.
Anticholinergic medicinal products should be used with caution in patients who have hiatus hernia/gastro-oesophageal reflux and/or who are concurrently taking medicinal products (such as bisphosphonates) that can cause or exacerbate oesophagitis.

Anticholinergic medicinal products should be used with caution in patients who have autonomic neuropathy, cognitive impairment or Parkinson's disease

Patients should be informed that heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as oxybutynin are used in a hot environment.
Oxybutynin may exacerbate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, tachycardia, hypertension and prostatic hypertrophy

Oxybutynin may lead to suppressed salivary secretions which could result in dental caries, parodontosis or oral candidiasis.

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of oxybutynin with other anticholinergic medicinal products or with other agents that compete for CYP3A4 enzyme metabolism may increase the frequency or severity of dry mouth, constipation, and drowsiness.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered medicinal products due to anticholinergic effects on gastrointestinal motility. As oxybutynin is metabolised by cytochrome P 450 isoenzyme CYP 3A4, interactions with medicinal products that inhibit this isoenzyme cannot be ruled out. This should be borne in mind when using azole antifungals (e.g. ketoconasole) or macrolide antibiotics (e.g. erythromycin) concurrently with oxybutynin.

The anticholinergic activity of oxybutynin is increased by concurrent use of other anticholinergics or medicinal products with anticholinergic activity, such as amantadine and other anticholinergic antiparkinsonian medicinal products (e.g. biperiden, levodopa), antihistamines, antipsychotics (e.g. phenothiazines, butyrophenones, clozapine), quinidine, tricyclic antidepressants, atropine and related compounds like atropinic antispasmodics, dipyridamole.

Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin (see section 4.7).

Oxybutynin may antagonize prokinetic therapies.

4.6 Pregnancy and lactation

There are no adequate data on the use of oxybutynin transdermal patch in pregnant women.
Studies in animals have shown minor reproductive toxicity (see section 5.3). Kentera should not be used during pregnancy unless clearly necessary.

When oxybutynin is used during breast-feeding, a small amount is excreted in the mother's milk. Use of oxybutynin while breast-feeding is therefore not recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Because Kentera may produce drowsiness, somnolence, or blurred vision, patients should be advised to exercise caution when driving or using machinery (see section 4.5).

4.8 Undesirable effects

The most commonly reported adverse drug reactions were application site reactions, occurring in 23.1% of patients. Other commonly occurring adverse drug reactions reported were dry mouth (8.6%), constipation (3.9%), diarrhoea (3.2%), headache (3.0%), dizziness (2.3%) and blurred vision (2.3%).

Tabulated list of adverse reactions

Adverse reactions from phase 3 and 4 clinical studies are listed below by system organ class and frequency grouping. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Post-marketing adverse reactions not seen in clinical trials are also included.

MedDRA System Organ Class	Incidence	Adverse reactions
Infections and infestations	Common	Urinary tract infection
	Uncommon	Upper respiratory tract infection, fungal infection
Psychiatric disorders	Uncommon	Anxiety, confusion, nervousness, agitation, insomnia
	Rare	Panic reaction#, delirium#, hallucinations#, disorientation#
Nervous system disorders	Common	Headache, somnolence
	Rare	Memory impairment#, amnesia#, lethargy#, disturbance in attention#
Eye disorders	Common	Blurred vision
Ear and labyrinth disorders	Common	Dizziness
Cardiac disorders	Uncommon	Palpitations
Vascular disorders	Uncommon	Urticaria, hot flushes
Respiratory, thoracic and mediastinal disorders	Uncommon	Rhinitis
Gastrointestinal disorders	Common	Dry mouth, constipation, diarrhoea, nausea, abdominal pain
	Uncommon	Abdominal discomfort, dyspepsia
Musculoskeletal and connective tissue disorders	Uncommon	Back pain
Renal and urinary disorders	Uncommon	Urinary retention, dysuria
General disorders and administration site conditions	Very common	Application site pruritis
	Common	Application site erythema, application site reaction, application site rash
Injury, poisoning and procedural complications	Uncommon	Inflicted injury

post-marketing adverse reactions from post-marketing reports only (not seen in clinical trials), with the frequency category estimated from clinical trial safety data, and reported in association with oxybutynin topical use (anticholinergic class effects).

Adverse reactions considered associated with anticholinergic therapy,in general or observed with oral administration of oxybutynin, but as of yet not with Kentera in clinical trials or post-marketing, are: anorexia, vomiting, reflux oesophagitis, decreased sweating, heat stroke, decreased lacrimation, mydriasis, tachycardia, arrhythmia, nightmares, restlessness, convulsion, intraocular hypertension and induction of glaucoma, paranoia, photosensitivity, erectile dysfunction.

Paediatric population

During post-marketing use in this age group, cases of hallucinations (associated with anxiety manifestations) and sleep disorders correlated with oxybutynin have been reported. Children may be more sensitive to the effects of the product, particularly the CNS and psychiatric adverse reactions.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

Plasma concentration of oxybutynin declines within 1 to 2 hours after removal of transdermal system(s). Patients should be monitored until symptoms resolve. Overdosage with oxybutynin has been associated with anticholinergic effects including CNS excitation, flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention. Ingestion of 100 mg oral oxybutynin chloride in association with alcohol has been reported in a 13 year old boy who experienced memory loss, and in 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 recovered fully with symptomatic treatment.

No cases of overdose have been reported with Kentera.

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, characterised 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 the 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.

Clinical efficacy:

A total of 957 patients with urge urinary incontinence were evaluated in three controlled studies comparing Kentera to either placebo, oral oxybutynin and/or tolterodine long acting capsules. Reductions in weekly incontinence episodes, urinary frequency, and urinary void volume were evaluated. Kentera led to consistent improvements in overactive bladder symptoms compared with placebo.

5.2 Pharmacokinetic properties

Absorption
Kentera has a concentration of oxybutynin sufficient to maintain continuous transport over the 3 to 4 day dosing interval. Oxybutynin is transported across intact skin and into the systemic circulation by passive diffusion across the stratum corneum. Following the application of Kentera, oxybutynin plasma concentration increases for approximately 24 to 48 hours, reaching average maximum concentrations of 3 to 4 ng/ml. Steady-state conditions are reached during the second application of the transdermal patch. Thereafter, steady concentrations are maintained for up to 96 hours. The difference in AUC and C_{max} of oxybutynin and the active metabolite N-desethyloxybutynin following transdermal administration of Kentera on either the abdomen, buttocks or hip is not clinically relevant.

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.

Metabolism
Oxybutynin administered orally is metabolised primarily by the cytochrome P450 enzyme systems, particularly CYP3A4, found mostly in the liver and gut wall. Metabolites include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and N-desethyloxybutynin, which is pharmacologically active. Transdermal administration of oxybutynin bypasses the first-pass gastrointestinal and hepatic metabolism, reducing the formation of the N-desethyl metabolite.

Excretion
Oxybutynin is extensively metabolised by the liver, see above 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 N-desethyloxybutynin.

5.3 Preclinical safety data

Pre-clinical data reveal no special hazard for humans based on studies for acute toxicology, repeat dose toxicity, genotoxicity, carcinogenic potential and local toxicity. At a concentration of 0.4 mg/kg/day oxybutynin administered subcutaneously, the occurrence of organ anomalies is significantly increased, but is observed only in the presence of maternal toxicity. Kentera delivers approximately 0.08 mg/kg/day. However, in the absence of understanding the association between maternal toxicity and developmental effect, the relevance to human safety cannot be addressed. In the subcutaneous fertility study in rats, while no effects were reported in males, in females, fertility was impaired and a NOAEL (no observed adverse effect level) of 5 mg/kg was identified.

Environmental Risk Assessment
The active substance oxybutynin is persistent in the environment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Backing film
Clear polyester/ethylene-vinyl acetate (PET/EVA)

Middle layer
Triacetin
Acrylic copolymer adhesive solution containing 2-ethylhexyl acrylate N-vinyl pyrrolidone and hexamethyleneglycol dimethacrylate polymer domains

Release Liner
Siliconised polyester

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not refrigerate or freeze.

6.5 Nature and contents of container

The transdermal patches are individually contained in LDPE/paper laminate sachets and supplied in Patient Calendar Boxes of 2, 8 or 24 patches.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Apply immediately upon removal from the protective sachet. After use the patch still contains substantial quantities of active ingredients. Remaining active ingredients of the patch may have harmful effects if reaching the aquatic environment. Hence, after removal, the used patch should be folded in half, adhesive side inwards so that the release membrane is not exposed, placed in the original sachet and then discarded safely out of reach of children. Any used or unused patches should be discarded according to local requirements or returned to the pharmacy. Used patches should not be flushed down the toilet nor placed in liquid waste disposal systems.

Activities that may lead to excessive sweating, or exposure to water or extreme temperature may contribute to adhesion problems. Do not expose the patch to the sun.

7. MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031 GA Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/270/001	8 transdermal patches
EU/1/03/270/002	24 transdermal patches
EU/1/03/270/003	2 transdermal patches

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15/06/2004
Date of latest renewal: 30/04/2009

10. DATE OF REVISION OF THE TEXT

December 2019

Detailed information on this product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu