ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 the national reporting system listed in Appendix V.

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

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

1. NAME OF THE MEDICINAL PRODUCT

Kentera 90.7 mg/g gel in sachet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet of 1 gram of gel contains 90.7 mg of oxybutynin (as 100 mg oxybutynin hydrochloride) resulting in a nominal delivery of approximately 4 mg/day.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gel in sachet.
Rapid drying, clear, smooth, odourless, and colourless hydroalcoholic gel.

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

Posology

The recommended dose is one sachet applied once daily which corresponds to a delivery dose of approximately 4 mg.

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).

Renal impairment

There is no experience with the use of Kentera in patients with renal impairment.

Hepatic impairment

There is no experience with the use of Kentera in patients with hepatic impairment.

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.

Method of administration

Kentera should be applied to dry, intact skin on the abdomen, upper arms/shoulders, or thighs. Application sites should be rotated. Application should not be made to the same site on consecutive days.

Avoid bathing, swimming, showering, exercising or immersing the application site in water for one hour after application (see section 4.4).

It is recommended to cover the application site with clothing once the gel has dried.

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 special precautions for use

As the stratum corneum is the rate-limiting step in transdermal delivery, any breach would provide direct access to the epidermis, potentially increasing penetration and facilitating the migration of the medicinal product to the blood stream. Kentera should therefore not be applied to a recently shaved or damaged skin surface.

Avoid bathing, swimming, showering, exercising or immersing the application site in water for one hour after application.

It is recommended to cover the application site with clothing once Kentera has dried.

The effect of fever, exposition to external heat sources, sun bathing and sauna on the absorption characteristics of Kentera have not been investigated.

Impaired metabolism

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 since oxybutynin is extensively hepatic metabolised. 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 medicinal products should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.

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, and 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.

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).

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 active substances that compete for CYP3A4 enzyme metabolism may increase the frequency or severity of dry mouth, constipation, and drowsiness. As oxybutynin is metabolised by the cytochrome P 450 isoenzyme CYP 3A4, interactions with medicinal products that inhibit this isoenzyme, or known inducers of CYP 3A4, cannot be ruled out. This should be borne in mind when administering azole antifungals (e.g. ketoconazole) or macrolide antibiotics (e.g. erythromycin) concurrently with oxybutynin. Consumption of grapefruit juice may also influence metabolism of oxybutynin.

Anticholinergic medicinal products may potentially alter the absorption of some concomitantly administered medicinal products due to anticholinergic effects on gastrointestinal motility.

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, and dipyridamole.

Oxybutynin may cause drowsiness or blurred vision. Drowsiness may be increased by consumption of alcohol. Because Kentera may cause drowsiness, somnolence, or blurred vision, patients should be advised to exercise caution when driving or using machinery (see section 4.7).

Oxybutynin may antagonise prokinetic therapies, such as cisapride and metoclopramide, and should be avoided in the presence of reduced gastrointestinal motility conditions.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing age should be tested for pregnancy before beginning therapy, and during therapy utilise some form of pregnancy contraceptive.

Pregnancy

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

Breast-feeding

Available information shows that oxybutynin is excreted in milk of rats, but is not known whether oxybutynin is excreted in human milk. Use of oxybutynin is not recommended during breast-feeding.

Fertility

Data on possible effects of the use of oxybutynin on human male and female fertility are not available. Fertility studies in rats suggest a 6-fold margin of safety in both male and female breeding adults when Kentera is administered as prescribed. (see section 5.3)

Patients on Kentera therapy should keep application sites covered with clothing when coming into contact with breast-feeding or pregnant women or breast-fed infants.

4.7 Effects on ability to drive and use machines

Kentera has minor influence on the ability to drive and use machines. Because Kentera may cause 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

Summary of the safety profile

The safety of Kentera was evaluated in patients with urge urinary incontinence in a randomised, double-blind, placebo-controlled, parallel group Phase 3 study that included 789 patients (with 389 patients receiving Kentera and 400 patients receiving placebo).

The most commonly reported adverse reaction was dry mouth (Kentera 6.9%, placebo 2.8%). Other adverse reactions reported were application site pruritus (Kentera 2.1%, placebo 0.8%), application site dermatitis (Kentera 1.8%, placebo 0.3%), dizziness (Kentera 1.5%, placebo 0.5%), headache (Kentera 1.5%, placebo 2.8%), constipation (Kentera 1.3%, placebo 1.0%), and pruritus (Kentera 1.3%, placebo 1.3%).

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	Uncommon	Urinary tract infections
Metabolism and nutrition disorders	Uncommon	Hypokalaemia
Psychiatric disorders	Uncommon	Anxiety, confusion, nervousness, agitation, insomnia
	Rare	Panic reaction#, delirium#, hallucinations#, disorientation#
Nervous system disorders	Common	Headache, dizziness
	Uncommon	Somnolence, dysgeusia, poor quality to sleep, tremor
	Rare	Memory impairment#, amnesia#, lethargy#, disturbance in attention#
Eye disorders	Uncommon	Dry eye
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Uncommon	Atrial fibrillation, atrial flutter, sinus arrhythmia
Vascular disorders	Uncommon	Flushing
Respiratory thoracic and mediastinal disorders	Uncommon	Cough, increased upper airway secretion
Gastrointestinal disorders	Common	Dry mouth, constipation
	Uncommon	Diarrhoea, nausea, dyspepsia, vomiting, haemorrhoids
Skin and subcutaneous tissue disorders	Common	Pruritus
	Uncommon	Rash, dry skin, rash pruritic
Renal and urinary disorders	Uncommon	Dysuria, haematuria, renal pain, urinary retention
General disorders and administration site conditions	Common	Application site pruritis, application site dermatitis
	Uncommon	Fatigue, oedema peripheral, application site papules, application site anaesthesia, application site erythema, application site irritation, application site pain, application site pustules
Investigations	Uncommon	Electrocardiogram abnormal, electrocardiogram change, blood chloride increased

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 the national reporting system listed in Appendix V.

4.9 Overdose

Overdose with oxybutynin has been associated with anticholinergic effects including CNS excitation, flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention. Patients should be monitored until symptoms resolve. Plasma concentrations of oxybutynin begin to decline 24 hours after Kentera application. Ingestion of 100 mg oral oxybutynin 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals, urinary antispasmodics, 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

The efficacy and safety of Kentera were evaluated in patients with urge urinary incontinence in a single Phase 3 study.

The Phase 3 study was a randomised, double-blind, placebo-controlled, parallel group study that included 789 patients. The 12-week double-blind treatment included daily applications of Kentera or matching placebo gel. A 14-week, open-label treatment was available for a subset of patients who completed the double-blind period. The majority of patients were Caucasian (86.3%) and female

(89.2%), with a mean age of 59.4 years (range: 18 to 88 years). Approximately 75% of patients had no prior pharmacological treatment for incontinence.

Patients treated with Kentera experienced a highly statistically significant decrease in the number of urinary incontinence episodes per day from baseline to endpoint (the primary efficacy endpoint) compared with placebo ($p<0.0001$), as well as for the secondary endpoints: a decrease in the average daily urinary frequency ($p=0.0017$), and an increase in the average urine volume per void ($p=0.0018$). Significant improvements in the quality of life evaluations measured during the study were also observed with Kentera.

Mean and median change from baseline in daily incontinence episodes (primary endpoint), urinary frequency, and urinary void volume between placebo and active treatment groups are summarised in the table below.

Mean and median change from baseline for incontinence episodes, urinary frequency, and urinary void volume at Week 12 (LOCF)

	Kentera (N=389)		Placebo (N=400)	
Parameter	Mean (SD)	Median	Mean (SD)	Median
Daily incontinence episodes				
Baseline	5.4 (3.26)	4.7	5.4 (3.28)	4.7
Change from baseline	-3.0 (2.73)	-2.7	-2.5 (3.06)	-2.0
P-value vs. placebo	<0.0001		--	
Daily urinary frequency				
Baseline	12.4 (3.34)	11.7	12.2 (3.32)	11.3
Change from baseline	-2.7 (3.21)	-2.7	-2.0 (2.82)	-1.7
P-value vs. placebo	0.0017		--	
Urinary void volume (ml)				
Baseline	163.4 (65.85)	160.1	167.9 (68.40)	160.6
Change from baseline	21.0 (65.33)	11.5	3.8 (53.79)	0.0
P-value vs. placebo	0.0018		--	
Daily nocturia episodes				
Baseline	2.5 (1.61)	2.3	2.5 (1.71)	2.3
Change from baseline	-0.7 (1.40)	-0.7	-0.7 (1.32)	-0.7
P-value vs. placebo	0.1372		--	

During the double-blind treatment a significant positive effect on quality of life was seen with Kentera based on the Incontinence Impact Questionnaire (IIQ). These results were evident after the first month of treatment and were maintained throughout double-blind treatment as shown in the table below.

Mean (SD) change from baseline for IIQ total score and subscales at Week 12 (LOCF)

Score	Kentera (N=389)	Placebo (N=400)	P-value (Kentera vs. Placebo)
Total score	-72.1 (80.01)	-49.5 (76.59)	0.0005
Travel subscale	-20.9 (25.55)	-15.1 (24.82)	0.0068
Physical activity subscale	-18.0 (23.23)	-13.0 (21.68)	0.0078
Social relationships subscale	-15.2 (20.07)	-9.7 (19.27)	0.0019
Emotional health subscale	-18.1 (21.96)	-11.8 (20.64)	0.0002

Significant positive effects were also noted for each subscale domain of the IIQ and for six of ten quality of life domains, including the incontinence impact domain, of the King's Health Questionnaire (KHQ) as shown in the table below.

Mean (SD) change from baseline in KHQ Domain Scores at Week 12 (LOCF)

Domain	Kentera (N=389)	Placebo (N=400)	P-value (Kentera vs. Placebo)
General health perception	0.4 (12.23)	0.1 (11.94)	0.6528
Incontinence impact	-27.9 (30.02)	-21.3 (27.05)	0.0023
Symptom severity	-20.6 (22.90)	-15.8 (21.84)	0.0024
Role limitations	-27.1 (29.24)	-21.3 (27.16)	0.0133
Physical limitations	-20.2 (30.04)	-16.8 (28.12)	0.1064
Social limitations	-11.5 (24.40)	-10.3 (23.46)	0.4468
Personal relationships	-11.2 (24.96)	-6.2 (19.77)	0.0489
Emotions	-11.7 (24.59)	-8.4 (24.89)	0.0649
Sleep and energy	-15.6 (24.18)	-10.3 (22.42)	0.0061
Severity (coping) measures	-15.3 (21.40)	-11.1 (19.16)	0.0058

5.2 Pharmacokinetic properties

Absorption

Kentera is formulated for daily application and is capable of maintaining therapeutic blood levels of oxybutynin. 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 7 days, reaching average maximum concentrations of 4 to 5 ng/ml. Steady-state conditions are reached after the seventh day of administration. The difference in AUC and Cmax of oxybutynin and the active metabolite N-desethyloxybutynin following

transdermal administration of Kentera on either the abdomen, upper arms/shoulders and thighs 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.

Biotransformation

Oxybutynin administered orally is metabolised primarily by the cytochrome P450 enzyme systems, particularly CYP3A4, found mostly in the liver and gut wall. The expression of CYP3A and CYP3A4 may vary by as much as 40 fold due to genetic polymorphism. 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.

Person-to-person transference

The potential for dermal transfer of oxybutynin from a treated person to an untreated person was evaluated in a single-dose study where subjects dosed with Kentera engaged in vigorous contact with an untreated partner for 15 minutes, either with (N=14 couples) or without (N=12 couples) clothing covering the application area. The untreated partners not protected by clothing demonstrated detectable plasma concentrations of oxybutynin (mean C_{max} = 0.94 ng/ml). Two of the 14 untreated subjects participating in the clothing-to-skin contact regimen had measurable oxybutynin plasma concentrations **(**$C_{max} \leq$ 0.1 ng/ml) during the 48 hours following contact with treated subjects; oxybutynin was not detectable with the remaining 12 untreated subjects.

Effects of showering

The effect of showering on the absorption of oxybutynin was evaluated in a randomised, steady-state crossover study under conditions of no shower, or showering 1, 2 or 6 hours after Kentera application (N=20). The results of the study indicate that showering after one hour does not affect the overall systemic exposure to oxybutynin.

Use with sunscreen

The effect of sunscreen on the absorption of oxybutynin when applied 30 minutes before or 30 minutes after Kentera application was evaluated in a single-dose randomised crossover study (N=16). Concomitant application of sunscreen, either before or after Kentera application, had no effect on the systemic exposure of oxybutynin.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies for acute toxicity, repeat dose toxicity, genotoxicity, carcinogenicity and local toxicity. Adverse reactions were observed in embryotoxicity studies in the rabbit. 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. 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

Ethanol (96 per cent)
Glycerol
Hydroxypropylcellulose
Sodium hydroxide (for pH-adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not refrigerate or freeze.

Kentera contains alcohol and is considered flammable and should not come in contact with an open flame.

6.5 Nature and contents of container

The sachet is constructed from a multi-layer foil based laminate pouch material (polymethacrylate/acrylonitrile copolymer/adhesive/aluminum/low density polyethylene/paper).

Each sachet contains 1 g of gel.
Cartons of 30 sachets.

6.6 Special precautions for disposal and other handling

After the sachets are opened and contents expelled, the gel should be used immediately.

After applying the gel, hands should immediately be washed thoroughly with soap and water. It is recommended to cover the application site with clothing once the gel has dried. Avoid bathing, swimming, showering, exercising or immersing the application site in water for one hour after application.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/270/004 30 sachets

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

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

1. NAME OF THE MEDICINAL PRODUCT

Kentera 90.7 mg/g gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose of 1 gram of gel contains 90.7 mg of oxybutynin (as 100 mg oxybutynin hydrochloride) resulting in a nominal delivery of approximately 4 mg/day.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gel.
Rapid drying, clear, smooth, odourless, and colourless hydroalcoholic gel.

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

Posology

The recommended dose is one metered dose from the multidose container with metering pump applied once daily which corresponds to a delivery dose of approximately 4 mg.

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).

Renal impairment

There is no experience with the use of Kentera in patients with renal impairment.

Hepatic impairment

There is no experience with the use of Kentera in patients with hepatic impairment.

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.

Method of administration

Kentera should be applied to dry, intact skin on the abdomen, upper arms/shoulders, or thighs. Application sites should be rotated. Application should not be made to the same site on consecutive days.

Avoid bathing, swimming, showering, exercising or immersing the application site in water for one hour after application (see section 4.4).

It is recommended to cover the application site with clothing once the gel has dried.

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 special precautions for use

As the stratum corneum is the rate-limiting step in transdermal delivery, any breach would provide direct access to the epidermis, potentially increasing penetration and facilitating the migration of the medicinal product to the blood stream. Kentera should therefore not be applied to a recently shaved or damaged skin surface.

Avoid bathing, swimming, showering, exercising or immersing the application site in water for one hour after application.

It is recommended to cover the application site with clothing once Kentera has dried.

The effect of fever, exposition to external heat sources, sun bathing and sauna on the absorption characteristics of Kentera have not been investigated.

Impaired metabolism

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 since oxybutynin is extensively hepatic metabolised. 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 medicinal products should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.

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, and 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.

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).

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 active substances that compete for CYP3A4 enzyme metabolism may increase the frequency or severity of dry mouth, constipation, and drowsiness. As oxybutynin is metabolised by the cytochrome P 450 isoenzyme CYP 3A4, interactions with medicinal products that inhibit this isoenzyme, or known inducers of CYP 3A4, cannot be ruled out. This should be borne in mind when administering azole antifungals (e.g. ketoconazole) or macrolide antibiotics (e.g. erythromycin) concurrently with oxybutynin. Consumption of grapefruit juice may also influence metabolism of oxybutynin.

Anticholinergic medicinal products may potentially alter the absorption of some concomitantly administered medicinal products due to anticholinergic effects on gastrointestinal motility.

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, and dipyridamole.

Oxybutynin may cause drowsiness or blurred vision. Drowsiness may be increased by consumption of alcohol. Because Kentera may cause drowsiness, somnolence, or blurred vision, patients should be advised to exercise caution when driving or using machinery (see section 4.7).

Oxybutynin may antagonise prokinetic therapies, such as cisapride and metoclopramide, and should be avoided in the presence of reduced gastrointestinal motility conditions.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing age should be tested for pregnancy before beginning therapy, and during therapy utilise some form of pregnancy contraceptive.

Pregnancy

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

Breast-feeding

Available information shows that oxybutynin is excreted in milk of rats, but is not known whether oxybutynin is excreted in human milk. Use of oxybutynin is not recommended during breast-feeding.

Fertility

Data on possible effects of the use of oxybutynin on human male and female fertility are not available. Fertility studies in rats suggest a 6 fold margin of safety in both male and female breeding adults when Kentera is administered as prescribed (see section 5.3).

Patients on Kentera therapy should keep application sites covered with clothing when coming into contact with breast-feeding or pregnant women or breast-fed infants.

4.7 Effects on ability to drive and use machines

Kentera has minor influence on the ability to drive and use machines. Because Kentera may cause 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

Summary of the safety profile

The safety of Kentera was evaluated in patients with urge urinary incontinence in a randomised, double-blind, placebo-controlled, parallel group Phase 3 study that included 789 patients (with 389 patients receiving Kentera and 400 patients receiving placebo).

The most commonly reported adverse reaction was dry mouth (Kentera 6.9%, placebo 2.8%). Other adverse reactions reported were application site pruritus (Kentera 2.1%, placebo 0.8%), application site dermatitis (Kentera 1.8%, placebo 0.3%), dizziness (Kentera 1.5%, placebo 0.5%), headache (Kentera 1.5%, placebo 2.8%), constipation (Kentera 1.3%, placebo 1.0%), and pruritus (Kentera 1.3%, placebo 1.3%).

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	Uncommon	Urinary tract infections
Metabolism and nutrition disorders	Uncommon	Hypokalaemia
Psychiatric disorders	Uncommon	Anxiety, confusion, nervousness, agitation, insomnia
	Rare	Panic reaction#, delirium#, hallucinations#, disorientation#
Nervous system disorders	Common	Headache, dizziness
	Uncommon	Somnolence, dysgeusia, poor quality to sleep, tremor
	Rare	Memory impairment#, amnesia#, lethargy#, disturbance in attention#
Eye disorders	Uncommon	Dry eye
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Uncommon	Atrial fibrillation, atrial flutter, sinus arrhythmia
Vascular disorders	Uncommon	Flushing
Respiratory thoracic and mediastinal disorders	Uncommon	Cough, increased upper airway secretion
Gastrointestinal disorders	Common	Dry mouth, constipation
	Uncommon	Diarrhoea, nausea, dyspepsia, vomiting, haemorrhoids
Skin and subcutaneous tissue disorders	Common	Pruritus
	Uncommon	Rash, dry skin, rash pruritic
Renal and urinary disorders	Uncommon	Dysuria, haematuria, renal pain, urinary retention
General disorders and administration site conditions	Common	Application site pruritis, application site dermatitis
	Uncommon	Fatigue, oedema peripheral, application site papules, application site anaesthesia, application site erythema, application site irritation, application site pain, application site pustules
Investigations	Uncommon	Electrocardiogram abnormal, electrocardiogram change, blood chloride increased

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 the national reporting system listed in Appendix V.

4.9 Overdose

Overdose with oxybutynin has been associated with anticholinergic effects including CNS excitation, flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention. Patients should be monitored until symptoms resolve. Plasma concentrations of oxybutynin begin to decline 24 hours after Kentera application. Ingestion of 100 mg oral oxybutynin 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals, urinary antispasmodics, 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

The efficacy and safety of Kentera were evaluated in patients with urge urinary incontinence in a single Phase 3 study.

The Phase 3 study was a randomised, double-blind, placebo-controlled, parallel group study that included 789 patients. The 12-week double-blind treatment included daily applications of Kentera or matching placebo gel. A 14-week, open-label treatment was available for a subset of patients who completed the double-blind period. The majority of patients were Caucasian (86.3%) and female

(89.2%), with a mean age of 59.4 years (range: 18 to 88 years). Approximately 75% of patients had no prior pharmacological treatment for incontinence.

Patients treated with Kentera experienced a highly statistically significant decrease in the number of urinary incontinence episodes per day from baseline to endpoint (the primary efficacy endpoint) compared with placebo ($p<0.0001$), as well as for the secondary endpoints: a decrease in the average daily urinary frequency ($p=0.0017$), and an increase in the average urine volume per void ($p=0.0018$). Significant improvements in the quality of life evaluations measured during the study were also observed with Kentera.

Mean and median change from baseline in daily incontinence episodes (primary endpoint), urinary frequency, and urinary void volume between placebo and active treatment groups are summarised in the table below.

Mean and median change from baseline for incontinence episodes, urinary frequency, and urinary void volume at Week 12 (LOCF)

	Kentera (N=389)		Placebo (N=400)	
Parameter	Mean (SD)	Median	Mean (SD)	Median
Daily incontinence episodes				
Baseline	5.4 (3.26)	4.7	5.4 (3.28)	4.7
Change from baseline	-3.0 (2.73)	-2.7	-2.5 (3.06)	-2.0
P-value vs. placebo	<0.0001		--	
Daily urinary frequency				
Baseline	12.4 (3.34)	11.7	12.2 (3.32)	11.3
Change from baseline	-2.7 (3.21)	-2.7	-2.0 (2.82)	-1.7
P-value vs. placebo	0.0017		--	
Urinary void volume (ml)				
Baseline	163.4 (65.85)	160.1	167.9 (68.40)	160.6
Change from baseline	21.0 (65.33)	11.5	3.8 (53.79)	0.0
P-value vs. placebo	0.0018		--	
Daily nocturia episodes				
Baseline	2.5 (1.61)	2.3	2.5 (1.71)	2.3
Change from baseline	-0.7 (1.40)	-0.7	-0.7 (1.32)	-0.7
P-value vs. placebo	0.1372		--	

During the double-blind treatment a significant positive effect on quality of life was seen with Kentera based on the Incontinence Impact Questionnaire (IIQ). These results were evident after the first month of treatment and were maintained throughout double-blind treatment as shown in the table below.

Mean (SD) change from baseline for IIQ total score and subscales at Week 12 (LOCF)

Score	Kentera (N=389)	Placebo (N=400)	P-value (Kentera vs. Placebo)
Total score	-72.1 (80.01)	-49.5 (76.59)	0.0005
Travel subscale	-20.9 (25.55)	-15.1 (24.82)	0.0068
Physical activity subscale	-18.0 (23.23)	-13.0 (21.68)	0.0078
Social relationships subscale	-15.2 (20.07)	-9.7 (19.27)	0.0019
Emotional health subscale	-18.1 (21.96)	-11.8 (20.64)	0.0002

Significant positive effects were also noted for each subscale domain of the IIQ and for six of ten quality of life domains, including the incontinence impact domain, of the King's Health Questionnaire (KHQ) as shown in the table below.

Mean (SD) change from baseline in KHQ Domain Scores at Week 12 (LOCF)

Domain	Kentera (N=389)	Placebo (N=400)	P-value (Kentera vs. Placebo)
General health perception	0.4 (12.23)	0.1 (11.94)	0.6528
Incontinence impact	-27.9 (30.02)	-21.3 (27.05)	0.0023
Symptom severity	-20.6 (22.90)	-15.8 (21.84)	0.0024
Role limitations	-27.1 (29.24)	-21.3 (27.16)	0.0133
Physical limitations	-20.2 (30.04)	-16.8 (28.12)	0.1064
Social limitations	-11.5 (24.40)	-10.3 (23.46)	0.4468
Personal relationships	-11.2 (24.96)	-6.2 (19.77)	0.0489
Emotions	-11.7 (24.59)	-8.4 (24.89)	0.0649
Sleep and energy	-15.6 (24.18)	-10.3 (22.42)	0.0061
Severity (coping) measures	-15.3 (21.40)	-11.1 (19.16)	0.0058

5.2 Pharmacokinetic properties

Absorption

Kentera is formulated for daily application and is capable of maintaining therapeutic blood levels of oxybutynin. 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 7 days, reaching average maximum concentrations of 4 to 5 ng/ml. Steady-state conditions are reached after the seventh day of administration. The difference in AUC and Cmax of oxybutynin and the active metabolite N-desethyloxybutynin following

transdermal administration of Kentera on either the abdomen, upper arms/shoulders and thighs 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.

Biotransformation

Oxybutynin administered orally is metabolised primarily by the cytochrome P450 enzyme systems, particularly CYP3A4, found mostly in the liver and gut wall. The expression of CYP3A and CYP3A4 may vary by as much as 40 fold due to genetic polymorphism. 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.

Person-to-person transference

The potential for dermal transfer of oxybutynin from a treated person to an untreated person was evaluated in a single-dose study where subjects dosed with Kentera engaged in vigorous contact with an untreated partner for 15 minutes, either with (N=14 couples) or without (N=12 couples) clothing covering the application area. The untreated partners not protected by clothing demonstrated detectable plasma concentrations of oxybutynin (mean C_{max} = 0.94 ng/ml). Two of the 14 untreated subjects participating in the clothing-to-skin contact regimen had measurable oxybutynin plasma concentrations **(**$C_{max} \leq$ 0.1 ng/ml) during the 48 hours following contact with treated subjects; oxybutynin was not detectable with the remaining 12 untreated subjects.

Effects of showering

The effect of showering on the absorption of oxybutynin was evaluated in a randomised, steady-state crossover study under conditions of no shower, or showering 1, 2 or 6 hours after Kentera application (N=20). The results of the study indicate that showering after one hour does not affect the overall systemic exposure to oxybutynin.

Use with sunscreen

The effect of sunscreen on the absorption of oxybutynin when applied 30 minutes before or 30 minutes after Kentera application was evaluated in a single-dose randomised crossover study (N=16). Concomitant application of sunscreen, either before or after Kentera application, had no effect on the systemic exposure of oxybutynin.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies for acute toxicity, repeat dose toxicity, genotoxicity, carcinogenicity and local toxicity. Adverse reactions were observed in embryotoxicity studies in the rabbit. 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. 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

Ethanol (96 per cent)
Glycerol
Hydroxypropylcellulose
Sodium hydroxide (for pH-adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not refrigerate or freeze. Store pump in the upright position.

Kentera contains alcohol and is considered flammable and should not come in contact with an open flame.

6.5 Nature and contents of container

The multidose container is comprised of an outer polypropylene bottle with a Low Density Polyethylene (LDPE) pouch liner, a polypropylene metering pump, with ethylene propylene diene monomer (EPDM) gaskets, and a polypropylene cap.

Each multidose container contains at least 30 grams of Kentera and dispenses 30 metered 1 gram doses.

Kentera is packaged in a carton containing 1 multidose container with metering pump.

6.6 Special precautions for disposal and other handling

Before using the pump for the first time the multidose container should be primed. To prime the pump, fully depress the pump mechanism repeatedly until gel is observed, then depress the pump one more time, and discard this portion of the medicinal product to assure precise dose delivery. The pump is now primed and ready for use. After the priming step is complete, 30 full doses will remain in the pump. The metered dose should be applied immediately.

Always place the small protective cap back firmly on the tip of the pump nozzle and the large pump cover over the top of the pump after each use. If prime is lost during the use (no gel is dispensed after depressing the pump), repeat as instructed above to re-prime the pump.

After applying the gel, hands should immediately be washed thoroughly with soap and water. It is recommended to cover the application site with clothing once the gel has dried. Avoid bathing,

swimming, showering, exercising or immersing the application site in water for one hour after application.

Empty multidose container must be discarded in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/270/005 1 multidose container with metering pump

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

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

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Kentera gel and gel in sachet:

Nicobrand Limited
189 Castleroe Road
Coleraine
BT51 3RP
Northern Ireland

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

Kentera transdermal patch:

Merckle GmbH
Ludwig-Merckle-Straße 3
89143 Blaubeuren
Germany

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

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance System:

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON (Containing 2, 8 and 24 transdermal patches)

1. NAME OF THE MEDICINAL PRODUCT

Kentera 3.9 mg / 24 hours transdermal patch
oxybutynin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each transdermal patch releases 3.9 mg of oxybutynin per 24 hours. Each patch of 39 cm^2 contains 36 mg of oxybutynin.

3. LIST OF EXCIPIENTS

Excipients: triacetin; acrylic adhesive (containing 2-ethylhexyl acrylate; N-vinyl pyrrolidone and hexamethyleneglycol dimethacrylate polymer domains).
Backing: polyester/ethylene-vinyl acetate film; siliconised polyester film.

4. PHARMACEUTICAL FORM AND CONTENTS

2 transdermal patches
8 transdermal patches
24 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For transdermal use only.
Do not use if seal on sachet is broken

Apply immediately upon removal from sachet.
Read the package leaflet before use.

Sun/Wed
Mon/Thu
Tue/Fri
Wed/Sat
Thu/Sun
Fri/Mon
Sat/Tue

Apply a new Kentera patch twice weekly (every 3 to 4 days).

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. 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>

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

kentera

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET (Contains 1 transdermal patch)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Kentera 3.9 mg / 24 hours transdermal patch
oxybutynin
For transdermal use only.

2. METHOD OF ADMINISTRATION

Apply immediately upon removal from sachet.
Read the package leaflet before use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Contains 1 transdermal patch.

6. OTHER

Do not refrigerate or freeze.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON (Containing 30 sachets)

1. NAME OF THE MEDICINAL PRODUCT

Kentera 90.7 mg/g gel in sachet
oxybutynin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet of 1 gram of gel contains 90.7 mg of oxybutynin (as hydrochloride) resulting in a nominal delivery of approximately 4 mg/day.

3. LIST OF EXCIPIENTS

Excipients: ethanol (96%), glycerol, hydroxypropylcellulose, sodium hydroxide (for pH adjustment), and purified water.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Gel

30 sachets of 1 gram.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Apply immediately upon opening.

Read package leaflet before use.

Cutaneous use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER (S)

EU/1/03/270/004 <30 sachets>

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

kentera gel

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET LABELLING

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Kentera 90.7 mg/g gel in sachet
oxybutynin
Cutaneous use

2. METHOD OF ADMINISTRATION

Read leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 gram

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER AND THE IMMEDIATE PACKAGING MULTIDOSE CONTAINER WITH METERING PUMP

1. NAME OF THE MEDICINAL PRODUCT

Kentera 90.7 mg/g gel
oxybutynin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each metered dose of 1 gram of gel contains 90.7 mg oxybutynin (as hydrochloride) resulting in a nominal delivery of approximately 4 mg/day.

3. LIST OF EXCIPIENTS

Excipients: ethanol (96%), glycerol, hydroxypropylcellulose, sodium hydroxide (for pH adjustment), and purified water.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Gel

1 multidose container with metering pump of 30 grams

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Apply immediately after gel is dispensed from the pump.

Read package leaflet before use.

Cutaneous use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze. Store pump in the upright position.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER (S)

EU/1/03/270/005 <1 multidose container with metering pump>

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

kentera gel

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Kentera 3.9 mg / 24 hours transdermal patch

Oxybutynin

Read all of this leaflet carefully before you start using Kentera.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist. See section 4.

In this leaflet:

1. WHAT KENTERA IS AND WHAT IT IS USED FOR

Kentera is used in adults to control the symptoms of urge incontinence and/or increased urinary frequency and urgency.

Kentera works by allowing the bladder to expand and accommodate more urine.

2. BEFORE YOU USE KENTERA

Do not use Kentera:

- If you are hypersensitive (allergic) to oxybutynin or any of the ingredients of Kentera.
- If you have a rare condition called myasthenia gravis that makes the muscles in the body become weak and tire easily.
- If you experience incomplete bladder emptying during urination, the use of oxybutynin may increase this problem. You should discuss this problem with your doctor before using Kentera.
- If you have digestion problems caused by reduced emptying of the stomach after a meal you should consult your doctor before using Kentera.
- If you have glaucoma or a family history of glaucoma, tell your doctor.

Take special care with Kentera:

If you have any of the following:
- Liver problems
- Kidney problems
- Difficulty urinating
- Intestinal blockage
- Bloody stools
- Generalized muscle weakness
- Painful swallowing

Since treatment with oxybutynin may cause decreased perspiration, there is an increased risk of fever and heat stroke if you are exposed to high environmental temperatures.

Kentera is not recommended for use in children or adolescents.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Applying the Kentera patch at the same time as taking other medicines that have similar side effects such as dry mouth, constipation and drowsiness, may increase how often and how severe these side effects are experienced.

Oxybutynin may slow the digestive tract and thereby influence the adsorption of other oral medicines, or the use of this medicine together with other medicines may increase the effect of oxybutynin. Especially:
- Ketoconasole, itraconazole or fluconazole (used for the treatment of fungal infections).
- Erythromycin a macrolide antibiotic (used to treat bacterial infections).
- Biperiden, levodopa, or amantadine (used to treat Parkinson's disease).
- Antihistamines (used in the treatment of allergies such as hayfever).
- Phenothiazines or clozapine (used to treat mental illness).
- Tricyclic antidepressants (used to treat depression).
- Dipyridamole (used to treat blood clotting problems).
- Atropine and other anticholinergic medicines (used for treatment in stomach disorders such as irritable bowel syndrome).

Using Kentera with food and drink

Oxybutynin may cause drowsiness or blurred vision. Drowsiness may be increased by consumption of alcohol.

Pregnancy and breast-feeding

Ask your doctor for advice before taking any medicine.

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.

Driving and using machines

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

3. HOW TO USE KENTERA

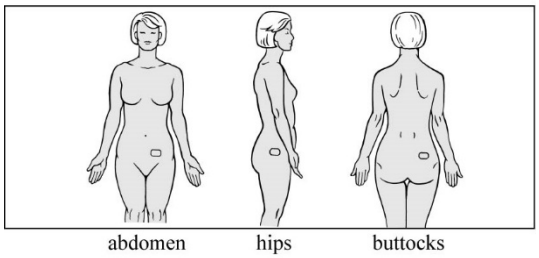
Always use Kentera exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are not sure.

Apply a new Kentera patch twice weekly (every 3 to 4 days) according to the instructions for use. Change the patch on the same two days every week, for example, every Sunday and Wednesday or Monday and Thursday. Printed on the inside flap of your Kentera package, you will find a Kentera calendar checklist that will help you to remember your dosing schedule. Mark the schedule you plan to follow and remember always to change your patch on the same two days of the week you have chosen

on your calendar. Make sure to wear only one patch at a time and wear your patch continuously, until it is time to apply a new one.

Where to apply

Apply the patch to a clean, dry, smooth area of skin on your abdomen, hips or buttocks. Avoid placing the patch in the waistline area to prevent tight clothing from rubbing against the patch. Do not expose the patch to the sun. Place the patch underneath your clothing. Rotate application sites with each new application. Do not apply a patch to the same place on your body for at least 1 week.



How to apply

Each patch is individually sealed in a protective sachet. Please read all the information below before you begin to apply Kentera.

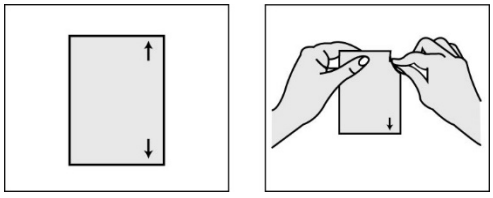
To apply Kentera:

Step 1: Choose a spot for the patch that is:

- Freshly washed, but dry and cool (wait a few minutes after taking a hot bath or shower).
- Free of body powder, lotion, and oil.
- Free of cuts, rashes or any other skin irritation.

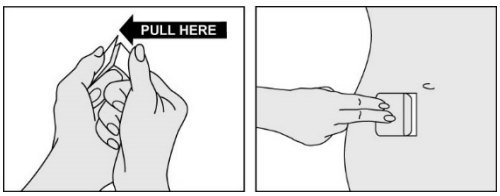
Step 2: Open the sachet that contains the patch.

- Tear open along arrows marked on the right side of the sachet as shown in drawing below.
- Do not cut the sachet with scissors, which might damage the patch inside.
- Pull the patch out.
- Apply immediately to your skin; do not keep or store the patch outside the sealed sachet.



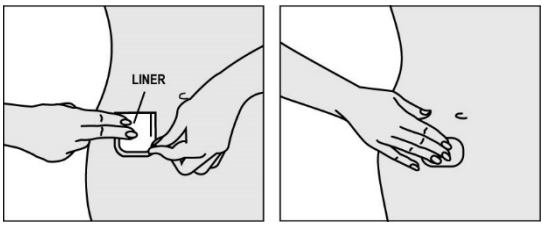
Step 3: Apply one half of the patch to your skin.

- Gently bend the patch and remove the first piece of protective liner, which covers the sticky surface of the patch.
- Without touching the sticky surface, firmly press the patch, adhesive face down, onto the part of the abdomen, hips or buttocks you have selected for application.



Step 4: Apply the second half of the patch to your skin.

- Bend the patch back over itself. Press down on the liner firmly.
- Push the liner forward a little to loosen the edge.
- Grab the loose edge at either corner and peel off the second piece of the liner. Try not to touch the sticky surface of the patch.
- Press the entire patch firmly onto the skin with your fingertips. Press for at least 10 seconds to make sure the patch will stay in place. Be sure all of it sticks to your skin, even around the edges.
- Discard the protective liners.



Bathing, showering, swimming and exercise:

You should wear each patch all the time until you apply a new one. Baths, showers, swimming and exercise should not affect the patch as long as you don't rub the patch as you wash. Avoid soaking in a hot bath for a long period of time, which can make the patch come off.

If the patch comes off:

If the patch starts to lift off your skin, apply a little bit of pressure using your fingertips. The patch is designed to re-stick. Very rarely will the patch come off completely. If it does, try putting the same patch back on the same spot. If it sticks firmly all over, leave it on. If not, take it off and put a new patch on a new spot. No matter what day this happens, continue with the twice-a-week schedule that you have marked on your patch box.

If you forget to change the patch after 3-4 days:

As soon as you remember, remove the old patch and apply a new one to a new spot on your abdomen, hips or buttocks. No matter what day this happens, continue with the same twice-a-week schedule for your next patch, even if it means changing the new patch before 3 to 4 days have elapsed.

<u>How to remove</u>

When changing the patch, remove the old patch slowly. Fold it in half (sticky sides together) and throw it away to keep out of the reach of children and pets. Mild redness may be present at the application site. This redness should disappear within several hours after removal of the patch. If irritation persists, please contact your doctor.

Gently washing the application site with warm water and a mild soap should remove any adhesive that remains on your skin after removal of the patch. A small amount of baby oil may also be used to remove any excess residue. Rings of adhesive that become soiled may require a medical adhesive removal pad that should be available from your pharmacist. Alcohol or other strong solvents may cause skin irritation and should not be used.

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.

If you use more Kentera than you should

The patient should not apply more than one patch at a time.

If you forget to use Kentera

Apply a Kentera patch as soon as you realise your patch is missing, or you have missed a scheduled day of application.

If you stop using Kentera

Your urge incontinence may return and you may have increased urinary frequency if you decide to stop using the patch. Continue to use Kentera as long as your doctor tells you to.

Talk to your doctor or pharmacist if you have any questions on the use of this medical product.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Kentera can cause side effects, although not everybody gets them.

The frequency of possible side effects listed below is defined using the following convention:
- Very common (affects more than 1 user in 10)
- Common (affects 1 to 10 users in 100)
- Uncommon (affects 1 to 10 users in 1,000)
- Rare (affects 1 to 10 users in 10,000)
- Very rare (affects less than 1 user in 10,000)
- Not known (frequency cannot be estimated from the available data)

Very common side effect:
- itching around the site of patch application

Common side effects:
- redness or rash at the site of patch application
- dry mouth
- constipation
- diarrhoea
- upset stomach
- stomach pain
- headache or sleepiness
- urinary tract infections
- blurred vision
- dizziness

Uncommon side effects:
- upper respiratory tract or fungal infections
- anxiety
- confusion

- nervousness
- agitation
- difficulty in sleeping
- palpitations
- hot flushes
- back pain
- urinary retention
- difficulty urinating
- common cold
- accidental injury

Rare side effects
- panic reaction
- mental confusion
- hallucinations
- disorientation
- memory impairment
- loss of memory
- abnormal tiredness
- poor concentration

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. STORING KENTERA

Keep out of the reach and sight of children.

Do not use Kentera after the date shown on the sachet and the carton.

Do not refrigerate or freeze.

The used patches 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 the 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.

6. FURTHER INFORMATION

What Kentera contains

The active substance is oxybutynin. Each transdermal patch releases 3.9 mg of oxybutynin per 24 hours. Each patch of 39 cm^2 contains 36 mg of oxybutynin.

The other ingredients are: Each patch contains triacetin, and acrylic adhesive solution. The oxybutynin, triacetin and acrylic adhesive are coated on clear PET/EVA backing film and covered with a siliconised polyester release liner.

What Kentera looks like and contents of the pack

Kentera is a transdermal patch and it is packaged in cartons containing 2, 8, and 24 patches. Each patch consists of a clear backing film that has the pharmaceutical ingredients coated on the side containing the protective backing film. The backing film is to be removed prior to patch application.

Marketing Authorisation Holder

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

Manufacturer

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

Merckle GmbH
Ludwig-Merckle-Straße 3
89143 Blaubeuren
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien Eurocept BV Tél/Tel: +31 (0) 35 528 8377	**Lietuva** UAB Teva Baltics Tel: +370 5 266 02 03
България Actavis EAD Tel: +359 2 489 95 85	**Luxembourg/Luxemburg** Eurocept BV Tél/Tel: +31 (0) 35 528 8377
Česká republika Teva Pharmaceuticals CR, s.r.o. Tel: +420 251 007 111	**Magyarország** Teva Gyógyszergyár Zrt. Tel: (+36) 1 288 6400
Danmark Recordati AB Sverige Tlf: +46 8 545 80 230 infoNordic@recordati.com	**Malta** V.J. Salomone Pharma Ltd Tel: +35 621 220 174
Deutschland Recordati Pharma GmbH Tel: +49 (0) 731 7047 0	**Nederland** Eurocept BV Tel: +31 (0) 35 528 8377
Eesti UAB Teva Baltics Eesti filiaal Tel: +372 661 0801	**Norge** Recordati AB Sverige Tlf: +46 8 545 80 230 infoNordic@recordati.com

Ελλάδα Recordati Hellas Pharmaceuticals A.E. Τηλ: +30 210-6773822	**Österreich** Haemo- Pharma Consult GmbH Tel: +43 (0) 2689 3116 0
España Laboratorios Gebro Pharma, S.A. Tel: +34 93 205 86 86	**Polska** Teva Pharmaceuticals Polska Sp. z o.o. Tel: +48 22 345 93 00
France Teva Santé Tél: +33 1 55 91 78 00	**Portugal** Jaba Recordati S.A. Tel: +351 21 4329 500
Hrvatska Pliva Hrvatska d.o.o. Tel: + 385 1 37 20 000	**România** Teva Pharmaceuticals S.R.L. Tel: +4021 230 65 24
Ireland Recordati Ireland Ltd. Tel: +353 (0) 21 4379400	**Slovenija** Pliva Ljubljana d.o.o. Tel: +386 1 58 90 390
Ísland Actavis Pharmaceuticals Iceland ehf. Sími: + 354 550 3300	**Slovenská republika** Herbacos Recordati s.r.o. Česká republika Tel: +420 466 741 915
Italia Innova Pharma S.p.A. Tel: +39 02 48787.1	**Suomi/Finland** Recordati AB Ruotsi/Sverige Puh/Tel: +46 8 545 80 230 infoNordic@recordati.com
Κύπρος Recordati Hellas Pharmaceuticals A.E. Ελλάδα Τηλ: +30 210-6773822	**Sverige** Recordati AB Tel: +46 8 545 80 230 infoNordic@recordati.com
Latvija UAB Teva Baltics filiāle Latvijā Tel: +371 67 323 666	**United Kingdom** Orion Pharma (UK) Ltd Tel: +44 (0) 1635 520300

This leaflet was approved in

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: http://www.ema.europa.eu

PACKAGE LEAFLET: INFORMATION FOR THE USER

Kentera 90.7 mg/g gel in sachet
Oxybutynin

Read all of this leaflet carefully before you start using Kentera

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist. See section 4.

In this leaflet:

3. WHAT KENTERA IS AND WHAT IT IS USED FOR

Kentera contains the active substance oxybutynin and is used in adults to control the symptoms of urge incontinence and/or increased urinary frequency and urgency.

Kentera works by allowing the bladder to expand and accommodate more urine.

4. BEFORE YOU USE KENTERA

Do not use Kentera

- If you are hypersensitive (allergic) to oxybutynin or any of the ingredients of Kentera.
- If you have a rare condition called myasthenia gravis that makes the muscles in the body become weak and tire easily.
- If you have glaucoma or a family history of glaucoma, tell your doctor.
- If you have difficulty emptying your bladder.
- If you are unable to have complete bowel movements.

Take special care with Kentera

If you have any of the following:
- Liver problems;
- Kidney problems;
- Difficulty urinating;
- Intestinal blockage;
- Bloody stools;
- Generalised muscle weakness;
- Painful swallowing;
- Unable to empty bladder during urination;
- Retained food in stomach after meals;

- Are above 65 years old;
- Chronic dry mouth that has resulted in periodontal disease or oral fungal infections;
- Nerve disorder that affects involuntary body functions including heart rate, blood pressure, perspiration and digestion;
- Problems with memory, language, or thinking abilities;
- A progressive neurological disease characterised by tremor of resting muscles, rigidity, slowness of movement, impaired balance, and a shuffling gait;
- Overactive thyroid gland which can cause increased appetite, weight loss, or sweating;
- Narrowing of the blood vessels that supply blood and oxygen to the heart;
- Heart problems which can cause shortness of breath or ankle swelling;
- Irregular heart beat;
- Faster heart beat;
- High blood pressure;
- Enlarged prostate.

Since treatment with oxybutynin may cause decreased perspiration, there is an increased risk of fever and heat stroke if you are exposed to high environmental temperatures.

Children and adolescents

Kentera is not recommended for use in children and adolescents under 18 years old.

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Applying Kentera while taking other medicines that have similar side effects, such as dry mouth, constipation, and drowsiness, may increase how often and how severe these side effects are experienced.

Oxybutynin may slow the digestive tract and thereby influence the adsorption of other oral medicines, interfere with bowel movement therapies, and the use of this medicine together with other medicines may increase the effect of oxybutynin. Especially:
- Ketoconazole, itraconazole or fluconazole (used for the treatment of fungal infections).
- Erythromycin a macrolide antibiotic (used to treat bacterial infections).
- Biperiden, levodopa, or amantadine (used to treat Parkinson's disease).
- Antihistamines (used in the treatment of allergies such as hayfever).
- Phenothiazines, butyrophenone or clozapine (used to treat mental illness).
- Tricyclic antidepressants (used to treat depression).
- Quinidine (used to treat abnormal heart rhythms).
- Dipyridamole (used to treat blood clotting problems).
- Atropine and other anticholinergic medicines (used in the treatment of stomach disorders such as irritable bowel syndrome).

Using Kentera with food and drink

Oxybutynin may cause drowsiness or blurred vision. Drowsiness may be increased by consumption of alcohol.

Pregnancy and breast-feeding

Ask your doctor for advice before taking any medicine.

Talk to your doctor before using Kentera if you are pregnant, might be pregnant or are planning to become pregnant. You should not use Kentera if you are pregnant unless your doctor has told you to.

If you are a woman of childbearing age, you should be tested for pregnancy before using Kentera. You should use some form of pregnancy contraceptive while using Kentera.

A small amount of orally administered oxybutynin is excreted in the mother's milk. Use of oxybutynin while breast-feeding is therefore not recommended.

Keep application sites covered with clothing when coming into contact with breast-feeding women or nursing babies.

Driving and using machines

Kentera may produce drowsiness, sleepiness, or blurred vision. Take special care when driving or using machinery.

3. HOW TO USE KENTERA

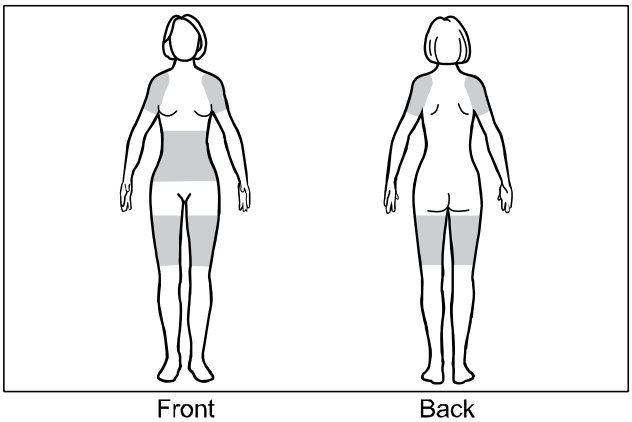
Always use Kentera exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose is one sachet applied once daily to dry, intact skin on the abdomen, upper arms/shoulders, or thighs, which delivers 4 mg of oxybutynin in 24 hours.

Important: Kentera is for application to the skin only. Kentera must not be taken by mouth. Avoid contact with eyes, nose, open sores, recently shaved skin, and skin with rashes or other areas not approved for the application of Kentera.

Step 1. The approved application sites for Kentera are the shaded areas shown in Figure A. These are the abdomen (stomach area), upper arms/shoulder, and thigh.
Select an approved site for the application of Kentera. Only apply Kentera to intact skin. Application sites should be rotated. You should not apply Kentera to the same site on consecutive days. Rotating approved application sites with each dose may help in reducing the risk of developing skin irritations. Do not apply Kentera in an area that is not approved.

Figure A:



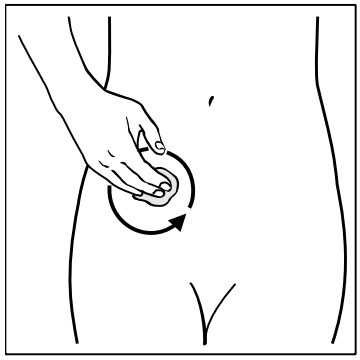
Step 2. Wash your hands with soap and water before applying Kentera.

Step 3. Wash the area where Kentera will be applied with mild soap and water.
Allow the area to dry completely.

Step 4. Gently rub Kentera into your skin until it dries.

Do not continue rubbing after Kentera has dried. If applying Kentera to the stomach, care should be taken to avoid the area around the navel (belly button). See Figure B.

Figure B:

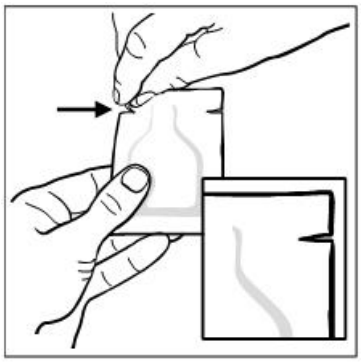


Step 5. After applying Kentera, immediately wash your hands thoroughly with soap and water.
Avoid bathing, swimming, showering, exercising or immersing the application site in water for one hour after application.
The application site may be covered with clothing once Kentera has dried.

How to use the sachets:

Step 1. Tear the sachet open at the indentation just before use. See Figure C.

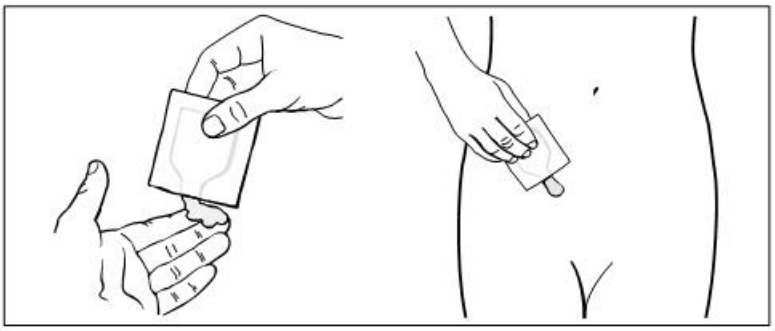
Figure C:



Squeeze the entire contents of the sachet onto your hand (palm or fingertips) or squeeze directly onto the application site. (See Figure D).

Squeeze from the bottom of the sachet toward the open end. Repeat until the sachet is empty. The amount of gel in each sachet will be about the size of a small coin (20 mm in diameter) on your skin.

Figure D:



Step 2. Carefully throw away the open sachet so that children and pets are not exposed to it.

If you use more Kentera than you should
You should not apply more than one sachet during a 24 hour period.

If you forget to use Kentera
Apply a single dose as soon as you realise you have missed an application.

If you stop using Kentera
Your urge incontinence may return and you may have increased urinary frequency if you decide to stop using the gel. Continue to use Kentera as long as your doctor tells you to.

Talk to your doctor or pharmacist if you have any questions on the use of this medicine.

4. POSSIBLE SIDE EFFECTS

Like all medicines Kentera can cause side effects, although not everybody gets them.

The frequency of possible side effects listed below is defined using the following convention:
- Very common (affects more than 1 user in 10)
- Common (affects 1 to 10 users in 100)
- Uncommon (affects 1 to 10 users in 1,000)
- Rare (affects 1 to 10 users in 10,000)
- Very rare (affects less than 1 user in 10,000)
- Not known (frequency cannot be estimated from the available data)

<u>Common side effects</u>
- headache
- dizziness
- dry mouth
- constipation
- itchiness
- itchiness, inflammation, or pain at the application site

<u>Uncommon side effects</u>
- bladder infection
- anxiety
- confusion
- nervousness
- agitation
- difficulty in sleeping
- low blood levels of potassium which can cause muscle weakness, twitching or abnormal heart rhythm

- feeling worried
- sleepiness, drowsy
- after taste, taste changed, abnormal sense of taste (i.e. metallic taste in mouth)
- not sleeping well
- shaking
- eyes feel sticky, gritty
- a feeling of dizziness or spinning
- irregular heart beat
- rapid irregular heart beat
- skin is markedly red
- cough
- increased mucous, phlegm
- loose or watery stools
- feeling sick, queasy
- indigestion, heartburn
- throwing up
- swelling of blood vessels around the anus
- rash
- dry skin
- itchy rash
- painful or difficulty urinating
- blood in urine
- kidney pain
- delayed or slow start of urinary flow
- tiredness, exhaustion
- swelling of ankles, feet or fingers
- small bumps at application site
- numbness at application site
- redness at application site
- irritation at application site
- pain at application site
- pus filled bumps at application site
- abnormal electrocardiogram (ECG or EKG, test of heart)
- change in ECG or EKG
- high chloride levels in blood

Rare side effects
- panic reaction
- mental confusion
- hallucinations
- disorientation
- memory impairment
- loss of memory
- abnormal tiredness
- poor concentration

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE KENTERA

Keep out of the reach and sight of children.

Do not use Kentera after the expiry date which is stated on the sachet and the carton after EXP. The expiry date refers to the last date of that month.

Do not refrigerate or freeze.

Kentera contains alcohol and is considered flammable. The product should not come in contact with an open flame.

Apply immediately after opening the sachet. Discard empty sachets and unused product in accordance with local requirements.

6. FURTHER INFORMATION

What Kentera contains

- The active substance is oxybutynin. Each sachet of 1 gram of gel contains 90.7 mg of oxybutynin resulting in a nominal delivery of approximately 4 mg/day.

- The other ingredients are: ethanol (96%), glycerol, hydroxypropylcellulose, sodium hydroxide (for pH adjustment), and purified water.

What Kentera looks like and contents of the pack

Kentera is a rapid drying, clear, smooth, odourless, and colourless hydroalcoholic gel that is packaged in single dose sachets. Each sachet contains 1 g of gel. Each carton contains 30 sachets.

The sachet is constructed from a multi-layer foil based laminated pouch material.

Marketing Authorisation Holder

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

Manufacturer

Nicobrand Limited
189 Castleroe Road
Coleraine
Northern Ireland
BT51 3RP

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

This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

PACKAGE LEAFLET: INFORMATION FOR THE USER

Kentera 90.7 mg/g gel

Oxybutynin

Read all of this leaflet carefully before you start using Kentera

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist. See section 4.

In this leaflet:

1. WHAT KENTERA IS AND WHAT IT IS USED FOR

Kentera contains the active substance oxybutynin and is used in adults to control the symptoms of urge incontinence and/or increased urinary frequency and urgency.

Kentera works by allowing the bladder to expand and accommodate more urine.

2. BEFORE YOU USE KENTERA

Do not use Kentera

- If you are hypersensitive (allergic) to oxybutynin or any of the ingredients of Kentera.
- If you have a rare condition called myasthenia gravis that makes the muscles in the body become weak and tire easily.
- If you have glaucoma or a family history of glaucoma, tell your doctor.
- If you have difficulty emptying your bladder.
- If you are unable to have complete bowel movements.

Take special care with Kentera

If you have any of the following:
- Liver problems
- Kidney problems
- Difficulty urinating
- Intestinal blockage
- Bloody stools
- Generalised muscle weakness
- Painful swallowing
- Unable to empty bladder during urination
- Retained food in stomach after meals

- Are above 65 years old
- Chronic dry mouth that has resulted in periodontal disease or oral fungal infections
- Nerve disorder that affects involuntary body functions including heart rate, blood pressure, perspiration and digestion
- Problems with memory, language, or thinking abilities
- A progressive neurological disease characterised by tremor of resting muscles, rigidity, slowness of movement, impaired balance, and a shuffling gait.
- Overactive thyroid gland which can cause increased appetite, weight loss, or sweating
- Narrowing of the blood vessels that supply blood and oxygen to the heart
- Heart problems which can cause shortness of breath or ankle swelling
- Irregular heart beat
- Faster heart beat
- High blood pressure
- Enlarged prostate

Since treatment with oxybutynin may cause decreased perspiration, there is an increased risk of fever and heat stroke if you are exposed to high environmental temperatures.

Children and adolescents

Kentera is not recommended for use in children and adolescents under 18 years old.

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Applying Kentera while taking other medicines that have similar side effects, such as dry mouth, constipation, and drowsiness, may increase how often and how severe these side effects are experienced.

Oxybutynin may slow the digestive tract and thereby influence the adsorption of other oral medicines, interfere with bowel movement therapies, and the use of this medicine together with other medicines may increase the effect of oxybutynin. Especially:
- Ketoconazole, itraconazole or fluconazole (used for the treatment of fungal infections).
- Erythromycin a macrolide antibiotic (used to treat bacterial infections).
- Biperiden, levodopa, or amantadine (used to treat Parkinson's disease).
- Antihistamines (used in the treatment of allergies such as hayfever).
- Phenothiazines, butyrophenone or clozapine (used to treat mental illness).
- Tricyclic antidepressants (used to treat depression).
- Quinidine (used to treat abnormal heart rhythms).
- Dipyridamole (used to treat blood clotting problems).
- Atropine and other anticholinergic medicines (used in the treatment of stomach disorders such as irritable bowel syndrome).

Using Kentera with food and drink

Oxybutynin may cause drowsiness or blurred vision. Drowsiness may be increased by consumption of alcohol.

Pregnancy and breast-feeding

Ask your doctor for advice before taking any medicine.

Talk to your doctor before using Kentera if you are pregnant, might be pregnant or are planning to become pregnant. You should not use Kentera if you are pregnant unless your doctor has told you to.

If you are a woman of childbearing age, you should be tested for pregnancy before using Kentera. You should use some form of pregnancy contraceptive while using Kentera.

A small amount of orally administered oxybutynin is excreted in the mother's milk. Use of oxybutynin while breast-feeding is therefore not recommended.

Keep application sites covered with clothing when coming into contact with breast-feeding women or nursing babies.

Driving and using machines

Kentera may produce drowsiness, sleepiness, or blurred vision. Take special care when driving or using machinery.

3. HOW TO USE KENTERA

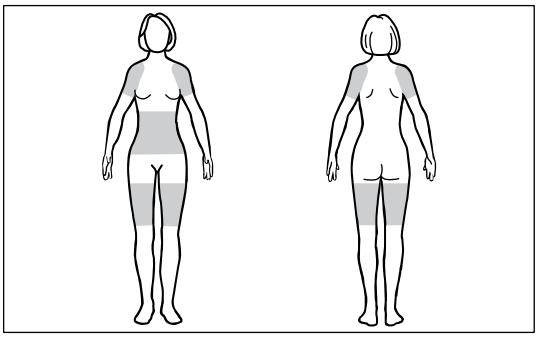
Always use Kentera exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose is the contents of one dispensed dose from the multidose container with metering pump applied once daily to dry, intact skin on the abdomen, upper arms/shoulders, or thighs, which delivers 4 mg of oxybutynin in 24 hours.

Important: Kentera is for application to the skin only. Kentera must not be taken by mouth. Avoid contact with eyes, nose, open sores, recently shaved skin, and skin with rashes or other areas not approved for the application of Kentera.

Step 1. The approved application sites for Kentera are the shaded areas shown in Figure A. These are the abdomen (stomach area), upper arms/shoulder, and thigh.
Select an approved site for the application of Kentera. Only apply Kentera to intact skin. Application sites should be rotated. You should not apply Kentera to the same site on consecutive days. Rotating approved application sites with each dose may help in reducing the risk of developing skin irritations. Do not apply Kentera in an area that is not approved.

Figure A:

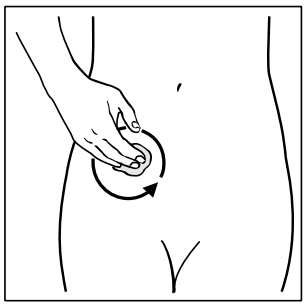


Step 2. Wash your hands with soap and water before applying Kentera.

Step 3. Wash the area where Kentera will be applied with mild soap and water.
Allow the area to dry completely.

Step 4. Gently rub Kentera into your skin until it dries.
Do not continue rubbing after Kentera has dried. If applying Kentera to the stomach, care should be taken to avoid the area around the navel (belly button). See Figure B.

Figure B:

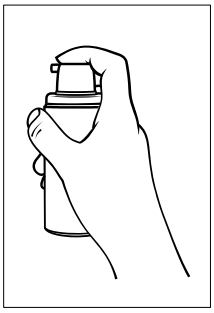


Step 5. After applying Kentera, immediately wash your hands thoroughly with soap and water. Avoid bathing, swimming, showering, exercising or immersing the application site in water for one hour after application.
The application site may be covered with clothing once Kentera has dried.

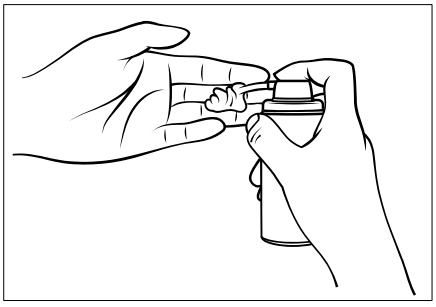
How to use the multidose container with metering pump:

It is important you read and follow these directions on how to use the Kentera pump properly.

Step 1. Before using the pump for the first time, you must prime the Kentera pump. To prime the pump, fully depress the pump mechanism repeatedly until gel is observed, then depress the pump one more time, and discard this portion of the product to assure precise dose delivery. The pump is now primed and ready for use. After the priming step is complete, 30 full doses will remain in the pump.



Step 2. Fully depress the pump once onto your hand (palm or fingers), or directly onto the application site. The amount of gel from one pump depression will be about the size of a small coin (20 mm in diameter) on your skin. Apply as directed above. Always place the small protective cap back firmly on the tip of the pump nozzle and the large pump cover over the top of the pump after each use. If prime is lost during the use (no gel is dispensed after depressing the pump), repeat as instructed above to re-prime the pump. After 30 doses, discard the Kentera pump. Kentera pump should be discarded in household trash in a manner that prevents accidental application or ingestion by household members or pets.



If you use more Kentera than you should
You should not apply more than a single metered dose during a 24 hour period.

If you forget to use Kentera
Apply a single dose as soon as you realise you have missed an application.

If you stop using Kentera
Your urge incontinence may return and you may have increased urinary frequency if you decide to stop using the gel. Continue to use Kentera as long as your doctor tells you to.

Talk to your doctor or pharmacist if you have any questions on the use of this medicine.

4. POSSIBLE SIDE EFFECTS

Like all medicines Kentera can cause side effects, although not everybody gets them.

The frequency of possible side effects listed below is defined using the following convention:
- Very common (affects more than 1 user in 10)
- Common (affects 1 to 10 users in 100)
- Uncommon (affects 1 to 10 users in 1,000)
- Rare (affects 1 to 10 users in 10,000)
- Very rare (affects less than 1 user in 10,000)
- Not known (frequency cannot be estimated from the available data).

Common side effects
- headache
- dizziness
- dry mouth
- constipation
- itchiness
- itchiness, inflammation, or pain at the application site

Uncommon side effects
- bladder infection
- anxiety
- confusion
- nervousness
- agitation
- difficulty in sleeping
- low blood levels of potassium which can cause muscle weakness, twitching or abnormal heart rhythm
- feeling worried
- sleepiness, drowsy
- after taste, taste changed, abnormal sense of taste (i.e. metallic taste in mouth)
- not sleeping well
- shaking
- eyes feel sticky, gritty
- a feeling of dizziness or spinning
- irregular heart beat
- rapid irregular heart beat
- skin is markedly red
- cough
- increased mucous, phlegm
- loose or watery stools
- feeling sick, queasy
- indigestion, heartburn
- throwing up
- swelling of blood vessels around the anus
- rash

- dry skin
- itchy rash
- painful or difficulty urinating
- blood in urine
- kidney pain
- delayed or slow start of urinary flow
- tiredness, exhaustion
- swelling of ankles, feet or fingers
- small bumps at application site
- numbness at application site
- redness at application site
- irritation at application site
- pain at application site
- pus filled bumps at application site
- abnormal electrocardiogram (ECG or EKG,test of heart)
- change in ECG or EKG
- high chloride levels in blood

Rare side effects
- panic reaction
- mental confusion
- hallucinations
- disorientation
- memory impairment
- loss of memory
- abnormal tiredness
- poor concentration

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE KENTERA

Keep out of the reach and sight of children.

Do not use Kentera after the expiry date which is stated on the multidose container with metering pump and the carton after EXP. The expiry date refers to the last date of the month.

Do not refrigerate or freeze. Store pump in the upright position.

Kentera contains alcohol and is considered flammable. The product should not come in contact with an open flame.

Apply immediately after dose delivered from the multidose container with metering pump. Discard empty multidose containers in accordance with local requirements.

6. FURTHER INFORMATION

What Kentera contains

- The active substance is oxybutynin. Each metered dose of 1 gram of gel contains 90.7 mg of oxybutynin resulting in a nominal delivery of approximately 4 mg/day.

- The other ingredients are: ethanol (96%), glycerol, hydroxypropylcellulose, sodium hydroxide (for pH adjustment), and purified water.

What Kentera looks like and contents of the pump

Kentera is a rapid drying, clear, smooth, odorless, and colorless hydroalcoholic gel that is packaged in a multidose container with metering pump. Each multidose container contains at least 30 grams of Kentera and dispenses 30 metered 1 gram doses. Each carton contains 1 multidose container with metering pump.

The multidose container is comprised of an outer bottle with a pouch liner, a metering pump and a cap.

Marketing Authorisation Holder

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

Manufacturer

Nicobrand Limited
189 Castleroe Road
Coleraine
Northern Ireland
BT51 3RP

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

This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu