SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Kentera. For information on changes after approval please refer to module 8.

1. Introduction

Urge incontinence involves a strong, sudden need to urinate immediately followed by a bladder contraction, resulting in an involuntary loss of urine.
The ability to hold urine and maintain continence is dependent on normal function of the lower urinary tract, the kidneys, and the nervous system. The bladder's ability to fill and store urine requires a functional sphincter and a stable bladder wall muscle (detrusor).
Two phases are involved in the process of urination: the filling and storage phase and the emptying phase.
Urge incontinence is basically a storage problem in which the bladder muscle contracts inappropriately. Often these contractions occur regardless of the amount of urine that is in the bladder.
Urge incontinence may result from neurological injuries (such as spinal cord injury or stroke), neurological diseases (such as multiple sclerosis), infection, bladder cancer, bladder stones, bladder inflammation, or bladder outlet obstruction. The majority of cases are classified as idiopathic.
Although urge incontinence may occur in anyone at any age, it is more common in women and the elderly. It is second only to stress incontinence as the most common cause of urinary incontinence (involuntary loss of urine). Approximately 1% to 2% of adult females are affected by urge incontinence.
In men, urge incontinence may be due to secondary bladder injuries caused by benign prostatic hypertrophy (BPH) or bladder outlet obstruction from an enlarged prostate.
Symptoms include sudden and urgent need to urinate (urinary urgency), frequent urination, in the daytime and at night, abdominal distension or discomfort, involuntary loss of urine (urinary incontinence).

Kentera is a transdermal system delivering 3.9 mg oxybutynin per 24 hours and is proposed for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and/or frequency.
The proposed posology is one patch applied twice weekly (every 3 to 4 days).
Studies have not been performed in children, therefore oxybutynin 3.9 mg per 24 hours transdermal patch is not recommended for use in children. The development of Kentera was based on the rationalethat a patch could ease the compliance, and that the dose delivery by the transdermal route would reduce undesirable side effects of the oral administration.

Oxybutynin, an anticholinergic agent, is a well known active substance for which there is extensive experience in the European Union for the treatment of overactive bladder.
This is a full marketing authorisation application. The provided data cover all aspects of the clinical characterization of safety and efficacy of oxybutynin. The applicant has submitted the results of non-clinical and clinical studies carried out by the applicant, and bibliographic references. The submission of bibliographical data is justified with reference to Art. 8 (3) of Directive 2001/83/EC, as amended., and to Part II.7 of Annex 1 to Directive 2001/83/EC, as amended by Directive 2003/63/EC.

2. Quality aspects

Composition
Kentera is presented as a 39cm^2 transdermal patch containing 36 mg oxybutynin base, designed to release 3.9 mg oxybutynin per day during the 3 to 4 day treatment period.
It is a thin flexible patch with rounded corners and consists of three layers: a non-removable polyester protective film (backing layer), the adhesive matrix containing the active substance and a polyester removable protective layer (release liner).

The backing film is made of polyethylene terephthalate (PET) / ethylene-vinyl acetate (EVA). The matrix adhesive layer is laminated on the PET side. The matrix layer contains Oxybutynin, glycerol triacetate as penetration enhancer and an acrylic pressure sensitive adhesive. The release liner consists of silicone-coated PET.
Each transdermal patch is packed in a heat sealed sachet.

Active substance
The chemical name of oxybutynin base is 4-(diethylamino)-but-2-ynyl (RS)-2-cyclohexyl-2-phenylacetate. It is a white crystalline powder freely soluble in ethanol 96%, methylene chloride and acetone and practically insoluble in water. The active substance is a racemic mixture of (R) and (S) isomers and exhibits no optical rotation or polymorphism.
Oxybutynin base is not described in PhEur Information about the active substance has been submitted via an EDMF.
As starting material for the synthesis of the active substance is used oxybutynin hydrochloride, which is covered by a certificate of suitability from the PhEur. Oxybutynin hydrochloride is transformed into oxybutynin base by treatment with sodium bicarbonate. The product is then crystallised.
Two potential impurities (oxybutacide and oxybumethyl) can be found in the starting material, but have never been observed in the active substance. The only known degradation product of oxybutynin base is oxybutacide, but it does not appear if the active substance is stored in plastic bags and fiber drums at room temperature and protected from humidity. The limits of the residual solvents used for the manufacture of the active are in accordance with the ICH guidelines.

Active substance specification
The specification of the active substance includes tests for description, identification (IR), colour and clarity of solution, assay (potentiometric titration), melting point, loss on drying, inorganic and organic impurities (HPLC) and residual solvents (GC).
Batch analysis data have been provided for 3 batches of oxybutynin base. The analytical results for these batches comply with the proposed specification.

In conclusion it has been proven that the tests and limits in the specification are appropriate for controlling the quality of the active substance.

Stability
Stability studies have been performed on 3 batches of oxybutynin base in accordance with ICH guidelines. Samples were stored at controlled room temperature (25 ^{o}C/ 60% RH) for 5 years, and accelerated conditions (40 ^{o}C/ 75% RH) for 6 months.
The parameters tested were description, assay, impurity profile (HPLC), loss on drying, colour of solution. The methods used were the same as those used for the release of oxybutynin base and are stability indicating.
All parameters evaluated comply with the active substance specification. The stability data presented support the proposed re-test period for oxybutynin base, when stored in a double polythethyl liner inside an aluminium foil lined fibreboard drum under the specified conditions.

Other ingredients
Other ingredients include an acrylic adhesive solution and glycerol triacetate (PhEur). Nitrogen NF is used as a processing aid. All materials used are of non-animal origin.
The adhesive is a pressure sensitive adhesive with 2-ethylhexyl acrylate, N-vinyl pyrrolidone and hexamethyleneglycol dimethacrylate polymer domain and has been previously used in transdermal patches.

The backing film of the transdermal patch is a PET/EVA transparent, thin, flexible film that provides the patch with occlusivity and physical integrity. The release liner consists of silicone-coated PET.

Kentera transdermal patches are packaged in resin/ aluminium / low-density polyethylene / paper laminate pouches.

Product development and finished product

Orally administered oxybutynin has been utilised in the treatment of urge incontinence for several years and is generally dosed at 2.5 to 5 mg two or three times daily. Oxybutynin is extensively metabolised in the liver upon oral absorption. The principle metabolite, N-desethyl oxybutynin, is also a potent antagonist of the action of acetylcholine at the receptor level and it is primarily responsible for the most common anticholinergic effect of oxybutynin referred to as "dry mouth". Hence transdermal administration was chosen in order to reduce the formation of this active metabolite by avoiding pre-systemic metabolism, as well as the dosing frequency and the blood levels variation.

Kentera is a matrix type transdermal patch. In this type of patch the active substance is dissolved directly in the adhesive, which is kept in contact with the intact skin. The matrix formulation is designed specifically to present a sufficiently high concentration of the active substance to the stratum corneum, which is the primary absorption controlling factor.

The following critical parameters were investigated during the development of Kentera: active ingredient concentration, adhesive quality and skin tolerability, skin permeability, skin flux enhancer compatibility- concentration and skin tolerability as well as stability. Particle size and physical form of the active substance were not considered critical since oxybutynin is dissolved in the adhesive.

As it is known, typical acid based salts of an active ingredient do not penetrate the stratum corneum satisfactorily. Therefore the free base of oxybutynin has been utilised as an active substance. The strength of the dosage form was based on the known efficacious doses administered orally, taking into account the effects of the first pass metabolism associated with oral administration.

In vitro skin permeability studies in human cadaver skin, combined with previous good experience, have indicated the adhesive as the most appropriate from a range of adhesives tested. A number of potential penetration enhancers were also examined for their effect on steady state flux of oxybutynin from matrix formulations using the adhesive at the same concentrations of oxybutynin and enhancer. Based on these studies and the fact that glycerol triacetate is a known compedial excipient, this compound was selected as the preferred skin permeation enhancer.

The rate and extent of skin permeation is fundamentally associated with the concentration of the active ingredient in the matrix composition. The selected concentration of oxybutynin is based on results from in vitro skin permeation studies of formulations containing variable concentrations of oxybutynin free base utilizing the selected adhesive and penetration enhancer, as well as on studies on the physical stability of the formulations with respect to crystal formation.

The labelled delivery rate was derived from pharmacokinetic studies with the developed formulation where used patches were recovered and analysed for residual drug content. The in vitro/in vivo analysis showed that the in vitro transport of oxybutynin through human epidermis closely reflects the apparent delivery rate in vivo, determined from residual analysis of worn patches

The patches used in clinical trials were the same composition as those intended for marketing.

The manufacturing process is established in accordance with Good Manufacturing Practices and with internal standard procedures. The finished product is manufactured in 3 steps: mixing, coating/drying/laminating and die cutting/ pouching. Oxybutynin, glyceryl triacetate and the adhesive solution are mixed. The solution is coated, dried, and the two film are laminated.

Regarding the manufacturing process development the following steps have been studied and optimised: mixing step, the metering pump speed, which delivers the oxybutynin casting solution onto the film and the speed and air temperature of the drying step. The heat sealing parameters were also investigated to guarantee the heat seal quality and integrity.

The three major steps of the manufacturing process have been validated in three industrial batches. Among the parameters tested were the mixing time and speed, the temperature and speed of the dryer and the sealing conditions.

Product specification

The product specifications include tests by validated methods for the appearance, content uniformity, assay, identification (HPLC), degradation products (UV, HPLC), residual solvents (GC), glycerol triacetate content (GC), drug release (dissolution testing), adhesion to steel and release liner peel.

The specification and control tests applied for the finished product at time of release and throughout the life of the product are in compliance with pharmacopoeial standards (including Ph Eur) and ICH guidelines. The limits for each specification test are supported by stability data.
Batch analysis data from 12 batches of the finished product have been provided. All batches met the test limits as defined in the release specification and test methodology valid at the time of batch release and indicated that patches of consistent quality are obtained.
Stability of the product

Stability studies have been conducted in accordance with ICH guidelines on 2 pilot-scale batches of the finished product. The samples were stored at controlled room temperature conditions (25°C/60%RH) for up to 24 months and at accelerated conditions (40°C/75%RH) for up to 6 months. Additional stability data have been presented on 2 small-scale batches stored under the same conditions and for the same period of time.

The parameters studied were oxybutynin assay and release, glycerol triacetate content, degradation products, adhesion to steel, release liner peel. The tests performed are the same as those used for the release of Kentera and are stability indicating.

Based on the results of the above-mentioned studies it has been concluded that the proposed shelf life for the commercially packaged product under the conditions specified in the SPC is acceptable.

Discussion on chemical, pharmaceutical and biological aspects.

The quality of Kentera is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. There are no major deviations from EU and ICH requirements. The active substance is stable, well characterised and documented. All critical aspects of the development of the transdermal patch formulation have been studied resulting in a manufacturing process that consistently produces patches which meet the predefined quality criteria. The packaging materials are commonly used and well documented.
Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

3. Non-clinical aspects

Introduction

Kentera is a formulation for percutaneous delivery of the active substance oxybutynin, intended for symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with unstable bladder. Oxybutynin is currently used in several countries as an oral drug.
The Non-clinical Pharmacology and Toxicology Section of this application are covered by a different number of sources. In addition to bibliographic scientific published data, it includes supportive data from investigations carried out in Japan, plus two GLP-controlled dermal irritation and sensitisation studies which examined the effects of patch formulations relevant to Kentera. The provided data cover all aspects of the non-clinical requirements for oxybutynin.

Pharmacology

- Primary pharmacodynamics (*in vitro/in vivo*)

The active substance of Kentera transdermal patch is oxybutynin, a racemic mixture, which acts as a competitive antagonist of acetylcholine at post-ganglionic parasympathetic muscarinic receptors (M1, M2, M3), resulting in relaxation of bladder smooth muscle. The R-isomer seems to be responsible for the pharmacological response. The relaxant effect of oxybutynin in the urinary bladder seems to be related to more than one mechanism: an anticholinergic effect, a direct anti-spasmodic effect and a local anaesthetic effect. In *in vitro* studies, oxybutynin has been found to be slightly more selective for M1 muscarinic receptors located in the cerebral cortex and parotid gland and M3 muscarinic receptors located in the smooth muscle of the ileum or bladder. In *in vivo* animal models

(rats, pigs and dogs), oxybutynin administered intravenously, subcutaneously or intravesically has been demonstrated to have beneficial urodynamic effects, such as reducing maximum intravesical pressure, increasing bladder threshold volume and increasing bladder capacity.

- Secondary pharmacodynamics

Antimuscarinic drugs have known adverse effects such as accommodation paralysis, constipation, tachycardia, and dryness of mouth. The secondary pharmacodynamic effects observed with oxybutynin result from a lack of selectivity for the bladder, resulting in actions at other organ systems, such as the iris, intestine, and salivary gland

- Safety pharmacology

No effects were observed on the respiratory and cardiovascular systems (respiration, blood pressure, heart rate and femoral artery blood flow rate) in rat and dog models under subcutaneous administration. In guinea pig and rabbit ventricular cells oxybutynin reduced the L-type Ca^{2+} current, inward-rectifier K^+ current and delayed-rectifier K^+ current by one-half at concentrations, respectively, of 16.1 µM, 18.2 µM, and 11.4 µM (rapid-activating) 28.7 µM (slow activating).
It was concluded that the drug is unlikely to have adverse effects on cardiac electrical activity. Studies using HERG channels were not available.
In the gastro-intestinal system, inhibition of carbon transport in mice from 6.25 mg/kg s.c., decrease of gastric secretion in rat from 0.39 mg/kg s.c, and decreased salivary secretion in rabbits from 25 mg/kg s.c.were observed.
No effects were observed on water and electrolyte excretion in rats with doses up to 6.25 mg/kg s.c, but a tendency for Na^+ and Cl^- excretion decrease was observed from 100 mg/kg s.c..
No effects were observed on platelet aggregation or hemolysis in rabbits with concentrations up to 10^{-5}g/ml and prolonged prothrombin time and activated partial thromboplastin time were obtained in rats treated with 400mg/kg but not with 100 mg/kg.

- Pharmacodynamic drug interactions

No formal studies on pharmacodynamic drug interactions were submitted. Kentera is used as a single agent in the treatment of patients with overactive bladder. Published literature concerning potential additive affects of concomitantly administered medications that possess antimuscarinic activity have been reviewed and appropriate warnings incorporated into the product information. No specific commonly used medications have been identified that pose a risk to patients undergoing treatment for overactive bladder with Kentera.

- Summary of salient findings

There is accumulated experience with the use of Oxybutynin in the European Union.
No new preclinical pharmacodynamic study have been carried out to investigate the efficacy of Kentera Transdermal Patch, while the data attained from the bibliographical sources submitted properly describe the pharmacodynamic properties with sufficient detail. In addition, the clinical utility of oxybutynin has already been demonstrated in clinical trials and in clinical practice, and transdermal application does not seem to alter the pharmacological activity profile of oxybutynin.
The pharmacodynamic profile of oxybutynin was summarised in the application, addressing in particular, and confirming the effects on the urinary bladder contractility.
The general pharmacology and the safety pharmacology information forwarded for oxybutynin reflect the anticholinergic properties of the compound.

Pharmacokinetics

- Absorption- Bioavailability

After single intravenous administration of 5 mg/Kg 14C oxybutynin to male rats the radioactivity half-life in plasma was ~40 hours. Following single percutaneous administration of oxybutynin preparations into rats or dogs, the plasma levels of the compound increased dose dependently and decreased rapidly in the 24 hours following the preparation removal. In general, the terminal half-life was around 40 hours.
When 10 mg/kg of oxybutynin was administered subcutaneously to rats once a day for 14 days the radioactivity in plasma at 24 hours post-dose increased steadily after each dose and reached steady-state concentrations by 6 days, remaining at that level until dosing was discontinued. After the last administration a Cmax of 1.09 µg eq/ml at 4 hours was observed which then disappeared gradually with a half-life of 3.4 hours.

- Distribution

In male rats, after single administration of 12 mg/body of 14C oxybutynin, the radioactivity levels in tissues at Tmax was the highest (excluding at the application site) in the white adipose tissue followed by liver, harderian gland, adrenal gland, kidney and lung. The disappearance of radioactivity from tissues was similar, or faster than, that of plasma until 216 hours, indicating that no residual radioactivity remained in the tissues.
After subcutaneous application of [^{14}C]-oxybutynin, associated radioactivity was found to transfer into rat milk, generating a radioactivity 10-fold higher than in plasma after 4 hours, indicating that oxybutynin or its metabolite is transferred into milk. By 24 hours post-dose the milk and plasma levels were similar. Likewise, transplacental distribution of ^{14}C from oxybutynin was observed. Foetal blood and tissue radioactivity was generally lower than that of maternal plasma, except for the liver, which was 2.5 times higher. The major organs were exposed to oxybutynin or metabolites. Transfer of radioactivity into the fetus was 0.01% of the administered dose.

- Metabolism (*in vitro/in vivo*)

The metabolism of oxybutynin following oral administration was shown to occur primarily in the liver of both rats and dogs. The metabolism of oxybutynin following percutaneous administration was poorly characterized. Following oral administration, oxybutynin is predominantly metabolised by CYP3A4 and CYP3A5 in the human liver. Since CYP3A has been reported to be expressed in skin keratinocytes, it seems likely that this enzyme is capable of metabolizing and eliminating topically applied oxybutyunin. However, involvement of cutaneous CYPs in the metabolisation of oxybutynin after transdermal application has not been investigated in animal models or in humans.
Enterohepatic circulation in rats after subcutaneous administration was observed.
Since unmetabolised oxybutynin reaches the liver via systemic circulation, pharmacokinetic interactions with drugs that are potentially going to be co-administered in the clinical situation and which are CYP3A4 substrates/inhibitors/inducers are possible. This issue is pointed out in the SPC.
Oxybutynin is widely distribution into tissues, breast milk and across the placenta observed in rats and is consistent with the large volume of distribution in man. In humans, oxybutynin is also known to be 85% bound to serum albumin.

- Excretion

Excretion following percutaneous administration of radiolabelled oxybutynin occurred primarily by the faecal route in rats, with approximately equals amounts in faeces and urine in dogs.

- Summary of pharmacokinetic parameters (in different species)

Following percutaneous administration of radiolabelled oxybutynin patch in rats, radioactivity in plasma increased with time until the dermal patch was removed at 48 hours. The radioactivity was highest (excluding at the application site) in white adipose tissue followed by the liver, harderian gland, adrenal gland, kidney and lung. The metabolism of oxybutynin following percutaneous administration was poorly characterized. Following oral administration, oxybutynin is predominantly metabolised by CYP3A4 and CYP3A5 in the human liver.
Sex differences have been observed in oxybutynin pharmacokinetics in rats. This is not reflected in the clinical studies, where the gender-related differences were minor and not considered clinically significant.

Toxicology

The toxicological information on the application included reports from studies available to the applicant and published scientific literature. Additional Local Tolerance studies to test for dermal irritation and sensitisation were sponsored to provide data relevant to Kentera Transdermal Patch - the patch delivery system containing oxybutynin, which is the subject of this marketing application.

- Single dose toxicity

In acute toxicity, major findings in rats and dogs after subcutaneous or percutaneous administration of oxybutynin are in relation with the expected pharmacological effects, such as anticholinergic and smooth muscle relaxation effects

- Repeat dose toxicity (with toxicokinetics)

In repeat-dose toxicity studies, pharmacological effects and secondary effects such as mydriasis, increased water intake and urine volume increase were observed. At high doses, the observed symptoms are the classical adverse effects of anticholinergics, but manifested in extreme forms: effects on the CNS and on the respiratory system occur. Non-specific toxicological effects, such as inhibition of weight gain and decreased food intake, suggest deterioration of general health. No other specific effects or sex differences were reported
The toxicokinetic data generated for the repeat-dose studies show that the subcutaneous route of administration does result in systemic exposure to oxybutynin and that this exposure increases with the increase in dose applied to the skin and with duration of repeated administration. The systemic exposures reached by the animals in the reported toxicology studies exceeded those expected in humans under the therapeutic conditions of Kentera.

- Genotoxicity *in vitro* and *in vivo* (with toxicokinetics)

The genotoxicity of oxybutynin has been investigated with respect to gene mutations in bacteria and chromosomal aberrations *in vitro* and *in vivo* in non-GLP compliant studies. The standard 3-test battery (tests for gene mutations in bacteria and chromosomal aberrations in vitro and in vivo) revealed no concerns over the safety of administration of oxybutynin. In addition, information on the genotoxic potential of the patch components (the backing film, adhesive and enhancer) has been provided by the applicant.

- Carcinogenicity

No formal carcinogenicity studies have been submitted. The Applicant has considered published investigations on preclinical and clinical safety of oxybutynin. The literature search looked for both preclinical and clinical evidence of carcinogenicity, and revealed no information on the potential of oxybutynin to increase tumour incidence or produce any effect that might be regarded as 'pre-cancerous' in animal models. Post-marketing experience gained by widespread clinical use of oral oxybutynin in man reveal no suspicion of a carcinogenic potential

- Reproductive and developmental studies

Reproduction studies with oxybutynin hydrochloride were reported in the mouse, rat, hamster and rabbit. In the subcutaneous fertility study in rats, while no effects were reported in males, in females, however, fertility was impaired and a NOAEL of 5 mg/kg was identified. In the embryotoxicity study in the rabbit, the occurrence of organ anomalies is significantly increased at a concentration of 0.4 mg/kg/day oxybutynin administered subcutaneously. Oxybutynin exposure is not recommended during pregnancy, however, no reports of fetal or embryotoxicity are known.

- Local tolerance

Dermal irritation studies in rabbits and Guinea pigs indicate that the Oxybutynin Transdermal Patch has low irritant potential. No dermal toxicity was observed following application of the transdermal patch to guinea pigs for 24 hours together with ultraviolet radiation. Although no delayed contact sensitisation has been observed in the clinical safety studies, discrepancy in the conclusions are obtained from the preclinical dermal sensitisation studies performed in Japan and the additional tests performed in the US. This discrepancy is due to subjective observations where it is difficult to differentiate between sensitization and irritation.
Various *in vivo* investigations of the components themselves, as well as standard tests of extract injections, were performed to demonstrate the safety of the inert film components, acrylic adhesive, and permeation enhancer of the Oxybutynin Patch. Preclinical investigations of these materials revealed no significant toxicity.

- Other toxicity studies

Various *in vivo* investigations of the components themselves, as well as standard tests of extract injections, were performed to demonstrate the safety of the inert film components, acrylic adhesive, and permeation enhancer of the Oxybutynin Patch. Preclinical investigations of these materials revealed no significant toxicity.
From the environmental risk assessment included, it seems unlikely that the transdermal patch would present a risk to the environment.

- Summary of salient findings

In acute and repeat-dose toxicity studies, major findings in rats and dogs are in relation with the expected pharmacological effects and secondary effects of anticholinergics, such as effects on the CNS and on the respiratory system, mydriasis, increased water intake, urine volume increase.
No concern over the safety of administration of oxybutynin is raised with regard to Genotoxicity and Carcinogenicity
Based on the results of local tolerance tests it has been concluded that the non-clinical Local Tolerance testing of all formulations of possible relevance to Kentera assessment revealed no adverse effects serious enough to prevent the development of a Transdermal Patch for human use.

Discussion on the non-clinical aspects

Adequate scientific publications, that are relevant to the proposed indication, as well as formal study data have been submitted, and cover all non-clinical aspects of the application
The pharmacodynamic profile of oxybutynin, and its anticholinergic properties, have been adequately presented in the application, referring in particular to the effects on the urinary bladder contractility.
Pharmacokinetic properties of oxybutynin have been described and show the highest distribution in white adipose tissue, followed by the liver, harderian gland, adrenal gland, kidney and lung. Metabolism of oxybutynin occurs primarily in the liver of both rats and dogs.
The non-clinical information for oxybutynin revealed that in principle the toxicological profile of oxybutynin in Kentera transdermal patch will be similar to that observed by oral route, possibly with the advantage of lower and more persistent exposures being reached with the patch. A non-clinical

safety assessment of the pharmacologically inert components of the Transdermal Patch did not reveal special concerns for local or systemic effects in human medicinal use.

4. Clinical aspects

Introduction

Kentera is a transdermal system delivering 3.9 mg oxybutynin per 24 hours and is proposed for symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with unstable bladder.
The proposed posology is one patch applied twice weekly (every 3 to 4 days).

Studies have not been performed in children, therefore oxybutynin 3.9 mg per 24 hours transdermal patch is not recommended for use in children.

According to the applicant, all US studies were performed in accordance with guidelines on Good Clinical Practice and in accordance with the World Medical Association's Declaration of Helsinki and its amendments.

Pharmacokinetics

Studies in this pharmacokinetics section include comparison of absorption from the transdermal patch and oral administration of immediate release and extended release oxybutynin tablets in both single-dose and steady-state and in healthy volunteers as well as in patients; bioequivalence between three sites of application (abdomen, hip and buttocks); a dose proportionality study; and population pharmacokinetic studies to assess the effect of different demographic and other factors, such as, age, weight, race, gender, tobacco use, and concurrent drug or disease states.
Other pharmacokinetics-related issues, such as protein binding, biotransformation, drug interactions, kinetics in special populations, etc., were not specifically evaluated as part of the development program. Information on these issues are summarised and reported from the literature. Plasma samples were analysed for racemic Oxybutynin and DEO concentrations using high performance liquid chromatography (HPLC) with mass spectrometric (MS) or tandem mass spectrometric (MS/MS) detection following solid-phase extraction.

- Absorption – Bioavailability

The absorption kinetics of oxybutynin following a single application of Kentera to the abdomen for 4 days has been investigated in a crossover comparison with a single dose of oral oxybutynin 5 mg in healthy subjects .
The average dose of oxybutynin delivered from the 39 cm^2 oxybutynin transdermal patch (Kentera) is 3.9 mg per 24 hours
Oxybutynin from Kentera is absorbed across intact skin and into the systemic circulation by passive diffusion across the stratum corneum. Following application of the Oxybutynin 3.9 mg per 24 hours transdermal patch, oxybutynin plasma concentration increases for approximately 24 to 48 hours, reaching average maximum concentrations of 3 to 4 ng/mL.
Steady-state is reached during the second application. Thereafter, steady concentrations are maintained for up to 96 hours. The relative plasma concentrations and AUC of oxybutynin, achieved during transdermal compared to oral administration indicate that therapeutic levels are achieved during transdermal treatment.

- Bioequivalence

A bioequivalence study involving three sites of application (abdomen, hip and buttock) was performed. Transdermal patch application to the buttock and hip resulted in bioequivalent oxybutynin delivery compared to the abdomen, the application site used in the pivotal Phase III clinical trial

- Distribution

In the blood, oxybutynin is approximately 85% bound to human serum albumin (Shinozaki et al 1986).
After intravenous administration in man, the apparent volume of distribution of oxybutynin is 193 L (Douchamps et al 1988). This is consistent with wide distribution to the tissues and this has been confirmed in animal studies, which also found that oxybutynin is distributed to breast milk and across the placenta.

- Metabolism and Elimination

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. Oxybutynin is extensively metabolised by the liver, with less than 0.1% of the administered dose excreted unchanged in the urine. Also, less than 0.1% of the administered dose is excreted as the metabolite N-desethyloxybutynin.

- Dose proportionality and time dependencies

The dose-related pharmacokinetics of oxybutynin and N-desethyloxybutynin following the application of oxybutynin patches have been investigated during a steady state in healthy subjects and in a Phase III trial in patients with overactive bladder (OAB).
The oxybutynin patches used in both studies all used the same formulation as proposed for Kentera, with the exception that in addition to the actual Kentera patch of 39 cm^2, smaller patches of 26 cm^2 and 13 cm^2 were also investigated.
Plasma levels of the active agents were measured until 24 hours after removal of the last patch. Measurement of AUCs over the 96 hours of the final application showed that the pharmacokinetics were dose-proportional for both active agents (oxybutynin and N-desethyloxybutynin metabolite)

The steady-state pharmacokinetics of oxybutynin and N-desethyloxybutynin following the application of Kentera have been investigated in two studies in healthy subjects and two clinical trials in patients with OAB .
The results from these studies show that steady-state plasma levels of both active agents do not rise during long-term treatment, confirming the lack of accumulation of drug found in healthy subjects. In addition, it can be seen that steady-state plasma levels of both active agents are comparable in healthy subjects and patients.

- Special populations

Since very little oxybutynin and N-desethyloxybutynin are excreted unchanged in the urine, it is believed unlikely that renal impairment will significantly affect their pharmacokinetics.

Since oxybutynin is extensively hepatically metabolised, it is possible that its metabolism will be influenced in patients with impaired hepatic function.

The use of Kentera in patients with liver impairment should be carefully monitored.
Analysis of pharmacokinetic data from Phase I studies indicates that females exhibit a slightly greater metabolism of oxybutynin than males. This is consistent with the known higher cytochrome CYP 3A4 activity in females (Beirle et al 1999). However, gender differences were not detected in the analysis of steady-state levels of oxybutynin and N-desethyloxybutynin in OAB patients in clinical trials and are probably of little clinical significance.
Similarly, age, weight, race, tobacco use and concurrent illness were not found to have a significant effect on steady-state levels of oxybutynin and N-desethyloxybutynin in patients with OAB, including in patients up to the age of 88 years.
The use of Kentera has not been studied in children. Kentera is not recommended for use in children.

- Interaction studies

The interaction profile for oxybutynin is well documented and supported by the submitted data and literature.
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 drugs due to anticholinergic effects on gastrointestinal motility. As oxybutynin is metabolised by cytochrome P 450 isoenzyme CYP 3A4, interactions with drugs that inhibits 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 drugs with anticholinergic activity, such as amantadine and other anticholinergic antiparkinsonian drugs (e.g. biperiden, levodopa), antihistamines, antipsychotics (e.g. phenothiazines, butyrophenones, clozapine), quinidine, tricyclic antidepressants, atropine and related compounds like atropinic antispasmodics, dipyridamole.

Pharmacodynamics

- Mechanism of action

Oxybutynin is a competitive antagonist of acetylcholine at post-ganglionic muscarinic receptors, resulting in relaxation of bladder smooth muscle.
Furthermore, the binding of oxybutynin to muscarinic receptors on human detrusor muscle samples has been confirmed.
From *in vitro* animal data, the anticholinergic activity of oxybutynin is mostly due to the R-enantiomer, which shows greater selectivity for the M1 and M3 subtypes of muscarinic receptor than the M2 receptor. Although the M2 receptor is the predominant subtype in human detrusor muscle, it is probable that the M3 receptor is most important in mediating bladder contraction.
Oxybutynin also has a direct muscle-relaxing effect on isolated animal detrusor muscle and whole bladder preparations (Yarker et al 1995). However, this effect is approximately 500 times weaker than the anticholinergic effect and so it is unlikely to have any clinical significance. Oxybutynin also has local anaesthetic actions in animal models (Yarker et al 1995), although the clinical significance of this effect is unknown.

- Primary and Secondary pharmacology

The pharmacological activity of Kentera is due in part to the parent compound oxybutynin, but also due to its active metabolite N-desethyloxybutynin. Kentera results in different concentrations of parent compound and active metabolite versus oral administration.
This lower N-desethyloxybutynin plasma concentration does not substantially influence the clinical efficacy. It is also possible that less adverse effects (dry mouth) are reported.
The pharmacodynamic effects of oxybutynin patches on the human detrusor muscle in vivo have been investigated in a Phase II dose-titration study on patients with OAB who were treated with either

oxybutynin patches (n = 38) or oral immediate-release oxybutynin (n = 38). In this study, 92% of patients were females, 95% were Caucasian and the mean age was 63-64 years. The diagnosis of OAB was based on a history of urge incontinence, with or without evidence of a neurogenic cause, but which had previously been confirmed cystometrically. The trial was a randomised, double-blinding, and placebo-controlled. All patients had to have been responding to oral oxybutynin at study entry. Patches were applied to the abdomen twice weekly for up to 6 weeks. The initial dose was based on the previous dose of oxybutynin and the dose was then titrated, according to tolerability, in the range one to four 13 cm^2 patches per application.The main pharmacodynamic measures employed in this trial were bladder volume at first detrusor contraction and maximum bladder capacity, both measured by cystometry. These volumes are decreased in patients with detrusor instability or detrusor hyperreflexia, and antispasmodic agents are known to increase both of them. The results from this study, demonstrate that in patients with overactive bladder, characterised by detrusor muscle instability or hyperreflexia, oxybutynin increases maximum urinary bladder capacity and increases the volume to first detrusor contraction. Oxybutynin 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 M1 and M3 muscarinic subtypes (predominant in bladder detrusor muscle and parotid gland) compared to the M2 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 in vitro studies, but has a greater binding affinity for parotid tissue than oxybutynin.. It is therefore expected that Kentera will act on the salivary glands, which, in the human, contain predominantly M3 receptors and some M1 receptors (Giraldo et al 1988).
The secondary pharmacodynamic effects of Kentera on saliva production have been examined in,a Phase I study in 13 healthy subjects. It was a randomised, open-label, crossover study in subjects adequately pharmacokinetically representative of patients. Findings from this study are consistent with the relatively higher levels of N-desethyloxybutynin following oral oxybutynin, and therefore causing a greater inhibition of saliva production than following Kentera. These results are consistent with findings in the literature that high levels of N-desethyloxybutynin seem to contribute to the high incidence of anticholinergic adverse effects observed following oral dosing of oxybutynin (Buyse et al 1998).

There is no evidence that oxybutynin has significant effect on the heart. This is consistent with the finding that oxybutynin is less selective for the M2 muscarinic receptor than other subtypes and that is the M2 muscarinic receptor is the predominant subtype in the human heart (Oxybutynin 1999).

Clinical efficacy

One phase II (dose tolerabilithy) and two phase III were performed in patients suffering from overactive bladder. The original clinical results have been supplemented by appropriate literature.

- Phase II Dose titration/tolerability study

The dose titration study was a multi-center, randomized, double-blind, active controlled, forced dose-titration Phase II study. Eligible participants were patients diagnosed with urge incontinence associated with detrusor instability or detrusor hyperreflexia who had symptomatic improvement on prior treatment with oral oxybutynin.
The primary objective was to compare the efficacy in treatment of urge urinary incontinence between transdermal delivery of oxybutynin and oral administration of oxybutynin. Evaluation was based on the percentage of responders in each treatment group. Patients were categorized as responders or non-responders to treatment based on the difference in the number of incontinent episodes reported prior to and during treatment.
A total of 70 evaluable patients were expected to complete the study. Four dose levels of each of the two treatments were used during this study: oxybutynin transdermal patches of 13, 26, 39 or 52 cm2 (equivalent to 1.3 to 5.2 mg/day) applied twice weekly (every 3.5 days) and over-encapsulated

Ditropan® tablets oral capsules, (each containing 2.5 mg Oxybutynin), 5, 10, 15 or 22.5 mg/day in divided doses. Each treatment included matching placebo and active formulations.
After 2 weeks treatment, the dose was titrated to the next higher dose level in patients who had none, or only mild, side effects, left at the same level in those patients who had tolerable side effects and reduced to the next lowest level in those who had intolerable side effects. The same titration procedure was employed after 4 weeks treatment, and the study concluded after 6 weeks treatment.

Transdermal treatment achieved comparable efficacy to oral treatment which included overall patient response to treatment, number of incontinent episodes, and influence of treatment on urinary cystometry parameters. The incidence and severity of dry mouth, the primary anticholinergic side effect associated with treatment, were significantly improved compared to treatment with the oral, immediate-release product.
The distribution of dose levels during the study were as follows:

At Baseline

Variable	***Oxybutynin patches***				***Oral Oxybutynin***			
Treatment level	*½*	*1*	*2*	*3*	*½*	*1*	*2*	*3*
*Dose regime**	*13 cm^2*	*26 cm^2*	*39 cm^2*	*52 cm^2*	*5 mg*	*10 mg*	*15 mg*	*22.5 mg*
Number patients	*0*	*27*	*9*	*2*	*0*	*28*	*9*	*1*

**Twice weekly for patches, per day for oral dosing*

After 6 Weeks Treatment

Variable	***Oxybutynin patches***				***Oral Oxybutynin***			
Treatment level	*½*	*1*	*2*	*3*	*½*	*1*	*2*	*3*
*Dose regime**	*13 cm^2*	*26 cm^2*	*39 cm^2*	*52 cm^2*	*5 mg*	*10 mg*	*15 mg*	*22.5 mg*
Number patients	*0*	*2*	*10*	*26*	*1*	*12*	*11*	*11*
*Mean dose**	*47 cm^2*				*15 mg/day*			

**Twice weekly for patches, per day for oral dosing*

Patients in the transdermal group generally had milder and fewer side effects leading to more dose levels increases than the oral group.

- Main studies

Two phase III studies were performed.

Phase III Placebo Controlled Dose Escalation Trial

This study was a 12-week multi-center, randomized, double-blind, placebo-controlled study with a 12-week open-label, dose-titration safety period and a 28-week open-label safety extension.
This study consisted of three periods for total study duration of 1 year:
-12-week, double-blind, placebo-controlled period evaluating three doses of oxybutynin transdermal delivery system (TDS), followed by
-12-week, open-label, dose-titration safety period, and
- Subsequent 28-week, fixed-dose, open-label safety extension.

METHODS

Study Participants

The double-blind period was a multi-center, randomized study in patients with a history of overactive bladder with symptoms of urgency, urge urinary incontinence, and urinary frequency that was not related to chronic illness, anatomical weakness or abnormalities, or medication use.
It consisted of a screening period of 3 to 4 weeks and a randomized, double-blind, placebo-controlled treatment period (12 weeks). The screening period included a 2-week period for washout from current pharmacological treatment and up to 2-week baseline evaluations.
The study enrolled 520 patients at 40 centers in the double-blind period to provide 447 patients evaluable for efficacy at the end of the 12 weeks of treatment. They were primarily elderly Caucasian women (mean age = 63 yrs, 91% Caucasian, 92% female). Patients who completed the double-blind period were eligible to enter the 12-week open-label, dose-titration safety period. In the open-label safety period, all patients began treatment with a single 13 cm^2 oxybutynin TDS applied twice weekly. The dose of medication was titrated by the investigator after 2 and 4 weeks of treatment based on the patient's symptoms and remained fixed for the last 8 weeks.
Patients who completed the 12-week open-label safety period had the option to continue into a 28-week, open-label, fixed-dose safety extension. Participation was limited to approximately 150 patients from the top-performing sites to ensure exposure in 100 patients.

Number of Patients (Planned and Analyzed):

Study Period	Planned to enroll/complete	Enrolled & Completed	Analyzed	
			Efficacy	Safety
Double-blind	450/400	520 & 447	515 (mITT[1])	520
12-Week open-label	300/300	411 & 358	385	411
28-Week extension	150/100	142 & 115	--	142

[1] Six patients were misrandomized during the double-blind treatment period. They were included in the mITT cohort by the treatment actually received. The ITT cohort includes these patients by randomized treatment assignment.

Treatments

Patients who met the eligibility criteria during the screening and baseline evaluations were randomized to one of the following treatment groups: 13 cm^2 Oxybutynin TDS, 26 cm^2 Oxybutynin TDS, 39 cm^2 Oxybutynin TDS, or placebo TDS. Doses were obtained using combinations of active and placebo 13 cm^2 and 26 cm^2 systems. All patients applied two systems, twice weekly (approximately every 3.5 days), to the abdomen for 12 weeks. The active TDS delivered a nominal dose of 0.1 mg Oxybutynin/cm^2 surface area per day.

Objectives

The primary objective of the double-blind period of the study was to compare the safety and efficacy of three doses of oxybutynin transdermal delivery system with placebo during 12 weeks of treatment.

The objectives of the 12-week open-label safety period included characterization of the distribution of doses used by the patients in the study, confirmation of continued efficacy using both objective and subjective measures, and continued treatment safety in approximately 300 patients. Changes in QoL scores over the 12-week open-label safety period were also evaluated, and plasma concentrations of Oxybutynin and its primary active metabolite were measured.

The objective of the 28-week open-label safety extension was to demonstrate continued treatment safety in approximately 100 patients who had been exposed to the Oxybutynin TDS for 1 year.

Outcomes/endpoints

The primary efficacy endpoint was the change from baseline to endpoint in the number of incontinent episodes recorded in the 7-day urinary diary.
The secondary endpoints of the double-blind period included comparisons of daily urinary frequency, urinary volume per void, quality of life (QoL) scores, Global Assessment of Disease State, and safety assessments. In addition, plasma concentrations of Oxybutynin and its primary active metabolite were measured to evaluate population pharmacokinetics.

Statistical methods

Four patient populations were defined for statistical analysis and data tabulation: the Safety cohort, the modified Intent-To-Treat (mITT) cohort, the Intent-To-Treat (ITT) cohort, and the Evaluable cohort. Two datasets were defined as observed cases (OC) and last observation carried forward (LOCF). Patient demographics, physical characteristics, and safety data were summarized for each analysis cohort and treatment group.
The primary efficacy analysis compared the change in number of urinary incontinence episodes per week from baseline to endpoint using LOCF imputation for patients who did not complete the double-blind period. The number of episodes was obtained from the 7-day urinary diary and was normalized to a 7-day value for patients with < 7 days of recorded data. This parameter was analyzed by an analysis of covariance (ANCOVA).
Supporting efficacy analyses compared the mean change in average daily urinary frequency and the mean change in average urinary volume per void from baseline to endpoint using LOCF imputation for patients who did not complete the double-blind period. Additional supporting efficacy analyses compared the mean Global Assessment of Disease State at baseline to endpoint and the mean change in the Global Assessment of Disease State at baseline to endpoint. Average daily urinary frequency was calculated by dividing the total number of events recorded in the 7-day urinary diary by the total number of days. Average urinary volume per void was calculated by dividing the sum of the voided volumes by the total number of voids recorded in the 2-day urine volume documentation. Quality of life was assessed using three validated questionnaires: the Short Form 36 (SF-36), the Incontinence Impact Questionnaire (IIQ), and the Urogenital Distress Inventory (UDI).

RESULTS

Outcomes and estimation

In the double-blind period, the number of urinary incontinence episodes from baseline to endpoint decreased in patients treated with the 39 cm^2 TDS. The decrease was statistically significant compared with placebo ($p = 0.0265$). The median number of incontinence episodes in the 39 cm^2 group decreased by 19 (61.3%) episodes per week, or nearly 3 episodes per day, compared with the median decrease of 15 episodes per week in the placebo group. Statistically significant improvements were also observed in the average daily urinary frequency (median decrease of 2 episodes per day, $p = 0.0313$) and the average urinary volume per void (median increase of 26 mL per void, $p = 0.0009$) in the 39 cm^2 group compared with placebo.

Patients treated with the 26 cm^2 TDS also showed significant improvements in the volume of urine per void, a trend toward improvement in the number of urinary incontinence episodes per week, and in average daily urinary frequency compared with placebo

The third supporting endpoint, the Global Assessment of Disease State, proved unable to distinguish among the different treatments. The incontinence-specific quality of life measure, the IIQ, indicated a significant positive effect of the 39 cm^2 treatment on IIQ total score at all study visits in comparison with placebo. This effect was also demonstrated for several IIQ subscales at various post-baseline time points. In general, treatment with the 13 cm^2 and 26 cm^2 systems showed similar trends as the

39 cm^2 systems in most parameters, but the magnitude of change was frequently not significant when compared with placebo. The substantial placebo response (50%) may have obscured any changes experienced in the 13 cm² and 26 cm² treatment groups.

Response to TDS treatment continued in the 12-week open-label safety period, with patients choosing final treatment levels that allowed them to attain roughly similar levels of response across final dose groups. The dose titration in the open-label safety period is supportive to the efficacy of the 39 cm^2 Oxybutynin TDS.
The choice of a final treatment dose was not obviously influenced by the assigned dose level in the double-blind period.

Phase III Placebo Controlled Active Comparator Trial

This study was a multi-center, randomized, double-blind, placebo-controlled study comparing oxybutynin transdermal systems versus Tolterodine long-acting capsules in patients with overactive bladder.

METHODS

Study Participants

The study considered patients with overactive bladder symptoms of urge urinary incontinence and urinary frequency with a beneficial response to current pharmacological treatment.
Patients participating in the study were primarily Caucasian women with a lengthy history of overactive bladder, although the overall study population included both men and women of Caucasian, Black, Asian/Pacific Islander and Hispanic ethnicity. The median duration of pharmacological treatment for overactive bladder was approximately 1 year. Patient age ranged from 18 to 89 years with an average age of 63 years.

The study included a Screening Period of 3 to 4 weeks duration and a 12-week Treatment Period. Screening consisted of a 2-week washout from current overactive bladder treatment, practice of bladder and fluid management techniques, and completion of a 3-day urinary diary at the end of the 2-week period. A repeat urinary diary was allowed if patients failed to accurately complete the diary.

Treatments

A total of 361 patients who met the eligibility criteria received one of 3 randomized treatments:

-121 patients received 39 cm^2 oxybutynin TDS (3.9 mg/day) plus placebo capsules,
-123 received 4 mg tolterodine long-acting capsules plus placebo TDS,
-117 received placebo treatment (capsules and TDS)

Transdermal systems were applied twice weekly (approximately every 3.5 days) to the abdomen and capsules taken orally once daily throughout the 12-week treatment period.

Objectives

The primary objective was to compare the safety and efficacy of transdermal Oxybutynin versus active and placebo controls in patients who had achieved a beneficial response from current pharmacological treatment for overactive bladder.

Outcomes/endpoints

The primary efficacy endpoint was the change in average number of urinary incontinence episodes per day from baseline to end of treatment as recorded on the 3-day urinary diary.
Secondary endpoints included change from baseline in average daily urinary frequency and average urinary volume per void; mean scores and changes from baseline for Global Assessment of Disease

State and two QoL instruments: the Incontinence Impact Questionnaire (IIQ) and the Urinary Distress Inventory (UDI).

Statistical methods

Four patient cohorts were defined a priori: Intent-to-Treat (ITT), modified Intent-to-Treat (mITT), Evaluable, and Safety. The two datasets were observed cases (OC) and LOCF. Patient demographics, physical characteristics, and safety data were summarized by descriptive statistics for each analysis cohort and treatment group.
Efficacy variables were analyzed by analysis of covariance (ANCOVA) following rank transformation for non-normal data sets with adjustment for unequal slopes as required. Baseline episodes were used as the covariate. Daily mean urinary diary parameters were rounded to the nearest integer.

RESULTS

Outcomes and estimation

Oxybutynin TDS treatment resulted in a significant decrease in urinary incontinence episodes from baseline to endpoint compared with placebo ($p = 0.0137$). Median daily incontinence episodes decreased by 3 for Oxybutynin TDS, compared with a decrease of 2 in the placebo group. Oxybutynin TDS and tolterodine were comparably effective, both treatments decreasing episodes by 3 per day, based on the 95% confidence interval for change in episodes (-1.0 to 0.0) [predefined interval -1.5 to 1.5; 95% CI].

Daily urinary frequency decreased by a median of 2 micturitions/day during Oxybutynin TDS treatment ($p = 0.1010$ at covariate mean of 12.3/day). Improvement was statistically significant compared with placebo at the baseline 3rd quartile value of 14 micturitions/day ($p = 0.0036$). Tolterodine also decreased episodes by 2 micturitions/day ($p = 0.0025$).
Average urinary void volume median increase was 24 mL during Oxybutynin treatment ($p = 0.0010$). Void volume also increased during tolterodine treatment (29 mL, $p = 0.0017$). Patient Global Assessment of Disease State also improved during Oxybutynin treatment ($p = 0.0106$).
Patient QoL was improved during Oxybutynin TDS treatment, indicated by total IIQ score ($p = 0.0271$) and trends in UDI. Individual IIQ subscales (travel, social relationships, emotional health, and physical activity) improved in general, but the magnitude of change was significant only for travel ($p = 0.0018$).

- Analysis performed across trials

No pooled analyses or meta-analysis were performed

- Discussion on clinical efficacy

In all three clinical trials in overactive bladder (OAB), the patients recruited were representative of patients seeking treatment of OAB in the EU, both in terms of their demographic characteristics and presentation of the condition.

The patients all had urge incontinence and so they represented the more severe end of the spectrum of OAB (Wein 2000). However, since less severe presentations of OAB, namely urgency and frequency, have has the same underlying pathophysiology (detrusor overactivity), it is reasonable to expect that the results from these studies can be applied to these presentations as well.

The Phase II trial established that the transdermal dose of oxybutynin provided by Kentera produces an adequate level of efficacy in the vast majority of patients. This dose was used in the two Phase III trials where Kentera showed statistically significantly improved urge incontinence compared with placebo, and improved frequency, symptoms and quality of life, but not always statistically significantly compared with placebo. This efficacy was maintained over 6 months of treatment.
The original clinical results have been supplemented by appropriate literature.

Clinical safety

- Patient exposure

A total of 1076 people have been exposed to oxybutynin patches using the same delivery system as found in Kentera, but including people who were exposed to systems of different sizes to Kentera and/or the earlier (but similar) formulation. Amongst the total population exposed, 663 were patients with OAB and 413 were healthy subjects.
A total of 758 subjects (580 with OAB and 178 healthy subjects) have been exposed to at least one administration of the final formulation of oxybutynin patches totalling 39 cm2 in area.

- Adverse events

Application site adverse events were the most common treatment-related adverse events and occurred in 23.1% of patients treated with active patches. Application site adverse events tended to increase with increasing patch dose and occurred most frequently in patients treated with 39 cm^2 patch. Pruritus was the most common application site adverse event at all dose levels and occurred in 14.5% of patients receiving active treatment. The greatest incidence of application site reactions occurred within the first 12 weeks of treatment, followed by a decline with continued treatment.
The incidences of treatment-related adverse events with the 39 cm^2 dose of oxybutynin patches during any phase of the three clinical trials in OAB (n = 454) are shown in the table below.

Incidence of treatment-emergent, treatment-related adverse events during any phase of the Phase II and III clinical trials with oxybutynin patches in those patients on the 39 cm^2 dose at onset (n = 454)

Adverse event (WHO-ART preferred term)	**Number (%) patients**	
Application site pruritus	47	(10.4)
Mouth dry	24	(5.3)
Application site erythema	22	(4.8)
Constipation	10	(2.2)
Application site reaction	10	(2.2)
Application site rash	10	(2.2)
Headache	7	(1.5)
Dizziness	7	(1.5)
Diarrhoea	6	(1.3)
Vision abnormal	5	(1.1)
Abdominal pain	4	(0.9)
Dysuria	4	(0.9)
Somnolence	4	(0.9)
Nausea	3	(0.7)
Back pain	2	(0.4)
Urinary tract infections	1	(0.2)
Inflicted injury	1	(0.2)
Rhinitis	1	(0.2)
Palpitation	1	(0.2)
Hot flushes	1	(0.2)
Any event	*148*	*(32.6)*

There is evidence of a dose-relationship for application site pruritus and erythema, and dry mouth.

There were no important differences in the incidence or profile of, or discontinuations due to, treatment-related adverse events in elderly (≥ 65 years) compared with younger patients taking oxybutynin patches in these trials, except that dizziness seemed to be more common in the elderly (3.6% of elderly patients vs 0.3% of younger patients).
The profile of treatment-related adverse events reported during the open-label extension study was comparable with that during the double-blind period, i.e. predominantly application site reactions. Therefore, there is no evidence that adverse reactions to oxybutynin patches become more frequent or more severe, or change in nature, during long-term administration; in fact, the incidence and severity seems to decline. This could be due to patients becoming more tolerant to the adverse effects over time and/or because intolerant patients discontinue therapy.

Certain other adverse effects have been attributed to oxybutynin in the literature. These include mydriasis, hallucinations, confusion, agitation and skin reactions. Others have also been described, and include anorexia, vomiting, dyspepsia, gastroesophageal reflux, esophagitis, decreased lagrimation, tachycardia, arrhythmia, fatigue, nightmares, restlessnes, anxiety, intraocular hypertension and induction of glaucoma, urinary retention and erectile dysfunction. Heat stroke has been reported in a patient taking oxybutynin in a high ambient temperature. Such effects have been seen with other anticholinergic agents and are due to inhibition of sweating, although were not observed during the development of Kentera.

- Serious adverse event/deaths/other significant events

No serious adverse events were reported. No death was reported.

- Laboratory findings

No clinically significant adverse trends with oxybutynin patches were identified in terms of vital signs, clinical laboratory variables, ECGs, or post-micturition residual urine volume during the clinical trials in patients (including during the open-label extension of Study O99009).
The ECG effects of oxybutynin have also been considered in a very elderly group of 21 patients (mean age 75), as reported in the literature (Hussain et al 1996). After 4 weeks of treatment at a mean daily dose of 7.6 mg, there were no adverse effects on the ECGs.

- Safety in special populations

Particular care should be put in the evaluation of the benefit risk evaluation in the elderly. Elderly people are possibly more sensitive to centrally acting anticholinergics. Also, differences in pharmacokinetics have been observed in the frail elderly nevertheless, in the clinical trials programme, elderly subjects up to the age of 88 years had a similar tolerability profile to oxybutynin patches as younger subjects, except perhaps for a slightly greater incidence of dizziness in the elderly. This is in contrast to the tolerability profile with oral oxybutynin, which was notably worse in the elderly particularly in terms of the high incidence of abnormal vision. This difference is presumably because Kentera produces much lower plasma levels of N-desethyloxybutynin than recommended doses or oral oxybutynin.
Since very little oxybutynin and N-desethyloxybutynin are excreted unchanged in the urine, it is unlikely that renal impairment will significantly affect their pharmacokinetics. However, it is appropriate that Kentera be used with caution in patients with renal impairment.
Kentera is to be administered with caution to hepatically impaired patients.

- Safety related to drug-drug interactions and other interactions

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 drugs due to anticholinergic effects on gastrointestinal motility. As oxybutynin is metabolised by cytochrome P 450 isoenzyme CYP 3A4, interactions with drugs that inhibits 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 drugs with anticholinergic activity, such as amantadine and other anticholinergic antiparkinsonian drugs (e.g. biperiden, levodopa), antihistamines, antipsychotics (e.g. phenothiazines, butyrophenones, clozapine), quinidine, tricyclic antidepressants, atropine and related compounds like atropinic antispasmodics, dipyridamole.

- Discontinuation due to adverse events

In patients treated with any dose of oxybutynin patch in any phases of the three clinical trials on OAB (n = 663), none of the treatment-related adverse events were serious. However, treatment-related adverse events did lead to discontinuation of study medication in 8.4% patients on oxybutynin patches 39 cm^2. This was almost entirely due to application site effects, with the remaining few cases (0.7% of patients) being due to dry mouth.

The information presented in the following table is a compilation of the relevant study reports. Additional statistical analyses indicate that the discontinuation rates in the active treatment groups of the Phase III Dose Escalation Trial were greater than the placebo rate, and that during the Phase III

Active Comparitor Trial, the TDS group exhibited a statistically greater discontinuation rate than the placebo group. Kentera also led to significantly greater discontinuation than the tolterodine group. This could be explained based on the patients enrolled into the study were previously on beneficial antimuscarinic treatment, selectively excluding patients that experienced significant intolerability to oral medications.

Table 8: Summary of incidence of discontinuation of treatment due to reported adverse events in Phase 3 trials.

Study	Parameter	Placebo	Oxytrol	Oxytrol	Oxytrol	Tolterodine
			1.3mg/d	2.6mg/d	3.9mg/d	4mg/d
O99009	n	6	15	17	15	---
	%	4.5	11.5	12.8	12.0	---
	p-value[1]	---	0.0371	0.0173	0.0292	---
O00011	n	3	---	---	16	4
	%	2.6	---	---	13.2	3.3
	p-value[1]	---	---	---	0.0024	0.7516
	p-value[2]	---	---	---	0.0045	---

[1]Chi-square test for difference in incidence between placebo and active treatment group.
[2]Chi-square test for difference in incidence between active treatment groups.

- Post marketing experience

Oral oxybutynin is marketed in several Member States and in the USA.
The Applicant presents reference from the UK national Agency as well as from the literature. The most common adverse effects of oxybutynin (dry mouth, nausea, rash, dizziness, headache, dyspepsia and diarrhoea) are all typical of anticholinergic agents.

- Discussion on clinical safety

The results of the clinical trials programme with oxybutynin patches indicate that the most clinically significant adverse effects of Kentera are application site reactions and dry mouth. Other anticholinergic effects occur at low rate and there is evidence that the overall incidence of adverse events is lower than that with recommend doses of immediate-release oral oxybutynin. The latter finding is consistent with the pharmacological finding that plasma levels of N-desethyloxybutynin are much lower following administration of Kentera than are found following usual doses of oral oxybutynin, and that N-desethyloxybutynin is associated with anticholinergic side-effects.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

The pharmacodynamic profile of oxybutynin has been well described in the application, addressing in particular and confirming, the effects on the urinary bladder contractility. The general pharmacology and the safety pharmacology information reflect the anticolinergic properties of the compound.
The applicant has given an adequate pharmacokinetic overview. Rats and dogs were the most relevant species referred. All pharmacokinetic findings with Kentera in healthy subjects can reasonably be applied to patients with overactive bladder.
The non-clinical information for this application revealed that in principle, the toxicological profile of oxybutynin in Kentera transdermal patch will be similar to that observed by oral route, possibly with the advantage of lower and more persistent exposures being reached with the patch.

Efficacy

The 39 cm^2 Oxybutynin TDS is effective, as demonstrated by the statistical significant reductions in the number of incontinence episodes and urinary frequency. However this reduction has a small effect size. The impact of a small decrease in incontinence episodes on the quality of life is questionable. However some of the subjective measures used as a secondary end-point do show a statistically relevant difference in favour of oxybutynin.
Efficacy results obtained with the patch are absolutely in line with what is established for the oxybutynin in the oral form, which is already on the market. Clinical trials in this dossier almost only enrolled women.

Safety

Clinical safety does not raise particular concerns. The profile of adverse events seen in the clinical studies is in line with what is known for anticholinergic drugs and acceptable. The most clinically significant adverse effects of Kentera are application site reactions and dry mouth. Other anticholinergic effects occur at low rate and there is evidence that the overall incidence of adverse events is lower than that with recommend doses of immediate-release oral oxybutynin.
Particular care should be put in the evaluation of the benefit risk evaluation in the elderly.

Benefit/risk assessment

The data submitted demonstrate the efficacy of 3.9 mg of oxybutynin transdermal patch, administered every 3 to 4 days, for symptomatic treatment of overactive bladder, including urgency, frequency and incontinence. In addition, the data submitted indicates that the treatment is safe at the indicated dose and has an acceptable margin of tolerability. Taking this into account, it can be concluded that the benefit/risk for this product is positive.

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk ratio of Kentera in the treatment of symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with unstable bladder was favourable and therefore recommended the granting of the marketing authorisation.