Scottish Medicines Consortium

oxybutynin 3.9mg/24h transdermal patch (Kentera®) No. (190/05)
UCB Pharma Ltd

8 July 2005

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

Oxybutynin transdermal patch (Kentera®) is accepted for restricted use within NHS Scotland for the treatment of urge incontinence and/or increased urinary frequency and urgency in patients with unstable bladder, restricted to patients who derive clinical benefit from oral oxybutinin but who experience intolerable anticholinergic side effects. It should be used in conjunction with non-pharmacological measures, including pelvic floor muscle exercises and bladder retraining.

Transdermal oxybutynin appears to have similar efficacy to oral antimuscarinics and a lower rate of anticholinergic adverse events. However, patients have the additional effect of application site reactions, which in some patients lead to treatment discontinuation. Transdermal oxybutynin has a lower total cost than oral tolterodine, but a higher total cost than oral oxybutynin.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Oxybutynin 3.9mg/24h transdermal patch (Kentera®)

Licensed indication under review

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

Dosing information under review

One 3.9mg transdermal patch applied twice weekly (every 3 to 4 days). The patch should be applied to intact skin on the abdomen, hip or buttock with a new application site selected with each new patch to avoid reapplication to the same site within 7 days.

UK launch date

April 2005

Comparator medications

Other oral antimuscarinic agents including oxybutynin, tolterodine, propiverine, trospium and solifenacin which was not recommended for use by SMC.

Cost per treatment period and relevant comparators

Basic NHS Costs from MIMS May 2005 unless otherwise stated

Approved name	Dose	Annual cost
Oxybutynin 3.9mg transdermal patch (Kentera®)	**One patch twice weekly**	**£354**
Oxybutynin tablets generic	2.5mg twice daily – 5mg four times daily	£70-£72
Oxybutynin tablets (Ditropan®)	2.5mg twice daily – 5mg four times daily	£59-£231
Oxybutynin MR tablets (Lyrinel XL®)	5-30mg daily	£150-£898
Propiverine tablets (Detrunorm®)	15mg once to four times daily	£159-£636
Tolterodine tablets (Detrusitol®)	1-2mg twice daily	£377-£397
Tolterodine MR capsules (Detrusitol XL®)	4mg daily	£377
Trospium tablets (Regurin®)	20mg twice daily	£316
*Solifenacin tablets (Vesicare®)***	*5-10mg daily*	*£335-£436*

*** solifenacin was not recommended for use by SMC in November 2004*

Summary of evidence on comparative efficacy

Oxybutynin is an antimuscarinic agent which acts by relaxing smooth muscle in the bladder. It has been available for many years as immediate and extended release oral formulations. This new transdermal formulation aims to ease compliance and reduce undesirable, mainly anticholinergic, side effects. These side effects arise from the active metabolite N-desethyl oxybutynin produced by pre-systemic metabolism after oral administration. Each patch contains 36mg of oxybutynin with an area of 39cm^2 releasing 3.9mg of oxybutynin per 24 hours during the 3 to 4 day treatment period.

The key efficacy data come from the results of three studies: one phase II (dose titration/tolerability) and two phase III studies, one of which included an active comparator.

The phase II study enrolled patients (n=76) with overactive bladder (OAB) who had responded to oral oxybutynin. After a 2-week washout, patients were randomised to receive transdermal or oral oxybutynin for 4 weeks with starting doses dependent onprior oral oxybutynin dose and titrated according to tolerability. The average number of daily incontinence episodes was reduced by approximately five from washout to end of treatment in both groups ($p<0.0001$) with no significant difference between treatments.

The largest phase III study enrolled patients (n=520) with OAB which was not related to chronic illness, anatomical weakness or abnormality, or medication. Eligible patients had baseline 7-day diary requirements following washout of $\geq$ 10 urge incontinence episodes, $\geq$ 56 voids and an average void volume $\leq$ 350ml. Patients were randomised to receive transdermal oxybutynin 1.3mg, 2.6mg or 3.9mg/day or matching placebo applied twice weekly in a double-blind manner for 12 weeks. The primary endpoint of the change from baseline in the number of incontinence episodes per week was significantly reduced after 12 weeks in the 3.9mg/day group compared with placebo (median of -19 versus -15, $p=0.017$). The lower doses of oxybutynin did not differ significantly from placebo. Similar trends were seen in the secondary endpoints which included changes from baseline in the average daily urinary frequency (mean of -2.3 with 3.9mg versus –1.7 with placebo, $p=0.046$) and average urinary volumes per void (median of +24ml for 3.9mg versus +6ml for placebo, $p=0.006$). The Global Assessment of Disease State (GADS) (visual analogue scale from 0-100) found no significant difference among the treatments. The Incontinence Impact Questionnaire (IIQ) and the Urogenital Distress Inventory (UDI) in women found significantly positive effects with 3.9mg/day oxybutynin compared to placebo.

The other phase III study, enrolled patients (n=361) with moderate to severe OAB who had a beneficial response to current treatment. Patients underwent a 2-week washout period from current treatment and then a 1-2 week period for completion of a baseline 3-day urinary diary which required $\geq$ 4 urge urinary incontinence episodes, $\geq$ 24 voids and average void volume $\leq$ 350ml. Patients were randomised to receive transdermal oxybutynin 3.9mg/day applied twice weekly, oral tolterodine LA 4mg/day or matching placebos in a double-blind manner for 12 weeks. The primary endpoint of the change from baseline in the number of incontinence episodes per day was significantly reduced after 12 weeks in the oxybutynin and tolterodine groups compared to placebo (means of –2.9, -3.2 and –2.1 respectively; $p=0.0137$ and $p=0.0011$ versus placebo respectively). In secondary endpoints, tolterodine but not oxybutynin significantly reduced the average daily urinary frequency compared to placebo (means of –2.2, -1.9 and –1.4 respectively). Both active treatments significantly increased average urinary volumes per void compared to placebo. In each of the primary and secondary outcomes described above, there were no significant differences between oxybutynin and tolterodine. In terms of quality of life measures, both oxybutynin and tolterodine significantly improved GADS and IIQ score compared to placebo.

Summary of evidence on comparative safety

The most frequently reported adverse events during studies were application site reactions, occurring in 23% of patients. Pruritus was the most common of these, occurring in 14%, followed by erythema 5.7% and rash 3.0%. During the phase II study with immediate release oral oxybutynin, dry mouth, the most frequently reported anticholinergic side effect, occurred in 38% of transdermal and 94% of oral patients ($p<0.001$). During the comparison with tolterodine, dry mouth occurred in 7.3% of tolterodine, 4.1% of transdermal oxybutynin and 1.7% of placebo patients ($p=0.04$ for tolterodine versus placebo and $p=0.27$ for transdermal oxybutynin versus placebo). The significance of tolterodine versus transdermal oxybutynin

was not reported. In this study, there were significantly more withdrawals due to adverse events in the transdermal oxybutynin group than the tolterodine group (13% versus 3.3%, p=0.0045).

Summary of clinical effectiveness issues

The populations of the three studies described comprise mainly female patients with moderate to severe disease and largely reflect the types of patients treated in Scotland. Two of the studies required enrolled patients to have responded to prior therapy (which in the majority of patients was either oxybutynin or tolterodine). This may have selectively favoured the response rates attained and excluded patients more likely to suffer intolerable anticholinergic side effects.

The double-blind phases of the phase III studies were of short duration, 12 weeks, and were associated with high placebo response rates. A recent Cochrane review also found that 45% of placebo-treated patients reported cure or improvement in symptoms. This review also found that the additional benefit of active treatment was about 15% more cured or improved which is similar to the level of improvement seen in these studies. The changes in the endpoints measured were relatively small and it is difficult to determine how the treatment effects in mean reduction in daily or weekly incontinence episodes would affect patients clinically. However, there were corresponding improvements in quality of life scores.

Transdermal oxybutynin appears to offer no advantage in terms of efficacy as demonstrated in the comparison with tolterodine. However, it is generally considered that selective antimuscarinics are equally effective. The key advantage appears to be in the relative tolerabilities. Transdermal oxybutynin was associated with a lower incidence of anticholinergic side effects compared to oral oxybutynin and tolterodine. However in the tolterodine study, there were significantly more discontinuations due to adverse events (mainly application site reactions) in the transdermal oxybutynin group. In the trials, patients were asked to apply patches to the abdomen and perhaps the larger recommended application site area of abdomen. Hip or buttock will help to minimise frequent reapplication to the same area.

Summary of comparative health economic evidence

Using a decision tree approach the manufacturers submitted a cost-minimisation analysis, whereby the total annual cost of transdermal oxybutynin 3.9mg daily was compared with other anticholinergic agents: oxybutynin immediate release (IR) 15mg daily, oxybutynin extended release (ER) 10mg daily, tolterodine IR 4mg daily and tolterodene ER 4mg daily, for a hypothetical cohort of 1000 patients with overactive bladder.

An assumption of equal efficacy (reduction in number of incontinence episodes per week) for all the agents was based on phase II and III clinical trial evidence for transdermal patch versus oral tolterodine ER and oral oxybutynin IR.

Withdrawal rates due to adverse events and other reasons are an important cost driver, although the cost attributed to this does not make a major difference to the relative cost-effectiveness of the products included in the economic evaluation – this was included in the decision tree model with estimates for each product based on an unpublished systematic review of the literature and oxybutynin phase III trials conducted by the manufacturer. For costing purposes, adverse events reported over the 12 week period of phase III trials were rather simplistically scaled up to 1 year with Scottish expert clinical opinion used to estimate

the proportion of adverse events occurring in the first 3 months (50%) and the resource use associated with them.

Costs included drug acquisition costs for drug doses reported in the Cochrane review of anticholinergic drugs for overactive bladder, GP and other specialist time, adverse event related treatment costs and costs of incontinence pads.

When all these costs are taken into account transdermal oxybutyin appears to result in lower total costs than oral tolterodine (IR or ER), but higher costs than oral oxybutynin, with this outcome largely driven by the difference in drug acquisition cost between the products.

Budget impact

The manufacturers submitted a 5 year budget impact assessment which was based on unclear assumptions regarding the impact on the market share of the main current treatment options for overactive bladder (OAB). Using an estimate that there are currently about 80,000 patients in Scotland receiving anticholinergic medication for OAB and assuming a base case uptake rate for transdermal oxybutynin of 4% (3208 patients), the net drug treatment cost in year 1 to the NHS in Scotland would be £32,000 increasing to £91,000 in year 5. These costs include both drug acquisition costs and resources associated with treating adverse events.

Guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) recently issued guidance on the management of urinary incontinence in primary care. This recommends a trial of oxybutynin, propiverine, tolterodine or trospium for patients with significant urgency with or without incontinence. Benefits and side effects should be assessed after 6 weeks with therapy reviewed to determine need for continued use after 6 months. The guideline comments that immediated release formulations of oxybutynin have the highest incidence of side effects and that modified release formulations have a lower incidence and severity of side effects. A comment relating to this new formulation states « Two studies from the United States show that transdermal oxybutynin is safe and effective. Sustained release transdermal preparations are not currently available within primary care. »

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including **16 May 2005.**

Drug prices are those available at the time the papers were issued to SMC for consideration.

The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

1. *European Medicines Evaluation Agency (EMEA). EPAR, scientific discussion Kentera 2004.*
2. *Davila GW, Daugherty CA, Sanders SW et al. A short-term, multicenter, randomised double-blind dose titration study of the efficacy and anticholinergic side effects of transdermal compared to immediate release oral oxybutynin treatment of patients with urge urinary incontinence. J Urol 2001; 166: 140-45.*
3. *Dmochowski RR, Davila GW, Zinner NR et al. Efficacy and safety of transdermal oxybutynin in patients with urge and mixed urinary incontinence. J Urol 2002; 168: 580-86.*
4. *Dmochowski RR, Sand PK, Zinner NR et al. Comparative efficacy and safety of transdermal oxybutynin and oral tolterodine versus placebo in previously treated patients with urge and mixed urinary incontinence Urology 2003; 62: 237-42.*
5. *Hay-Smith J, Herbison P, Ellis G, Moore K. Anticholinergic drugs versus placebo for overactive bladder syndrome in adults (Cochrane Review). In: The Cochrane Library, Issue 4. Chichester, UK: John Wiley & Sons, Ltd, 2003.*
6. *SIGN Guidance No 79. Management of urinary incontinence in primary care, January 2005.*