Scottish Medicines Consortium

Re-Submission

solifenacin succinate tablets 5mg, 10mg (Vesicare®)No. (129/04) Yamanouchi

New chemical entity

4 October 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 resubmission

Solifenacin succinate (Vesicare®) is accepted for use within NHS Scotland for the symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome.

Solifenacin is effective in reducing symptoms associated with overactive bladder, including frequency, urgency and incontinence. It is associated with adverse events typical of antimuscarinic agents used in this condition.

There are cheaper antimuscarinics available that would normally be used as first-line agents.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

solifenacin succinate tablets 5 mg, 10 mg (Vesicare®)

Licensed indication under review:

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

Dosing information under review:

5 mg once daily, increased if necessary to 10 mg daily.

UK launch date

August 2004

Comparator medications

Tolterodine, oxybutynin, flavoxate, propiverine, trospium

Cost per treatment period and relevant comparators

Preparation and dose	Cost for 52 weeks
Solifenacin (Vesicare®) 5 to 10 mg daily	**£335 to £436**
Flaxoxate (Urispas®) 200 mg three times a day	£144
Oxybutynin (non-proprietary) 2.5 mg twice daily to 5 mg four times daily	£43 to £358
Oxybutynin (Cystrin®) as above	£99 to £397
Oxybutynin (Ditropan®) as above	£59 to 231
Oxybutynin (Lyrinel XL®) 5 to 30 mg daily	£150 to £898
Propiverine (Detrunorm®) 15 mg daily to 15 mg four times daily	£159 to £636
Tolterodine (Detrusitol®) 1 to 2 mg twice daily	£377 to £397
Tolterodine (Detrusitol XL®) 4 mg daily	£377
Trospium (Regurin®) 20 mg twice daily	£315

Summary of evidence on comparative efficacy

Over-activity of the bladder (OAB) results in increased frequency of micturition and nocturia, urgency and incontinence. Antimuscarinic agents inhibit parasympathetic stimulation of the detrusor muscles, which are involved in bladder contraction. Solifenacin is stated to have a tissue-selective effect on the M_3 sub-type of cholinergic receptors.

Solifenacin has been directly compared with tolterodine extended release (ER) tablets in adult patients with OAB of at least 3 months' duration. During a 2-week single-blind placebo run-in period, a 3-day diary was completed and patients were required to demonstrate an average micturition frequency of ≥8 per 24 hours and either ≥1 incontinence episode/24 hours or ≥1 episode of urgency/24 hours. Eligible patients were randomised in a double-blind fashion to solifenacin 5 mg or tolterodine ER 4 mg. After 4 weeks at this dosage, patients could request an increase in dose based on their satisfaction with response and tolerability, and this would be discussed with the investigator. Since tolterodine was being given at the maximum recommended dose, only patients who were receiving solifenacin could be granted a dose increase, to 10 mg daily. Blinding was preserved using a double-dummy design. The overall treatment period was 12 weeks.

The primary end-point was non-inferiority of solifenacin over tolterodine for the change from baseline in the mean number of micturitions per 24 hours. In a per-protocol population of 1049, solifenacin was associated with a reduction in micturition frequency of 2.45 per 24 hours from a baseline of 11.7 (n=525) compared with a reduction of 2.24 per 24 hours from a baseline of 11.6 with tolterodine (n=524, p=0.004 for non-inferiority). The estimated treatment difference in favour of solifenacin corresponded to a reduction of 0.19 episodes per 24 hours over that achieved with tolterodine.

Previously, solifenacin had been assessed in four 12-week Phase III placebo-controlled trials sharing a similar design and with similar entry criteria to the comparative trial. One of those trials also included a fixed dose of tolterodine 2 mg twice daily as an active control, but the trial was not designed to detect differences between active treatments. In a combined analysis the net reduction in micturition frequency over placebo was 0.9 episodes per 24 hours for solifenacin 5 mg and 1.3 for solifenacin 10 mg. In a single trial, tolterodine achieved an active-placebo treatment difference of 0.7 for the reduction in episodes per 24 hours.

For secondary end-points in the comparative trial, significant superiority of solifenacin over tolterodine ER was shown for the 24-hour frequency of urgency, incontinence, urge incontinence and incontinence pad usage, but not for micturition or nocturia. The estimated treatment difference for solifenacin compared with tolterodine was less than 0.6 episodes per 24 hours in all cases. There were also significant differences in favour of solifenacin for the proportion of patients incontinent at baseline who achieved ≥50% reduction in episodes (74% vs 66%) or who met defined criteria for continence during treatment (59% vs 49%). Both solifenacin and tolterodine were associated with an increase in the volume voided per micturition and an improvement in the patient's perception of bladder condition. However, these improvements were significantly greater for solifenacin.

After 4 weeks, when given the opportunity to increase their dose, 48% of the solifenacin 5 mg group and 51% of the tolterodine ER 4 mg group requested a dose increase.

In an open-label extension to two of the placebo-controlled studies, patients were assigned to solifenacin 5 mg irrespective of their original treatment allocation. The dose could be increased to 10 mg after 4 weeks at the investigator's discretion. For all patients the mean exposure to solifenacin was 307 days, and the change from the double-blind baseline to the end of the extension period was -2.9 micturitions per 24 hours or -22%. For patients who had received solifenacin 5 or 10 mg in the double-blind phase, there was a slight further reduction of 0.29 micturitions per 24 hours between the start and end of the extension phase. There was an equivalent decrease of 0.71 per 24 hours for patients originally treated with tolterodine.

Summary of evidence on comparative safety

The most frequently reported adverse events were typical of antimuscarinic drugs and the most common was dry mouth. In the comparative trial, the incidence of common adverse events were reported as follows for the safety population (n=593 for solifenacin and n=607 for tolterodine):

Treatment-Emergent Adverse Event	**Mild**		**Moderate**		**Severe**	
	solifenacin*	**tolterodine XL 4mg****	**solifenacin***	**tolterodine XL 4mg****	**solifenacin***	**tolterodine XL 4mg****
Dry Mouth %	17.5	14.8	10.8	7.7	1.7	1.5
Constipation %	3.2	1.3	2.7	1.0	0.5	0.2
Blurred Vision %	0.7	0.7	0.0	1.0	0.0	0.0

* 5mg/ 10mg groups combined
** tolterodine groups combined
The severity of adverse events was determined by the investigator according to the following guidelines:
Mild: Causing discomfort but no disruption of normal daily activity
Moderate: Causing discomfort sufficient to reduce or affect normal daily activity
Severe: Resulting in inability to work or perform daily activity

The rate of discontinuation due to adverse events in the full analysis set was 20/578 (3.5%) for solifenacin and 18/599 (3.0%) for tolterodine.

Summary of clinical effectiveness issues

In all trials, the number of patients included in the analysis varied widely between individual end-points because only patients who had recorded episodes for that end-point at baseline were included. Thus, for example, that patients who did not record incontinence in the baseline diary would not be included in the analysis of this end-point.

In the comparative trial solifenacin was assessed over the recommended range of 5 to 10 mg while tolterodine ER was given at a fixed maximum dose. While this corresponded to the recommended dose for the ER formulation it would not permit dose reduction, e.g. in the case of intolerance. In clinical practice, this would be possible through the use of the conventional formulation. Similarly, in the placebo-controlled trials, all active treatments were given at fixed dose. This may have influenced results, including the comparative safety of solifenacin and tolterodine.

Patients were predominantly female (about 70-90%) and Caucasian (ranging from 83-99% in individual groups within trials).

Solifenacin has not been compared to medicinal products other than tolterodine or to non-drug therapy such as patient guidance or behavioural interventions. About a quarter to a third of patients in the placebo-controlled trials had a history of non-drug therapy.

In the placebo-controlled trials, patients received intensive support, e.g. encouragement of compliance with medication, which is likely to differ from normal clinical practice. This was less evident in the report of the comparative trial, but in all trials the intensive diary keeping probably differed from normal practice.

Summary of comparative health economic evidence

The manufacturer submitted a cost minimisation analysis which compares the weighted average cost of solifenacin with that of tolterodine of £29.67 for solifenacin and £32.40 for tolterodine.

This analysis is complicated by the omission of 1mg tolterodine which would reduce the weighted average for tolteredine to £31.17. Solifenacin could displace the use of oxybutynin, non-proprietary formulations of which are cheaper than both solifenacin and tolterodine.

The cost-minimisation analysis would support the positioning of solifenacin as an alternative to tolterodine.

Guidelines and protocols

A SIGN guideline on the management of urinary incontinence was published in December 2004 and updated January 2005. It recommends a trial of oxybutynin, propiverine, tolterodine or trospium for patients with significant urgency with or without urge incontinence The dose should be titrated to combat adverse effects. Antimuscarnic therapy should be tried for a period of six weeks to enable an assessment of the benefits and side effects, and should be reviewed after six months to ascertain continuing need.

Solifenacin is not discussed except to note that it has been granted authorisation. A section on physical therapies states that bladder retraining should be offered to patients with urge urinary incontinence, and that pelvic floor exercises should be considered as part of a treatment plan for urge urinary incontinence.

Additional information

In July 2005, following a full submission, SMC advised that 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.

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 15 September 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.

Subsequent publication: Randomized, double-blind placebo and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder Chapple CR et al B J U International (2004) 93, 303 – 310

Subsequent publication: Randomized, double blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. Cardozo L et al J Urol (2004) 172 1919 – 1924

Subsequent publication: Long term open-label solifenacin treatment associated with persistence with therapy in patients with overactive bladder syndrome. Haab F et al European Urology 47 (2005) 376 - 384

A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: the results of the STAR study Chapple et al European Urology 2005, accepted for publication.

Scottish Intercollegiate Guidelines Network. Management of urinary incontinence in primary care. A national clinical guideline. Number 79. December 2004. Edinburgh.
www.sign.ac.uk