

# Solifenacin

Concise evaluated information to support the managed entry of new medicines in the NHS

## Summary

- Solifenacin is a long acting muscarinic receptor antagonist with high affinity for muscarinic receptors in the bladder. It is licensed for the treatment of overactive bladder (OAB).
- Other available antimuscarinics for this indication include oxybutynin, tolterodine and trospium.
- In the only fully published phase III study of solifenacin for OAB (1081 patients), solifenacin was shown to be statistically superior to placebo, but to have similar efficacy to tolterodine in reducing the number of episodes of urgency, incontinence, the number of voids and the volume of urine voided. The incidence of dry mouth was similar with both solifenacin and tolterodine but the incidence of constipation and blurred vision was higher with solifenacin. The rate of discontinuation due to adverse effects was similar in all groups.
- Available data do not indicate that solifenacin is clinically superior to tolterodine in either effectiveness or tolerability. Until further data are available solifenacin should be reserved for when other antimuscarinics e.g. oxybutynin, that have a greater evidence base, are not effective and/or not tolerated.
- Solifenacin (5mg daily) is slightly cheaper than tolterodine (2mg twice daily) but more expensive than oxybutynin (5mg three times a day).

## Introduction

Overactive bladder (OAB) is characterised by urinary urgency with or without urge incontinence, urinary frequency and nocturia. Approximately 17% of adults, mainly in older age groups, have OAB; this is a similar incidence to that of other chronic diseases such as asthma and coronary heart disease. OAB is often not reported by affected individuals but can have profound effects on quality of life.<sup>1</sup>

Muscarinic receptors play an important role in the pathogenesis of OAB. Three muscarinic receptor subtypes are present in the bladder; the M<sub>1</sub> receptor subtype facilitates release of acetylcholine, and both M<sub>2</sub> and M<sub>3</sub> contribute to detrusor muscle contraction. Actions on muscarinic receptors in other parts of the body can lead to dose limiting adverse effects e.g. dry mouth (M<sub>1</sub> and M<sub>3</sub> subtype in salivary glands).<sup>1</sup>

Antimuscarinic drugs are the first-line pharmacological treatment for OAB. Oxybutynin, the most commonly used agent, has relatively high affinity for all three receptor subtypes in bladder tissue.<sup>1</sup>

Solifenacin succinate, a long-acting muscarinic receptor antagonist, has recently been licensed for the treatment of OAB<sup>2</sup> and has relative selectivity for M<sub>3</sub> muscarinic receptors in the bladder.<sup>1,3</sup>

## Evidence

The only fully published phase III study<sup>3</sup> of solifenacin was conducted internationally at 98 centres; such multicentre studies often have attendant problems with standardisation of protocols and data collection. In the study participants were eligible for enrolment if they were ≥18 years of age and had symptoms of OAB for three months or more. Symptoms included an average frequency of ≥8 voids/24hr for at least three months and at least three episodes of urgency and/or incontinence within a three day period during the two-week run in phase. Patients were excluded if they had been receiving drug treatment for incontinence or

**Brand Name, (Manufacturer):** Vesicare, (Yamanouchi)

**BNF Therapeutic Class:** Drugs for urinary frequency, enuresis and incontinence (7.4.2).

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

**Dosage and Administration:** 5mg once daily (by mouth) may be increased to 10mg.

**Marketed:** August 2004

**Cost Comparisons: MIMS August 2004**

Cost for 28 days treatment.



N.B. Doses shown for general comparison and do not imply therapeutic equivalence

## Solifenacin

taking drugs with muscarinic or antimuscarinic side effects within 30 days before study enrolment.

After a two week run-in to establish baseline data, 1081 patients were randomised to tolterodine 2mg twice daily, placebo twice daily and solifenacin 5mg daily or 10mg daily (plus matched placebo) for 12 weeks. The main outcome measures were the change from baseline in the mean number of urgency episodes in 24 hours and mean number of all incontinence and urge incontinence episodes.

Overall, 1033 patients had received at least one dose of study medication and were included in the efficacy analysis. Both solifenacin (5mg and 10mg) and tolterodine significantly reduced the mean number of urgency episodes in 24 hours compared to placebo (-2.85, -3.07, -2.05, -1.41, respectively,  $P < 0.001$  for both doses of solifenacin and  $P = 0.05$  for tolterodine vs. placebo). Solifenacin, 5mg and 10mg, significantly reduced the mean number of all incontinence episodes in 24 hours compared to placebo (-1.42, -1.45, -0.76, respectively,  $P = 0.008$  and  $P = 0.004$ , respectively) but tolterodine did not (-1.14,  $P = 0.112$ ). However, a statistically or clinically significant difference between solifenacin and tolterodine for this outcome is unlikely.

The study also found that both solifenacin (5mg and 10mg) and tolterodine significantly reduced the mean number of voids in 24 hours compared to placebo (-2.19, -2.61, -1.88, -1.20, respectively;  $P = 0.003$ ,  $P < 0.001$ ,  $P = 0.014$ , respectively) and increased the mean volume voided/void ( $P < 0.001$  for all vs. placebo).

Other studies of solifenacin are currently only available in poster or abstract form. Brief details of two are given below.

Cardozo et al<sup>4</sup> randomised 911 patients with OAB to solifenacin 5mg, 10mg or placebo daily. Solifenacin was found to be more effective than placebo, with similar results to those of the above study (see Appendix II). Additionally, the study found that in patients who used incontinence pads, the mean number used in 24 hours

decreased in all three groups:

- -1.32 (-46%) solifenacin 5mg
- -1.16 (-43%) solifenacin 10mg
- -1.07 (-33%) placebo

Although no statistical significance is quoted, the numerical difference in the number of pads used between the solifenacin and placebo groups is small. Quality of life, assessed by the King's Health Questionnaire, was significantly improved on solifenacin compared to placebo in five areas including incontinence impact and symptom severity.

In two prospective studies (combined  $n = 1208$ ) by Kaufman et al<sup>5</sup> (see Appendix II for more details) solifenacin 10mg significantly increased the proportion of patients who were continent at the end of the 12 week study period compared to placebo (53.0% vs. 31.4%, respectively,  $P < 0.001$ ).

### Safety

Adverse effects were more common with solifenacin than placebo. The most frequently reported effects were dry mouth (14.0%, 21.3%, 4.9% for 5mg, 10mg and placebo, respectively), constipation (7.2%, 7.8% and 1.9%) and blurred vision (3.6%, 5.6% and 2.6%).<sup>3</sup> Tolterodine had a similar incidence of dry mouth compared to that reported with solifenacin (18.6%) but had lower incidence of constipation (2.6%) and blurred vision (1.5%). In general reactions were mild and resulted in a similar rate of discontinuation in all groups.<sup>3</sup> The incidence of adverse effects associated with solifenacin appears to increase with dose.<sup>3,6</sup>

Solifenacin, like other antimuscarinics, is contra-indicated in patients with urinary retention and uncontrolled narrow angle glaucoma.<sup>2</sup> *In vitro* studies have shown that solifenacin does not inhibit hepatic isoenzymes and is therefore unlikely to affect drugs metabolised by this route. However, it is metabolised by CYP3A4 and concurrent use of CYP3A4 inhibitors such as ketoconazole can result in raised blood levels. The manufacturer recommends a maximum dose of 5mg daily when solifenacin is taken simultaneously with CYP3A4 inhibitors.<sup>2</sup>

### Place in Therapy

Current treatments for OAB include pelvic floor exercises and other antimuscarinic drugs such as oxybutynin, tolterodine and trospium.

Solifenacin has been shown to be more effective than placebo for the treatment of patients with OAB. To date, it appears to have similar efficacy to tolterodine, but with a higher incidence of constipation and blurred vision.<sup>3</sup>

It is likely that solifenacin will be promoted for OAB on the basis of its greater selectivity for muscarinic receptors in the bladder and therefore, theoretically lower incidence of adverse effects. This is not supported by the available data. There are no data to indicate that solifenacin is any different in this respect to other antimuscarinics. It may also be promoted on the basis of increased patient compliance as it is only taken once daily compared with oxybutynin (three times a day) or tolterodine (twice daily).

In the long term many patients with OAB are non compliant with antimuscarinics due to adverse effects; no such data are available for solifenacin. Further studies, especially with oxybutynin, are necessary to clarify solifenacin's place in therapy.

### Key Paper

3. Chapple CR, Rechberger T, Al-Shukri S et al. Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder *BJU Int* 2004; **93**: 303-10

### Appendix I: Bibliography Appendix II: Table of Clinical Trials

### Risk Management Issues:

No major issues identified.

Produced for the UK Medicines Information Service

By Pam Buffery, North West Medicines Information Centre, Pharmacy Practice Unit, 70 Pembroke Place, Liverpool, L69 3GF. Tel: 0151 794 8117 Email: [druginfo@liv.ac.uk](mailto:druginfo@liv.ac.uk)

The information contained in this document will be superseded in due course.  
Not to be used for commercial purposes. May be copied for use within the NHS.

## Appendix I

### Bibliography

#### References

1. Andersson KE. Antimuscarinics for treatment of overactive bladder. *Lancet Neurol* 2004; **3**: 46-53
2. Yamanouchi. Vesicare. Summary of product characteristics. August 2004
3. Chapple CR, Rechberger T, Al-Shukri S et al. Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder. *BJU Int* 2004; **93**: 303-10
4. Cardozo L, Kuzmin I, Lisec ML et al. YM905 (solifenacin succinate; Vesicare) in symptomatic overactive bladder: results of a phase 3, randomized, placebo-controlled trial. Abstract DP47. Data on file Yamanouchi.
5. Kaufman J, Knapp P, Siami P et al. YM905 (solifenacin succinate; Vesicare) 10mg increases the proportion of male and female patients with overactive bladder who become continent. Abstract P168. Data on file Yamanouchi
6. Chapple CR, Arano P, Bosch JLHR et al. Solifenacin appears effective and well tolerated in patients with symptomatic idiopathic detrusor overactivity in a placebo- and tolterodine-controlled phase 2 dose-finding study. *BJU Int* 2004; **93**: 71-7

## Solifenacin

### Appendix II

**Table 1. Randomised clinical trials of Solifenacin**

Ref No	Trial Design	Trial Population	Treatment	Outcomes			
3	International phase 3 placebo-controlled, double-blind RCT – 2 weeks placebo run in, 12 weeks of study medication.	Men and women $\geq 18$ years with OAB for $\geq 3$ months duration  1281 patients enrolled, 1081 randomised, 1033 evaluated for efficacy (had at least one dose of study medication, data from baseline and data from at least one study visit). Patients were excluded if they were on medication to treat incontinence or that had muscarinic or antimuscarinic side effects.	<ul style="list-style-type: none"> <li>• solifenacin 5mg daily</li> <li>• solifenacin 10mg daily</li> <li>• tolterodine 2mg twice daily</li> <li>• placebo</li> </ul>	Placebo	Solifenacin 5mg	Solifenacin 10mg	Tolterodine
				Change from baseline in the mean number of urgency episodes/24hr:			
				-1.41	-2.85 (P<0.001)	-3.07 (P<0.001)	-2.05 (P=0.05)
				Change from baseline in the mean number of urge incontinence episodes/24hr:			
				-0.62	-1.41 (P=0.002)	-1.36 (P=0.003)	-0.91 (P=0.239)
				Change from baseline in the mean number of incontinence episodes/24hr:			
				-0.76	-1.42 (P=0.008)	-1.45 (P=0.004)	-1.14 (P=0.112)
				Change from baseline in the mean number of voids/24hr:			
				-1.20	-2.19 (P=0.003)	-2.61 (P<0.001)	-1.88 (P=0.015)
				Change from baseline in mean volume voided/void (ml):			
				7.4	32.9 (P<0.001)	39.2 (P<0.001)	24.4 (P<0.001)
				Discontinuation rate for adverse effects:			
				3.7%	3.2%	2.6%	1.9%
				Incidence of dry mouth:			
				4.9%	14.0%	21.3%	18.6%
				Incidence of constipation:			
1.9%	7.2%	7.8%	2.6%				
Incidence of blurred vision:							
2.6%	3.6%	5.6%	1.5%				

## Solifenacin

4 (Poster)	European and New Zealand RCT – 2 weeks placebo run in, 12 weeks study medication.	Men and women $\geq 18$ years of age with symptoms of OAB.  911 patients randomised, 907 received at least one dose of study drug and 857 completed the study.	<ul style="list-style-type: none"> <li>• solifenacin 5mg daily</li> <li>• solifenacin 10mg daily</li> <li>• placebo daily</li> </ul>	Placebo	Solifenacin 5mg	Solifenacin 10mg
				Change from baseline in number of micturitions/24hr:		
				-1.5	-2.4 (P<0.01)	-2.8 (P<0.01)
				Change from baseline in urgency/24hr:		
				-1.96	-2.69 (P<0.01)	-2.94 (P<0.001)
				Change from baseline in incontinence/24hr:		
				-1.08	-1.73 (P<0.05)	-1.58 (P<0.05)
				Change from baseline in urge incontinence/24hr:		
				-0.81	-1.33 (P<0.05)	-1.24 (P<0.05)
				Increase in volume voided/micturition (ml):		
				10.7	30.9 (P<0.001)	35.9 (P<0.001)
				Decrease in mean number of incontinence pads from baseline:		
				-1.07	-1.32	-1.16
				Percentage of patients who reported adverse effects:		
38.9%	43.5%	48.2%				
5 (Poster)	Two US RCTs – 2 week run in, 12 weeks study medication.	Two studies with a total 1306 patients with OAB, 1208 patients included in the analysis.	<ul style="list-style-type: none"> <li>• solifenacin 10mg daily</li> <li>• placebo</li> </ul>	<ul style="list-style-type: none"> <li>• Mean number of incontinence episodes/24hr was significantly reduced by solifenacin vs. placebo (-2.0 vs. -1.2, p&lt;0.001 for pooled and individual trials).</li> <li>• 930 patients were incontinent at baseline. Of these 53.0% of patients on solifenacin vs. 31.4% (P&lt;0.001) on placebo became continent by study end.</li> <li>• 61% and 74% on placebo and solifenacin had an ADR, most common was dry mouth (5% placebo and 32% solifenacin)</li> </ul>		

**Key:**

RCT = randomised controlled trial

OAB = overactive bladder

P = statistical significance of active treatment vs. placebo

N/S = not stated

ADR = adverse drug reaction

QoL = quality of life