Solifenacin for the treatment of overactive bladder

Overactive bladder, defined as a symptom complex of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology, is a bothersome condition known to affect quality of life. Whilst the majority of patients will initially benefit from conservative measures in the first instance, drug therapy remains integral in the management of patients with overactive bladder. The development of the newer bladder selective M_3 specific antagonists such as solifenacin has introduced the possibility of increasing efficacy whilst minimizing the antimuscarinic adverse effects of dry mouth, constipation, somulence and blurred vision. Solifenacin, launched in the UK in 2004, has been investigated in a large series of Phase III clinical trials documenting efficacy in treating all symptoms of the overactive bladder syndrome. More recently a Phase IV development program has assessed the use of solifenacin in specific patient groups and also in comparative studies with other antimuscarinic drugs. This manuscript will provide a brief overview of overactive bladder as well as reviewing the efficacy and safety data from the solifenacin clinical development program.

KEYWORDS: antimuscarinics ■ detrusor overactivity ■ overactive bladder ■ solifenacin ■ urinary incontinence

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Urinary incontinence, the "complaint of any involuntary leakage of urine" [1] is a common and distressing condition known to adversely affect quality of life (QoL) [2]. Whilst bladder retraining and conservative measures should initially be used in the management of patients with overactive bladder (OAB) syndrome, many patients will benefit from antimuscarinic therapy. Unfortunately, however, lack of efficacy and unpleasant antimuscarinic adverse events, such as dry mouth, constipation and blurred vision, often affect compliance and persistence rates [3].

Nevertheless the most recent Cochrane meta-analysis has concluded that the use of anticholinergic drugs by people with OAB syndrome results in statistically significant improvements in symptoms and that this is associated with modest improvement in QoL [4].

Overactive bladder

Overactive bladder is the term used to describe the symptom complex of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology [5].

Epidemiology

The overall prevalence of OAB in women has been reported to be 16.9% and the prevalence increases with age, being 4.8% in women under 25 years and rising to 30.9% in those over the age of 65 years [5]. Recent European prevalence data from a population-based survey has shown that the overall prevalence of OAB in individuals aged 40 years and above was 16.6% and again was found to increase with age [6]. Frequency was the most commonly reported symptom (85%) with 54% complaining of urgency and 36% of urge incontinence. Of those individuals with symptoms, 60% had consulted a physician and only 27% were currently receiving treatment.

A more recent population-based study of lower urinary tract symptoms in Canada, Germany, Italy, Sweden and the UK involving 19,165 men and women over the age of 18 years has also been reported [7]. Overall, 11.8% complained of OAB symptoms and 64.3% of the total population sampled reported at least one urinary symptom. Nocturia was the most prevalent lower urinary tract symptom being reported by 48.6% of men and 54.5% of women.

Muscarinic receptors

The symptoms suggestive of the OAB syndrome are thought to be due to involuntary contractions of the detrusor muscle during the filling phase of the micturition cycle. These involuntary contractions are termed detrusor overactivity [8] and are mediated by acetylcholine-induced stimulation of bladder muscarinic receptors [9].

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It has been estimated that 64% of patients with OAB have urodynamically proven detrusor overactivity and that 83% of patients with detrusor overactivity have symptoms suggestive of OAB [10].

Molecular cloning studies have revealed five distinct genes for muscarinic acetylcholine receptors and there are five receptor subtypes (M_1–M_5) corresponding to these gene products [11]. In the human bladder the M_2 and M_3 subtypes have been demonstrated, although M_1 are not demonstrated in the bladder [12]. The M_3 receptor is thought to cause a direct smooth muscle contraction [12] whilst the M_2 receptor may mediate indirect detrusor contractions and oppose sympathetically mediated smooth muscle relaxation.

Solifenacin

Solifenacin is a potent M_3 receptor antagonist that has selectivity for the M_3 receptors over M_2 receptors and has much higher potency against M_3 receptors in smooth muscle than it does against M_3 receptors in salivary glands.

In vitro and *in vivo* tissue selectivity studies have also demonstrated that the inhibitory effect of solifenacin for bladder smooth muscle cells was 3.6-fold more potent than that for salivary gland cells. In the anesthetized rat model solifenacin dose-independently inhibited carbachol-induced intravesical pressure elevation and salivary secretion and exhibited functional selectivity, 3.7–6.5-fold, for the bladder (pKi = 8.12) over the salivary gland (pKi = 7.57). Tolterodine was also 2.2–2.4-fold more selective whilst oxybutynin, darifenacin and atropine showed no functional selectivity [13].

Clinical efficacy: Phase II studies

Two large Phase II studies have investigated the efficacy and safety of solifenacin in the USA and Europe.

Solifenacin was evaluated in the treatment of patients with OAB in a 4-week placebo-controlled dose finding study in the USA. Overall, 211 patients received medication with 2.5, 5, 10 or 20 mg solifenacin once daily and 53 patients received placebo [14].

There was a statistically significant reduction in the frequency of micturitions observed at the 10 and 20 mg/day dosage (p = 0.001) although a significant reduction in incontinence episodes was only observed with 10 mg (p = 0.005). Commonly reported adverse effects included dry mouth and constipation, and the incidence was dose related. The overall discontinuation rate was 9.8%. The discontinuation rate due to adverse events was 6.4%, with dry mouth being the most common reason (29.4%).

A further dose finding 4-week placebo and active-controlled study has also been conducted in Europe evaluating solifenacin in 225 patients. Overall, 150 patients received 2.5, 5, 10 or 20 mg solifenacin once daily, 38 received placebo and 37 received tolterodine (immediate release) 2 mg twice daily [15]. There was a statistically significant reduction in the frequency of micturition and a statistically significant increase in volume voided per micturition at the 5, 10 and 20 mg dosage when compared with placebo [16]. Additionally solifenacin led to a greater reduction in frequency of micturition when compared to tolterodine. Once again, the most common adverse effects were dry mouth and constipation [17].

Clinical efficacy: Phase III studies

Overall six large-scale Phase III clinical studies of solifenacin have been performed involving over 3700 patients.

Two Phase III, randomized, double-blind, placebo-controlled studies have been performed in the USA and have assessed the efficacy and safety of solifenacin 10 mg once daily in 1208 patients with OAB [18]. Both found solifenacin to be superior to placebo in reducing micturition frequency, incontinence episodes and episodes of urgency in addition to increasing the volume voided with each micturition.

The clinical efficacy of solifenacin has also been assessed in a 12-week European multicenter, randomized, double-blind, parallel group, placebo-controlled study of solifenacin 5 mg and 10 mg once daily in 857 patients with OAB [19].

Overall there was a statistically significant reduction in micturition frequency with both 5 and 10 mg doses when compared with placebo and the largest effect was observed with the higher dose (**Tables 1 & 2**). In addition, solifenacin was found to be superior to placebo with respect to the secondary efficacy variables of mean volume voided per micturition, episodes of urgency per 24 h, number of incontinence episodes and episodes of urge incontinence.

The discontinuation rate because of adverse events was low and was comparable amongst treatment groups (2.3, 3.9 and 3.3% in the 5 mg, 10 mg and placebo groups respectively). The most frequently reported adverse events leading to discontinuation were dry mouth and constipation.

Table 1. Efficacy of solifenacin 5 mg and 10 mg once daily in the treatment of overactive bladder.

	Placebo	Solifenacin 5 mg o.d.	Solifenacin 10 mg o.d.
Micturitions/24 h	n = 281	n = 286	n = 290
– Baseline mean	12.31	12.05	12.12
– Change from baseline	-1.66	-2.45	-2.88
– Difference to placebo (p)	–	-0.78 (0.0018)	-1.22 (0.0001)
Urge incontinence/24 h	n = 126	n = 141	n = 138
– Baseline mean	2.34	2.02	2.02
– Change from baseline	-0.91	-1.30	-1.21
– Difference to placebo (p)	–	-0.38 (-)	-0.29 (0.23)
Incontinence episodes/24 h	n = 153	n = 173	n = 165
– Baseline mean	3.21	2.65	2.82
– Change from baseline	-1.25	-1.63	-1.57
– Difference to placebo (p)	–	-0.39 (-)	-0.30 (0.22)

o.d.: Once daily.
Data taken from [58].

Solifenacin has also been compared to tolterodine 2 mg twice daily in a Phase III randomized, double-blind, parallel group, placebo and active controlled multicenter study in Europe and South Africa [20].

In total, 1033 men and women were recruited. The primary outcome measure revealed a statistically significant reduction of micturition frequency with both solifenacin 5 mg and 10 mg when compared with placebo, the former being a reduction of 2.2 voids/24 h and the latter 2.6. Tolterodine showed a smaller reduction of 1.9 micturitions/24 h.

Solifenacin was also found to be superior to placebo when considering the secondary outcome variables (Table 3). In those patients who were incontinent, 37.3% of the placebo group were continent at the end of the study compared to 51.1, 50.6 and 48.4% in the 5 mg, 10 mg and tolterodine groups, respectively.

The long-term safety and efficacy of solifenacin has also been investigated in a multicenter open label long term follow-up study, lasting 52 weeks [21]. This was an extension of two previous double-blind, placebo-controlled Phase III studies and included 1637 patients.

The efficacy of solifenacin was maintained in the extension study and micturition frequency was reduced by 22.1% by the end of the study (Table 4). As one may expect those patients who had received placebo in the initial studies noticed an improvement in micturition frequency, mean volume voided and the mean number of urge incontinence episodes/24 h. Interestingly those patients who had originally been randomized to tolterodine in the Phase III studies noticed a similar improvement in frequency, volume voided per micturition and urgency episodes per 24 h, and these were comparable to those improvements seen in the solifenacin arms of the previous studies.

Table 2. Efficacy of solifenacin 5 and 10 mg once daily in the treatment of overactive bladder.

	Placebo	Solifenacin 5 mg o.d.	Solifenacin 10 mg o.d.
Urgency episodes/24 h	n = 278	n = 284	n = 289
– Baseline mean	5.62	6.04	5.52
– Change from baseline	-2.05	-2.98	-3.00
– Difference to placebo (p)	–	-0.86 (0.003)	-0.92 (0.002)
Nocturia episodes/24 h	n = 240	n = 254	n = 259
– Baseline mean	2.05	1.96	1.89
– Change from baseline	-0.53	-0.60	-0.73
– Difference to placebo (p)	–	-0.07 (0.48)	-0.19 (0.036)
Nocturnal voids/24 h	n = 257	n = 261	n = 269
– Baseline mean	2.31	2.21	2.17
– Change from baseline	-0.62	-0.61	-0.78
– Difference to placebo (p)	–	0.01 (-)	-0.15 (0.13)

o.d.: Once daily.
Data taken from [58].

The most commonly reported adverse events were dry mouth (20.5% of all patients), constipation (9.2%) and blurred vision (6.6%) and were the primary reason for discontinuation in 4.7% of patients. Those patients who received solifenacin 10 mg once daily had a higher incidence of adverse effects when compared to those taking the 5 mg preparation (55.0 vs 46.4%) and the number of patients experiencing severe adverse effects was also higher (6.1 vs 3.5%). However, the percentage of patients who discontinued the study because of adverse events was similar in the two groups (3.4 vs 2.4%).

Phase III pooled analyses

Four pooled analyses, examining the effect of solifenacin in specific patient groups, have now been reported from some of the large-scale Phase III studies.

The first of these pooled analysis studies investigated the use of flexible-dose solifenacin in four randomized, placebo-controlled trials [22]. Of the 2848 subjects 975 (34%) were 'dry' at baseline. Both solifenacin 5 mg and 10 mg were significantly more effective than placebo for improving urgency ($p < 0.001$), frequency ($p < 0.001$) and volume voided ($p < 0.001$) and in addition the higher dose was more effective in reducing nocturia ($p < 0.01$). Resolution of urgency occurred significantly more often ($p < 0.05$) with solifenacin 5 mg (37%) and 10 mg (33%) than with placebo (25%). In addition, more patients experienced reduction of frequency of micturition with both solifenacin 5 mg (29%) and solifenacin 10 mg (35%) when compared to placebo (19%).

The second pooled analysis assessed the use of solifenacin in patients with OAB 'wet' [23]. Overall, 1873 subjects were included, all of whom complained of OAB with urge incontinence, and were randomized to solifenacin 5 or 10 mg. Over the 12-week duration of the study, over 50% of the subjects became continent with solifenacin (51 and 52% with 5 and 10 mg, respectively; $p < 0.001$ vs placebo). In addition, there was a significant reduction in incontinence episodes and higher continence rates were seen. These were irrespective of age, severity of incontinence or urgency severity at baseline.

The third pooled analysis focused on those patients with severe symptoms, with baseline severity being defined by the number of incontinence episodes, urgency episodes and voids per 24 h [24]. Overall, both solifenacin 5 mg and 10 mg were significantly ($p < 0.05$) more effective than placebo in reducing episodes of incontinence, urgency episodes, voiding frequency and in increasing volume voided amongst those patients with greater disease severity at baseline.

The last of these *post-hoc* analyses reviewed the role of solifenacin in the treatment of the elderly [25]. Overall, 1045 patients (mean age 71.9 years) were included from the 12-week double-blind

Table 3. Efficacy of solifenacin 5 and 10 mg once daily when compared to tolterodine in the treatment of overactive bladder.

	Placebo	Solifenacin 5 mg o.d.	Solifenacin 10 mg o.d.	Tolterodine 2 mg b.i.d.
Micturitions/24 h	n = 253	n = 266	n = 264	n = 250
Baseline mean	12.20	12.08	12.32	12.08
Change from baseline	-1.20	-2.19	-2.61	-1.88
Difference to placebo (p)	–	-0.98 (0.0003)	-1.41 (0.0001)	-0.67 (0.0145)
Urge incontinence/24 h	n = 127	n = 113	n = 127	n = 119
Baseline mean	2.02	2.33	2.14	1.86
Change from baseline	-0.62	-1.41	-1.36	-0.91
Difference to placebo (p)	–	-0.78 (0.0020)	-0.73 (0.0028)	-0.29 (0.2390)
Incontinence episodes/24 h	n = 153	n = 141	n = 158	n = 119
Baseline mean	2.71	2.64	2.59	2.32
Change from baseline	-0.76	-1.42	-1.45	-1.14
Difference to placebo (p)	–	-0.66 (0.0080)	-0.70 (0.0038)	-0.38 (0.1122)
Mean volume voided/24 h	n = 253	n = 266	n = 264	n = 250
Baseline mean	143.8	149.6	147.2	147.0
Change from baseline	7.4	32.9	39.2	24.4
Difference to placebo (p)	–	25.4 (0.0001)	31.8 (0.0001)	17.0 (0.0001)

b.i.d.: Twice daily; o.d.: Once daily.
Data taken from [58].

Table 4. Efficacy of solifenacin (5 and 10 mg) in the long-term continuation study.

	Change from baseline to end point: mean (%)
Mean number of micturitions/24 h	-2.97 (-23.0)
Mean volume voided/micturition (ml)	39.8 (31.0)
Mean number of incontinence episodes/24 h	-1.74 (-66.0)
Mean number of urgency episodes/24 h	-3.48 (-63.0)
Mean number of nocturia episodes/24 h	-0.70 (-32.0)

Data taken from [58].

studies and 509 (mean age 71.2 years) from the long-term, open-label study. Completion rates were 85.5 and 80.0%, respectively, and the most commonly reported adverse events were dry mouth, constipation and lower urinary tract infections. Overall, there was no significant difference in efficacy rates in this more elderly population. Continence rates were 49.1 and 47.3% for the 5 and 10 mg groups, respectively (placebo 28.9%; $p < 0.001$ for both doses), whilst urgency resolved in 34.6 and 24.9%, respectively (placebo 16.9%; $p < 0.001$ for 5 mg and $p < 0.01$ for 10 mg).

Clinical efficacy: Phase IV studies

Following the launch of solifenacin in August 2004, the clinical research program has continued with an extensive series of postmarketing studies both in the USA and Europe.

Solifenacin: comparative studies

Solifenacin 5 mg and 10 mg o.d. have been compared with tolterodine extended release (ER) 4 mg once daily (o.d.) in the Solifenacin (flexible dosing) o.d. and Tolterodine ER 4 mg o.d. as an Active comparator in a Randomized trial (STAR) [26]. This was a prospective double-blind, double-dummy, two-arm, parallel-group, 12-week study with the primary aim of demonstrating noninferiority of solifenacin to tolterodine ER. Overall, 1200 patients (593 on solifenacin and 607 on tolterodine ER) were recruited in 117 study sites in 17 countries. The primary efficacy analysis demonstrated that solifenacin was noninferior to tolterodine ER with respect to change in the mean number of micturitions per 24 h (reduction of 2.45 micturitions/24 h vs 2.24 micturitions/24 h; $p = 0.004$). Additionally, solifenacin was shown to result in a statistically significant improvement in urgency ($p = 0.035$), urge incontinence ($p = 0.001$) and overall incontinence when compared with tolterodine ER. Of those patients taking solifenacin, 59% who were incontinent at baseline became continent by the study end point, compared with 49% of those receiving tolterodine ER ($p = 0.006$). The most common adverse events were dry mouth, constipation and blurred vision. Discontinuation rates were similar in both arms (3.5% in the solifenacin arm vs 3.0% in the tolterodine arm).

Whilst the STAR study is representative of real-life clinical practice, a potential criticism of the study is that it is comparing flexible dosing of solifenacin with a single fixed dose of tolterodine ER. Consequently, a *post-hoc* analysis has been performed comparing solifenacin 5 mg and tolterodine ER 4 mg for the first 4 weeks of the study [27]. Overall mean improvements in the symptoms of urgency, frequency, incontinence and nocturia were greater in those patients taking solifenacin although this only reached statistical significance for incontinence (mean reduction in incontinence episodes/24 h: -1.30 vs -0.90; $p = 0.0181$), representing a 44% additional improvement. There was also an associated reduction in pad use (-1.21 vs -0.80; $p = 0.0089$).

The effect of switching antimuscarinic therapy has been assessed in the Vesicare Efficacy and Research Study US (VERSUS) study [28]. This was an open-label, flexible dosing, multicenter study assessing the efficacy and safety of solifenacin in 441 patients who were currently taking tolterodine ER 4 mg. Overall there were significant improvements ($p < 0.0001$) in urgency episodes, daytime frequency, incontinence episodes and nocturia in those patients who were 'switched' from tolterodine ER to solifenacin.

Solifenacin has also been compared to propiverine, a combined antimuscarinic and calcium antagonist, in a Japanese, multicenter, 12-week randomized double-blind, placebo- and propiverine-controlled trial [29]. In total, 1593 patients were randomized to solifenacin (5 or 10 mg), propiverine 20 mg or placebo. Overall, there was a greater reduction in voiding frequency and urgency incontinence episodes with both solifenacin (5 and 10 mg) and propiverine when compared with placebo. However, solifenacin 10 mg was found to have a significantly greater effect on nocturia, urgency episodes and volume voided when compared with propiverine. Whilst QoL improvement

and discontinuation rates were similar with both drugs, solifenacin 5 mg was associated with less dry mouth ($p = 0.003$), although there was a higher incidence of dry mouth ($p = 0.012$) and constipation ($p = 0.004$) with the 10 mg dose when compared to propiverine 20 mg.

Solifenacin and oxybutynin immediate release (IR) have also been compared in the VEsicare in Comparison To Oxybutynin for OAB patients (VECTOR study) [30]. This was a Canadian randomized, multicenter, prospective, double-blind, double-dummy study of 132 patients. The primary end point investigated the incidence and severity of dry mouth and this was significantly higher with oxybutynin 5 mg when compared to solifenacin 5 mg (83 vs 35%; $p < 0.001$). Severity was also significantly worse in the oxybutynin arm (28 vs 13%; $p = 0.0001$). A subsequent subanalysis has also shown that there was no effect of age on the incidence and severity of dry mouth [31].

Solifenacin: cognitive effect study

The possible cognitive effects of antimuscarinic medication remains problematic in the elderly. The effect of solifenacin has been explored in the Solifenacin Cognitive Function Pilot Exploratory Study (SCOPE) study; a randomized double-blind, placebo- and oxybutynin-controlled crossover study in 12 elderly (≥65 years) patients [32]. Assessment of cognitive function, assessing aspects of learning, memory, information processing, mood and alertness, was performed using the Cognitive Drug Research (CDR) computerized system. Whilst oxybutynin 10 mg was consistently associated with impairment of attention, memory and alertness, there was no such effect noted with solifenacin 10 mg.

Solifenacin: bladder retraining study

Bladder retraining and pelvic floor exercises remain important as first-line therapy in patients with OAB and previous studies have suggested that the addition of an antimuscarinic agent may improve outcome. The use of solifenacin with a bladder retraining regimen has been investigated in the SOLAR study [33].

This was a prospective randomized, parallel group, open-label study involving 643 patients (86% women) in 92 European centers. Patients were randomized to solifenacin 5 mg o.d. alone or with bladder retraining for 8 weeks when they could request a dose increase to 10 mg solifenacin if required. Micturition frequency was significantly reduced at 8 weeks in those patients on solifenacin 5 mg o.d. and this effect was augmented by adding in bladder retraining (-2.18 vs -2.87, respectively ($p < 0.0001$). A similar effect was seen at 16 weeks in patients taking solifenacin 5 mg and 10 mg alone and with bladder retraining (-2.42 vs -3.11; $p = 0.0005$). However there were no significant differences between groups in the secondary outcome parameters of urgency, incontinence episodes and urgency incontinence episodes. Equally there were no significant differences between groups in patient-reported outcomes and QoL assessment. Whilst this study confirms the additive effect of behavioral therapy as an addition to drug therapy it maybe that the simplified type of bladder retraining used in the study was insufficient to show a clinically important effect.

Solifenacin: patient-related outcomes

The importance of patient-related outcomes is becoming increasingly recognized and these have been addressed in the Vesicare Open Label Trial (VOLT) study. This was a 12-week prospective, flexible-dosing North American trial in 207 centers involving 2225 patients [34]. Assessments included the Patient Perception of Bladder Condition (PPBC) scale, bother visual analog scales and also the OAB questionnaire (OAB-q). Overall, 1743 (78.3%) completed the study and there was a significant improvement in perception of bladder condition, a significant reduction in patient-reported bother and a corresponding significant improvement in QoL. Solifenacin 5 mg and 10 mg were well tolerated with rates of dry mouth and constipation being 21.4 and 13.3%, respectively, and this led to discontinuation in 216 (9.7%) patients. A subsequent *post-hoc* analysis has confirmed that solifenacin improved symptom bother in recent onset OAB as well as long-standing chronic OAB [35].

An analysis of VOLT and VERSUS studies has examined the effect of patient-reported outcomes in the elderly and found that there was a similar improvement in PPBC, a reduction in OAB bother and a corresponding significant improvement in QoL and that these findings were no different to those in the full study population [36].

The relationships between symptoms, patient bother and health-related QoL in patients with OAB have also been assessed in the VIBRANT study examining the effect of solifenacin and placebo on 738 patients [37]. Overall improvements in urinary diary variables were significantly associated with greater improvements in patient-related outcome measures, demonstrating that objective improvements correlate well with subjective improvements in patient symptoms.

Solifenacin: treatment of urgency

Urgency may be regarded as the cardinal symptom of the OAB syndrome and is known to drive the symptoms of daytime frequency and nocturia by reducing the intervoid interval and may also be responsible for causing urgency incontinence [38]. However, reduction in daytime frequency is generally used as the primary outcome measure in studies of antimuscarinic drugs in the management of OAB, although, more recently, two solifenacin studies have been reported using urgency as the primary outcome measure.

The first of these studies was Solifenacin in the treatment of UrgeNcy symptoms of OAB in a RISing dose, randomized, placebo-controlled double-blind Efficacy trial (SUNRISE) [39]. This was a large European 16-week multicenter study of solifenacin 5 and 10 mg in 863 patients. The primary efficacy variable was the reduction in the number of episodes of severe urgency with or without urgency incontinence measured using the Patient Perception of Intensity of Urgency Scale (PPIUS). Secondary outcome variables included patient reported outcomes for bladder condition (PPBC), urgency bother and overall treatment satisfaction. Solifenacin 5 mg and 10 mg was found to be significantly more effective than placebo in reduction of severe urgency with or without incontinence (-2.6 vs -1.8; $p < 0.001$). In addition, solifenacin was found to be significantly better than placebo in the secondary outcome measures of patient-orientated outcomes. Interestingly the rate of dry mouth and constipation reported in this was lower than in those reported previously (15.8 and 6.9%, respectively) (**Table 5**).

The second trial to examine urgency as a primary outcome measure was Vesicare Efficacy and safety in patieNts with Urgency Study (VENUS), which was conducted in the USA [40]. This was a randomized, double-blind, placebo-controlled, parallel group flexible dosing study of 739 patients and patients could reduce as well as increase the dose of solifenacin. Urgency was assessed using bladder diaries, validated urgency scales and warning time. Warning time refers to the time interval between the first sensation of urgency and the time of bladder emptying [41]. There was a significantly greater reduction in urgency episodes in the solifenacin arm when compared to placebo; 3.91 versus 2.73 per 24 h, respectively ($p < 0.001$). In addition there was a significant increase in median warning time in the solifenacin arm compared to placebo; 31.5 vs 12.0 s ($p = 0.032$). A further *post-hoc* analysis has demonstrated a similar reduction in urgency episodes with solifenacin compared with placebo in continent (-3.4 vs -2.3) and incontinent patients (-4.2 vs -2.9) and by end of study 58% of patients were continent in the solifenacin arm compared to 42% in the placebo arm. This demonstrates the efficacy of solifenacin regardless of baseline continence status [42].

Safety & tolerability

The Phase I and Phase II clinical trial program included 623 individuals (262 healthy volunteers and 361 patients) who received solifenacin, 141 participants (50 healthy volunteers and 91 patients) who received placebo and 37 who received tolterodine. Solifenacin was shown to be well tolerated at doses of up to 20 mg once daily with the most commonly reported adverse effects being anticholinergic. The incidence of dry mouth was dose related with an incidence of 8, 9, 12, 33 and 48% at the placebo, 2.5, 5, 10 and 20 mg dosage groups, respectively. The overall discontinuation rate was 9.8% and that associated with adverse events was 6.4%, the most frequent being dry mouth (24%).

Patient characteristics

Pharmacokinetic studies have shown no effect of age on metabolism [43]. Equally there were no differences in drug pharmacokinetics following multiple dosing [44]. Furthermore, studies in

Table 5. SUNRISE efficacy results.

	Mean change from baseline placebo (SD)	Mean change from baseline solifenacin (SD)	p-value
Primary efficacy variable severe urgency episodes/24 h (PPIUS Grades 3 and 4)	-1.8	-2.6	<0.0001
Secondary efficacy variables all urgency episodes/24 h (PPIUS Grades 1–4)	-1.6 (3.3)	-2.3 (3.0)	= 0.0006
Max urgency intensity	-0.6 (0.9)	-0.8 (0.9)	= 0.0006
Micturitions/24 h	-1.3 (2.7)	-2.1 (2.6)	<0.0001
Incontinence episodes/24 h	-1.4 (2.0)	-1.7 (2.2)	= 0.0003
Urgency incontinence episodes/24 h	-1.3 (2.0)	-1.7 (2.2)	= 0.0002

PPIUS: Patient Perception of Intensity of Urgency Scale; SUNRISE: Solifenacin in the treatment of UrgeNcy symptoms of OAB in a RISing dose, randomized, placebo-controlled double-blind Efficacy trial.
Data taken from [58].

Caucasian and Asian men have shown no effect of race on metabolism [45].

Drug interaction studies

Solifenacin is metabolized mainly by cytochrome P450 3A4 (CYP3A4) and consequently the effect of ketoconazole, a potent inhibitor, has been studied [46]. Ketoconazole increases the AUC and the C_{max} in addition to extending the mean half-life. However, there was no difference in clinical parameters, laboratory investigations or ECG findings, suggesting that the effect is not clinically relevant.

Since ethinyl estradiol and levonogestrel are substrates of CYP3A4, the effect of solifenacin on the oral contraceptive pill has also been investigated [47]. There was no effect on the PK of either and consequently solifenacin may be safely used by women taking oral contraceptives.

Drug interaction studies indicate that there is no effect of solifenacin on the pharmacodynamics and pharmacokinetics of warfarin or digoxin [48].

Renal impairment

The safety of solifenacin in patients with renal impairment has been reported in a study of 18 patients with mild, moderate or severe renal disease. There was a significant correlation between creatinine clearance and pharmacokinetic parameters and apparent oral clearance. Consequently, no special precautions are required for patients with mild-to-moderate renal insufficiency although those patients with severe renal disease should only receive 5 mg o.d. [49].

Hepatic impairment

The safety of solifenacin in patients with hepatic impairment has been assessed in an open-label study of solifenacin 10 mg in eight patients and eight controls. There were no clinically relevant differences in safety and moderate hepatic impairment was found to increase drug levels. The mean elimination half-life of solifenacin and its metabolites was found to be longer. However, C_{max} values were comparable between the groups. Consequently in patients with mild hepatic impairment solifenacin may be used without special caution, although in those patients with moderate impairment, doses greater than 5 mg should not be used and the 5 mg dose should be used with caution [50].

Cardiovascular safety

A large, postmarketing, open-label, cardiovascular safety and tolerability study has been reported in 4450 patients over a 12-week period [51]. At the end of the study, 72.4% of patients were taking solifenacin 5 mg with 19.1% receiving solifenacin 10 mg o.d.. Overall, there were no clinically relevant alterations in mean heart rate or mean blood pressure during the course of the study and no ECG abnormalities were detected.

Pediatrics

The safety and efficacy of solifenacin 5 mg o.d. has been investigated in a small study of 29 children with a symptomatic diagnosis of OAB. Overall, there was an improvement in symptoms in 87% of patients, with 39% becoming fully continent during the day and night [52].

In addition, a prospective, nonrandomized study of 18 preschool children with neurogenic bladder dysfunction has also been reported. Bladder volumes were found to increase significantly with 1.25 mg solifenacin and there were no serious adverse effects [53]. More recently a Canadian open-label study has been reported in 72 children with refractive OAB using doses of 1.25 to 10 mg solifenacin with bladder diary and urodynamic follow-up over 3 months [54]. Overall, there was an increase in bladder capacity and a decrease in the number of uninhibited bladder contractions. Overall the drug was well tolerated and continence was improved in all patients with 24 being completely dry by the end of the study.

Pregnancy & lactation

In animal models there was no solifenacin-related maternal toxicity or adverse effects on embryonic organogenesis at dose levels of up to 50 mg/kg/day. However, there have been no adequate studies performed in pregnant women and it remains unknown if solifenacin is excreted in breast milk.

Solifenacin: cost–effectiveness

There have been three published studies examining the cost–effectiveness of solifenacin in the management of patients with OAB.

The first used a Markov model to estimate the cost per quality adjusted life year (QALY) over a period of 12 months using data from the Phase III studies [55]. Overall the incremental cost per QALY for solifenacin 5 mg and 10 mg compared with placebo was £17,602 and £24,464 respectively and the authors concluded that both solifenacin 5 mg and 10 mg were cost effective in the management of OAB.

A cost–utility analysis comparing solifenacin and tolterodine has also been reported from the UK [56]. A 1-year Markov model compared flexible dose solifenacin (5 and 10 mg) with

tolterodine immediate release (IR) 2 mg twice daily and ER 4 mg o.d. Overall solifenacin was found to be a less expensive and more effective treatment than tolterodine; one year costs being £509 with solifenacin as compared to £526 for tolterodine. The cost–effectiveness of solifenacin has also been compared to some of the other antimuscarinic agents on the market using a 1-year decision tree model with treatment success being defined separately for urgency, frequency and incontinence. Efficacy, persistence rates and utility values were calculated using previously published data and direct treatment costs were analyzed. Overall solifenacin was associated with the highest QALY gain for all three outcomes and was found to be dominant relative to fesoterodine, tolterodine ER and tolterodine IR and cost effective relative to propiverine ER for urgency, frequency and incontinence. Solifenacin was not found to be cost-effective relative to oxybutynin IR for frequency and incontinence outcomes with an incremental cost–effectiveness ratio of more than £30,000/QALY threshold [57].

Conclusion

Solifenacin, an M_3-specific antimuscarinic antagonist launched in 2004, would appear to be a further advance in the treatment of patients with OAB. The data from the Phase II/III clinical trials have demonstrated that solifenacin offers an effective combination of efficacy and tolerability in addition to providing clinically meaningful improvements in lower urinary tract symptoms. Long-term continuation studies have also confirmed the long-term efficacy and safety of solifenacin which is important in a chronic condition such as OAB.

Evidence from the STAR study has shown that solifenacin is superior in terms of efficacy to tolterodine and both the SUNRISE and VENUS studies are the first to use urgency as the primary outcome measure in an OAB study. More recent studies have confirmed the efficacy of solifenacin in particular treatment groups including those with severe OAB symptoms, the elderly and also the mildly cognitively impaired.

Overall, the solifenacin clinical development program, from the early Phase I studies through to the more recent Phase IV studies, provides comprehensive evidence of the efficacy of solifenacin in the treatment of all symptoms associated with the OAB syndrome. Objective clinical efficacy data is supported by more subjective patient reported outcomes suggesting that these changes are both statistically significant and also, more importantly, clinically meaningful to patients.

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Executive summary

- Overactive bladder (OAB) is a common and distressing condition known to have a significant impact on quality of life.
- OAB is defined as a symptom complex of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology.
- Solifenacin is a bladder-selective antimuscarinic agent, which has a greater affinity for M_3 receptors than M_2.
- The safety and efficacy of solifenacin has been investigated in a comprehensive series of Phase I and II clinical trials whilst Phase III and IV studies have investigated all components of the OAB syndrome.
- The results of the STAR study suggest solifenacin is noninferior to tolterodine.
- The SUNRISE and VENUS studies are the first OAB studies to investigate urgency as the primary end point.
- The efficacy of solifenacin has also been investigated using a number of differing quality of life measures and patient-reported outcome measures.
- Solifenacin has been shown to be cost-effective in the management of OAB.

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