Int Urol Nephrol (2009) 41:293–298
DOI 10.1007/s11255-008-9448-2

UROLOGY - ORIGINAL PAPER

The cost utility of solifenacin in the treatment of overactive bladder

Leona Hakkaart · Paul Verboom · Richard Phillips · Maiwenn J. Al

Received: 14 November 2007 / Accepted: 28 July 2008 / Published online: 15 August 2008

Abstract
Objectives Overactive bladder may cause significant discomfort to patients. The standard therapy for overactive bladder includes behavioural therapy and sometimes medication. Recently, a new medication (solifenacin 5 and 10 mg) was developed for treatment of overactive bladder. The objective of this study was to assess the cost utility of solifenacin 5 and 10 mg for overactive bladder.
Methods We developed a Markov model to estimate the cost per quality adjusted life years (QALY) over a period of 12-months. Model parameters were based on randomized clinical trials for solifenacin 5 and 10 mg. Data on utility scores were taken from the literature.
Results The incremental cost per QALY for solifenacin 5 mg and solifenacin 10 mg compared with placebo were £17,602 and £24,464 respectively. Sensitivity analyses showed that these results were robust to changes of relevant input data.
Conclusion Solifenacin 5 and 10 mg are cost-effective treatments in patients with overactive bladder.

L. Hakkaart (✉) · P. Verboom · M. J. Al
Institute for Medical Technology Assessment, Erasmus MC, PO Box 1738, Rotterdam 3000 DR, The Netherlands
e-mail: l.hakkaart-vanroijen@erasmusmc.nl; hakkaart@bmg.eur.nl

R. Phillips
Goffin Consultancy Ltd, Stelling Minnis, Canterbury, UK

Keywords Urinary incontinence · Muscarinic receptor antagonist · Overactive bladder · Cost-utility analysis · Markov-model

Introduction

People with overactive bladder syndrome report urgency, usually in combination with frequency and or nocturia [6]. Urgency is the sudden and compelling desire to pass urine, which is difficult to defer. Sometime patients experience involuntary leakage of urine with the feeling of urgency (urge urinary incontinence). Urgency and urge urinary incontinence usually result from an involuntary increase in bladder pressure due to over-activity of the bladder smooth muscle. Frequency is the complaint of needing to void often during the day or night. In clinical practice a person who voids more than eight times in 24 h is considered to have frequency. Frequency, urgency, urge urinary incontinence, or the combination of these symptoms, are a common problem in the community. In a large European survey ($n = 16{,}776$) the prevalence of overactive bladder in the adult population was 16.6% [5]. The prevalence of overactive bladder rises with age for men and women [5]. In people with neurological conditions such as multiple sclerosis, overactive bladder appears to be more common than in the neurologically unimpaired population [2]. Overactive bladder influences the quality of life negatively.

Study showed that frequency and/or urgency may just as bothersome as actual leakage [5]. Patients are likely to socialize less, resulting in a decrease of quality of life.

The two treatment options for overactive bladder are conservative management, e.g. bladder training, electrical stimulation, behavioural therapies and pharmacotherapy, and anticholinergic drugs. The rationale for using anticholinergic drugs in the treatment of overactive bladder is to block the parasympathetic acetylcholine pathway and thus abolish or reduce the intensity of detrusor muscle contraction. Unfortunately, none of the anticholinergic drugs that are available to date are specific to the muscarinic receptors in the bladder [6]. As a result, the drugs can cause side effects by acting on other parts of the body too; these include dry mouth and eyes, constipation, or nausea.

According to a recent Cochrane review, the use of anticholinergic drug by people with overactive bladder results in statistically significant improvements in symptoms [6]. The Cochrane review included 61 effectiveness studies on anticholinergic drugs for overactive bladder. However, cost effectiveness studies on medication for overactive bladder are rare. Our study concerns a cost utility analysis of solifenacin 5 and 10 mg (Vesicare). A cost utility analysis is a special case of cost effectiveness analysis where the effects are measured in terms of quality-adjusted life years (QALY). The objective of this study is to assess whether the costs of solifenacin 5 and 10 mg balance the gains in effectiveness and decrease in costs, from a health payer perspective. We developed a Markov model to estimate the cost per QALY over a period of 12-months. Model parameters were based on randomized clinical trials of solifenacin 5 and 10 mg. Data on utility scores were taken from the literature.

Methods

Clinical data

We used raw data from clinical trials on solifenacin 5 mg and solifenacin 10 mg. The clinical studies were described in detail by Cardozo and others [1]. Data were pooled from four phase III studies evaluating the short-term efficacy, safety, and acceptability of solifenacin [1]. The four studies were conducted globally in 16 countries and involved over 200 study centres. Maintaining consistency across studies was a key consideration during the development of the protocols, with case report forms, diary cards, and statistical analysis plans being similar for each trial [1]. All clinical studies were randomized, double-blind, parallel group, placebo-controlled, multi-national, multi-centre trials. The study populations consisted of male and female patients aged $\geq$18 with symptoms of overactive bladder (including urinary frequency, urgency, or urge incontinence) for more than three months. Patients included had to have a micturition frequency of more than 8 times per 24 h. Patients also had to experience at least three episodes of urgency and/or three episodes of urinary incontinence during a three-day micturition diary. The study comprised of a single-blind, two-week placebo run-in period followed by a randomized, double-blind, placebo-controlled treatment period of 12 weeks. Patients visited the clinic at screening (visit 1), at the end of the placebo run-in period (visit 2), and after 4, 8, and 12 weeks of double-blind treatment (visits 3, 4, and 5).

The primary efficacy variable was change from baseline to study end point in mean number of micturitions per 24 h. Secondary efficacy variables included change from baseline in mean number of urgency, nocturia and incontinence episodes per 24 h, and mean volume voided per micturition. Primary reasons for discontinuation and loss to follow up were mentioned. The database included data on incidence, disease severity based on the number of micturitions and leakages per day, score adverse events, medication use and diaper use. In total these studies generated data for a total of 1,890 patients.

Markov model

We applied a Markov model technique that allowed patients to move from one disease state to all other disease states within a certain time period with a given transition probability, assuming that a patient is always in one of a finite number of states of health [7]. All events of interest are modelled as transitions from one state to another. We divided the total time horizon of the model, 12 months, into equal periods of one month. Based on Kobelt et al., we distinguish five states according to the number of micturitions and leakages per day, where state 1 was considered

"mild" and state 5 "severe" [4]. Kobelt calculated cut-off points between the states based on data from a Swedish willingness-to-pay survey [3].

The model is set up such that all patients start, according to the distribution seen in the clinical studies, in one of the five health states. Each month, patients move from one state to another (or stay in their current health state); dropout is a sixth possible state. After 12 months the model terminates. The model is run separately for patients receiving solifenacin or placebo.

Transition probabilities were calculated from the trial data. Patients who dropped out of treatment were included in our calculation of transfer probabilities between treatment states until the last available data point and then used to calculate the probabilities of drop out.

The model was divided into two periods. We assumed an improvement immediately after initiating the treatment: this improvement was assumed to occur within the first three months (period 1). Thereafter, we assumed that patients remained in the disease state they were in at the end of period 1; the only transition allowed in this period was from the current health state to dropout. In the model we assumed that the probability of dropping out of treatment during the monthly cycles in period 2 (3–12 months) was similar to the drop out rate in period 1.

Utilities

Utility score per disease state was derived from a study by Kobelt et al. [4]. A Swedish willingness-to-pay survey [3], showed that quality of life and utility scores derived from the descriptive part of the EuroQol (EQ-5D) correlated significantly with the health states that were defined on the basis of the number of micturitions and leakages per day (number of symptoms). In this Swedish survey a total of 541 patients with urge or mixed incontinence (response rate 85%) were included. Besides willingness-to-pay, information was also collected about the number of micturitions and urinary leakages, health-related quality of life, and socio-economic characteristics of the patients in the study. Utility weights for the Markov states, based on similar number of symptoms in our study, were obtained by linear regression analysis of the correlation between urinary symptoms and the EQ-5D score in the Swedish willingness-to-pay survey [3, 4]. In our study, patients who dropped out of treatment were assumed to generate no utilities. Table 1 presents the symptom scores (micturitions/day plus leakages/day) and utilities per Markov state.

Costs

Costs per state were based on the cost of medication and on diaper usage. We estimated costs for the year 2004. We distinguished three types of diaper for use in mild, moderate, and severe leakages, respectively, with different unit costs (Table 1). Diaper and medication use were collected in the clinical trials. The costs of solifenacin 5 mg and solifenacin 10 mg were £0.99 and £1.29 per tablet, respectively. The unit costs for diapers ranged from £0.27 to £0.58 per pad. No other health costs were included, because detailed data on other health care resource utilisation were not available. Dropouts were assumed not to generate costs.

Cost utility

The cost utility was evaluated by relating the difference between average costs per patient receiving solifenacin 5 mg or solifenacin 10 mg compared with placebo to the difference in terms of QALYs, which yield an incremental cost per QALY gained (ICER).

Sensitivity analyses

We performed sensitivity analyses for different utilities scores for patients who drop out of treatment. First, we assumed patients dropped out of treatment because they reached the best health state and were no longer in need of medication, e.g. Markov state 1.

Table 1 Symptoms, diaper use, and utilities per patient with overactive bladder by health state

Health state	1	2	3	4	5
Symptoms	<9	9–<12	12–<15	15–<18	≥18
Type of diaper used	Mild	Mild	Moderate	Moderate	Severe
Cost per diaper	0.27	0.27	0.4	0.4	0.58
No. of diapers per day	0.52	1.07	1.69	2.35	3.59
Utility score	0.742	0.712	0.676	0.640	0.598

We also assumed the opposite—that patients dropped out because medication was not effective and they therefore experienced the worst health state, i.e. Markov state 5. Finally, we tested the impact of a scenario that assumed that patients who dropped out reverted to the same health state as during the start mode.

Results

At baseline the distribution by Markov states 1–5 was, respectively, 7%, 33%, 28%, 16%, and 16%. The clinical effectiveness of solifenacin 5 and 10 mg is illustrated by the increased number of patients in the states with fewer symptoms and better quality of life. After three months the distribution of patients in the state with basically no symptoms (state 1) was 42%, 43%, and 28% for solifenacin 5 and 10 mg and placebo, respectively. After 12 months the corresponding distribution was 33%, 39%, and 21% respectively. Table 2 presents the distribution of patients after 3 and 12 months for the five health states by treatment arm.

Utility

Total utility in the treatment groups (solifenacin 5 and 10 mg) showed better quality of life than placebo. For solifenacin 5 and 10 mg the mean QALY per patient was similar, 0.711. For the placebo group the mean QALY per patient was 0.697, see Table 3.

Costs

For the placebo arm no medication was taken; the mean cost per year was £253 (Fig. 1). The use of solifenacin 5 mg reduced costs of diapers to £191, however the medication cost was, on average, £292, resulting in a total yearly cost of £484. Solifenacin 10 mg reduced the yearly cost of diapers to £182 but increased the medication costs substantially to £414. On average the total yearly costs were £597 (Fig. 1).

Table 3 Cost, effects, and incremental cost-effectiveness ratio (ICER) for solifenacin 5 and 10 mg (in pounds, 2004)

	Placebo	Solifenacin 5 mg	Solifenacin 10 mg
Diapers	253	191	182
Medication	0	292	414
Total costs	253	484	597
QALY	0.697	0.711	0.711
ICER		17,602	24,464

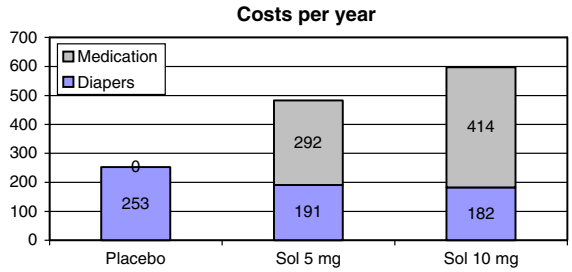

Fig. 1 Average costs of medication and diapers per year (in pounds, 2004) for overactive bladder patients using solifenacin 5 mg, solifenacin 10 mg, and placebo

Cost utility

The average costs for diapers per patient per year were £253, £191, and £182 for placebo and solifenacin 5 and 10 mg respectively (Table 3). The average cost for medication per patient per year was on average £484 and £597 for solifenacin 5 and 10 mg, respectively. The ICER relates the difference

Table 2 Cohort distributions for placebo and solifenacin 5 and 10 mg by health state 1–5 for overactive bladder and dropouts

Health state	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	Dropouts (%)
Baseline	7.1	32.6	27.9	16.5	15.9	
3 months						
Placebo	27.9	29.2	15.5	8.3	7.3	11.8
Solifenacin 5 mg	41.6	29.6	11.6	3.8	4.3	9.1
Solifenacin 10 mg	43.3	28.6	12.7	4.8	3.0	7.6
12 months						
Placebo	21.3	22.3	11.9	6.3	5.6	32.6
Solifenacin 5 mg	32.7	23.3	9.10	3.0	3.4	28.4
Solifenacin 10 mg	38.9	25.8	11.4	4.3	2.7	16.8

between the average total costs per patient receiving solifenacin 5 or 10 mg compared with placebo to the difference in QALY's. So, for the medication arms the incremental costs per QALY for solifenacin 5 and 10 mg were £17,602 and £24,464, respectively (Table 3).

Sensitivity analyses

We performed sensitivity analyses for different health states for patients who drop out of treatment (Table 4). First, we assumed that patients dropped out because they had no symptoms (state 1). Total yearly costs would remain the same but the mean QALY per patient would increase to 0.707, 0.716, and 0.715 for placebo and solifenacin 5 and 10 mg, respectively. The costs per incremental QALY increased to £25,470 and £44,191 for solifenacin 5 and 10 mg, respectively. This increase was because the placebo arm had the highest number of drop outs compared with the medication arms.

We also assumed the opposite—that patients dropped out because the medication was not effective. We assumed they had severe symptoms and consequently the worst utility score i.e. state 5. This lowered the incremental cost per QALY for solifenacin 5 and 10 mg to £16,667 and £15,072, respectively (Table 4).

Finally, we assumed patients who drop out reverted to the same state as they had at the start of the study, so the incremental costs per QALY were between the first two scenarios. The incremental cost per QALY for solifenacin 5 and 10 mg amounted to £20,391 and £23,122 respectively (Table 4).

Table 4 Cost, effects, and incremental cost-effectiveness ratio (ICER) for solifenacin 5 and 10 mg (in pounds, 2004); sensitivity analyses

	Placebo	Solifenacin 5 mg	Solifenacin 10 mg
Total costs	253	484	597
Dropouts utility state 1			
QALY	0.707	0.716	0.715
ICER		25,470	44,191
Dropouts utility state 5			
QALY	0.675	0.689	0.698
ICER		16,667	15,072
Dropouts utility as at start			
QALY	0.692	0.703	0.707
ICER		20,391	23,122

Discussion

The time horizon of the clinical trials was limited, only 12 weeks. However, it seems likely that the major response will be at the start of treatment, and thus we think that the time horizon applied in this model, one year, is sufficiently long.

One major assumption in our model was that the utility of patients who drop out was set to zero. This may be a limiting assumption, but applying different alternative scenarios to this utility estimate had marginal effect on the ICERs found. Overall, this seems a conservative assumption as the number of dropouts was higher for the control group. Hence, if we were to perform a scenario assuming costs for dropouts, solifenacin would be even more cost-effective than the control group compared with the scenario of assuming no costs to drop-outs.

Unfortunately, the trial data did not provide data on utility score by severity. Therefore, we had to use data from the literature based on a large study on patients with urge and mixed incontinence [4]. The health states based on the number of micturitions and leakages used in that study were comparable with those in our study. Kobelt et al. showed decreased utility with both the level of micturitions and leakages [4]. The utility weights for the Markov states were obtained by linear regression analysis of the correlation between urinary symptoms and EQ-5D scores in a Swedish willingness-to-pay study by Johannesson [3]. That study showed that willingness-to-pay increased significantly with both the level of micturitions and leakages, with the size of the reduction in micturitions and leakages, and with increased income. The magnitude of the impact of these significant variables on willingness-to-pay seemed reasonable and overall support the validity of measuring willingness-to-pay of health changes using survey methods.

It might also be argued that our analysis is limited in the sense that we did not include the side effects associated with solifenacin. According to the results of the clinical study the side-effects in a minor part of the study population were dry-mouth, constipation,

and blurred vision [1]. These side-effects are probably not severely physically handicapping and it therefore seems reasonable to assume that these side-effects do not generate hospitalization or other significant healthcare consumption that may result in high health care costs. Furthermore, the clinical study showed that treatment with solifenacin 5 and 10 mg was well tolerated. This result was consistent with the low rate of discontinuation due to adverse events across all treatment groups (3.9% for solifenacin 10 mg, 2.3% for solifenacin 5 mg, and 3.3% for placebo) [1].

The National Institute for Clinical Excellence (NICE) makes decisions about whether or not treatments will be funded through the National Health Service (NHS) based on assessment of their clinical and cost-effectiveness. According to the current guidelines, NICE is likely consider treatment cost-effective if they cost less than £30.000 per QALY (www.nice.org.uk). Hence, based on the currently available data, solifenacin can be considered a cost-effective treatment for patients with overactive bladder.

Conclusion

The clinical effectiveness of solifenacin 5 and 10 mg was illustrated by the increased number of patients in states with limited symptoms and better utilities at 3 and 12 months compared with placebo. Additionally, the number of patients who dropped out of treatment was less than in the placebo group, which could be interpreted as better clinical effectiveness.

The incremental cost per QALY for solifenacin 5 mg and solifenacin 10 mg compared with placebo was £17,602 and £24,464, respectively. Hence, the incremental cost per QALY is within the range of socially acceptable cost per QALY. Sensitivity analyses showed that these results were robust to changes of relevant input data.

Acknowledgement This study was funded by an unrestricted fund of Yamanouchi Europe, The Netherlands.

References

1. Cardozo L, Castro-Diaz D, Gittelman M et al (2006) Reductions in overactive bladder-related incontinence from pooled analysis of phase III trials evaluating treatment with solifenacin. Int Urogynecol J Pelvic Floor Dysfunct 17:512–519. doi:10.1007/s00192-005-0058-6
2. Hennessey A, Robertson NP, Swingler R et al (1999) Urinary, faecal and sexual dysfunction in patients with multiple sclerosis. J Neurol 246:1027–1032. doi:10.1007/s004150050508
3. Johannesson M, O'Conor RM, Kobelt-Nguyen G et al (1997) Willingness to pay for reduced incontinence symptoms. Br J Urol 80:557–562
4. Kobelt G, Jonsson L, Mattiasson A (1998) Cost-effectiveness of new treatments for overactive bladder: the example of tolterodine, a new muscarinic agent: a Markov model. Neurourol Urodyn 17:599–611. doi:10.1002/(SICI)1520-6777(1998)17:6<599::AID-NAU4>3.0.CO;2-J
5. Milsom I, Abrams P, Cardozo L, Roberts RG et al (2001) How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int 87:760–766. doi:10.1046/j.1464-410x.2001.02228.x
6. Nabi G, Cody JD, Ellis G, Herbison P et al (2006) Anticholinergic drugs versus placebo for overactive bladder syndrome in adults. Cochrane Database Syst Rev CD003781
7. Sonnenberg FA, Beck JR (1993) Markov models in medical decision making: a practical guide. Med Decis Making 13:322–338. doi:10.1177/0272989X9301300409