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Long-Term Open-Label Solifenacin Treatment Associated with Persistence with Therapy in Patients with Overactive Bladder Syndrome

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Abstract

Objective: To examine safety and tolerability findings as primary endpoints, and efficacy outcomes as secondary endpoints, of solifenacin treatment over a period of up to 1 year. Long-term efficacy in the treatment of overactive bladder (OAB) syndrome depends in part on the patient's persistence with pharmacologic therapy. Agents with a favourable therapeutic index supporting high levels of patient satisfaction and persistence are needed.

Methods: The present study was a 40-week open-label extension of two 12-week, placebo-controlled, double-blind studies of solifenacin treatment in patients with OAB. Patients who completed the 12-week studies were offered participation in the open-label extension study. All patients who entered the open-label extension study initially received solifenacin 5 mg daily for 4 weeks, after which a flexible dosing regimen allowed patients to individualise their treatment (5 mg or 10 mg) at each of the 3 study visits. Safety and tolerability assessments (the primary variable) included adverse event reporting. Efficacy data were collected from micturition diaries completed at weeks 16, 28, 40, and 52.

Results: Ninety-one percent (1637/1802) of patients who completed the two 12-week randomised studies chose to participate in the long-term open-label extension study. A total of 81% of patients completed 40 weeks of open-label treatment. Solifenacin treatment was safe and well tolerated, and rates of anticholinergic side effects were relatively low. Only 4.7% of patients discontinued treatment owing to adverse events. Improvements in major symptoms of OAB were noted for all patients for up to 52 weeks of treatment. In patients randomised to solifenacin in the double-blind studies, there were small incremental improvements in all efficacy parameters (reductions in episodes per 24 hours of urgency, reductions in frequency and urge incontinence, and increases in volume voided per micturition) over the course of the extension study. Efficacy was confirmed when outcomes were assessed as a function of total solifenacin exposure. Patient satisfaction with solifenacin tolerability (85%) and efficacy (74%) were high. These results indicate that long-term treatment with solifenacin was well tolerated and associated with improvements in efficacy parameters based on patient diary data recorded over the 12-month treatment period. Moreover, the high level of patient satisfaction reported appeared to correlate well with the quantified improvements in key symptoms demonstrated in this study.

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Conclusions: Long-term therapy with solifenacin resulted in a favourable tolerability profile, and was associated with improvements in efficacy parameters based on diary data recorded over a 12-month period. This balance of tolerability and efficacy with solifenacin was associated with excellent persistence with therapy. These results suggest that solifenacin may be useful for the long-term treatment of the chronic symptoms associated with OAB.

Keywords: Antimuscarinics; Detrusor overactivity; Incontinence; Nocturia; Overactive bladder; Urinary urgency; Void volume

1. Introduction

Overactive bladder (OAB) syndrome is a serious, potentially debilitating condition that is estimated to affect the lives of some 50 million patients worldwide [1–3]. The manifestations of OAB, arising from dysfunctional contractions of the detrusor muscle during bladder filling, constitute a symptom complex comprising urinary urgency, with or without urge incontinence, usually accompanied by frequency and nocturia [1,4,5]. OAB is associated with other comorbidities, including falls and fractures, urinary tract infections, skin infections, sleep disturbances, and depression [6]. The symptoms and comorbidities of OAB are associated with serious negative effects on the physical, social, and emotional well-being of patients [6–8].

Because OAB is a chronic condition, effective treatment must be long term and continuous. Antimuscarinic agents have constituted the first-line treatment of OAB since the 1960s, but their effectiveness has been limited by poor compliance due to the occurrence of anticholinergic side effects [9,10]. Dry mouth has been the most common and problematic side effect, frequently leading to discontinuation of treatment [1]. Long-term efficacy in the treatment of OAB depends in part on persistence, which is the ability of patients to stay on long-term therapy. Persistence requires an acceptable balance between tolerability and efficacy. There remains a need for agents to treat OAB that offer a favourable therapeutic index, contributing to high levels of patient satisfaction and persistence.

Solifenacin succinate is a once-daily, oral antimuscarinic agent developed in 2 dosage strengths, 5 mg—the recommended dose—and a 10 mg dose. In two large, randomised, double-blind, 12-week, phase 3 clinical trials, treatment with solifenacin 5 mg and 10 mg once daily significantly reduced the major symptoms of OAB (urgency, incontinence, and frequency), and was associated with a favourable tolerability profile, particularly at the 5 mg dose. For patients receiving solifenacin 5 mg in these trials, 11% reported experiencing dry mouth [11,12].

The present study, an open-label extension of the 2 double-blind studies of solifenacin in patients with OAB, was designed to examine the safety, tolerability, and efficacy of solifenacin 5 mg and 10 mg once daily over a total treatment period of up to 1 year. Both original double-blind studies were placebo controlled; results from these studies have been reported previously [11,12]. One of the 2 studies also included tolterodine 2 mg twice daily (bid) as an active treatment arm; this study was only powered to compare active treatments with placebo. This paper presents outcomes observed during the open-label extension study of long-term solifenacin treatment.

2. Methods

2.1. Patients

Patients completing treatment in the two previous randomised, double-blind, 12-week studies were offered participation in the 40-week open-label extension study. Patients eligible for the double-blind studies comprised men and women aged 18 years and older with symptoms of OAB (including urinary frequency, urgency, or urge incontinence) for ≥3 months [11,12]. Inclusion criteria for the double-blind studies were ≥8 micturitions per 24 hours, in addition to either ≥1 urgency episode per 24 hours or ≥1 incontinence episode per 24 hours [11,12].

To be eligible for the extension study, patients had to give informed consent and had to have completed treatment in the previous double-blind studies ≤14 days prior to extension-study entry. Exclusion criteria for the extension study included clinically significant outflow obstruction, postvoid residual urine >200 ml, persistent or recurrent urinary tract infection, bladder stones, chronic interstitial cystitis, previous pelvic irradiation or previous or current malignant disease of the pelvic organs, and any medical condition contraindicating the use of anticholinergic medication (including narrow-angle glaucoma and urinary or gastric retention). Women of child-bearing potential who were pregnant or nursing, or intended to become pregnant during the study, or who were not practicing a reliable method of contraception were also not eligible.

All patients who received at least 1 dose of study medication in the open-label extension study ($n = 1633$) were included in the safety analysis. Several treatment groups were defined for the adverse event analyses; 2 groups will be reported here as follows: (1) patients who were receiving solifenacin 5 mg immediately prior to the start of the adverse event, and (2) patients who were receiving solifenacin 10 mg immediately prior to the start of the adverse event.