141

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LONG-TERM TOLERABILITY AND SAFETY OF DARIFENACIN DEMONSTRATED IN A 2-YEAR EXTENSION STUDY IN PATIENTS WITH OVERACTIVE BLADDER

Hypothesis / aims of study

Overactive bladder (OAB) is a chronic and prevalent condition, for which antimuscarinic agents are the most common treatment. Since the post-junctional M_3 receptor is considered to be primarily responsible for mediating detrusor contraction during bladder emptying, indiscriminate muscarinic receptor blockade could potentially give rise to adverse effects such as cognitive impairment, tachycardia and blurred vision, as well as the more typical antimuscarinic effects of dry mouth and constipation. A manageable tolerability profile is expected to improve persistence with treatment. Darifenacin is a recently approved muscarinic M_3 selective receptor antagonist for the treatment of OAB, with proven efficacy in phase III clinical trials (1). The objective of the present study was to examine the long-term efficacy, tolerability and safety of darifenacin in the first 2-year open-label study of an extended release formulation to be reported with any antimuscarinic OAB therapy, the tolerability and safety results of which are presented here.

Study design, materials and methods

This was a multicentre, open-label, 2-year extension study that enrolled patients from two 12-week, double-blind studies (feeder studies), which evaluated the efficacy and tolerability of placebo versus controlled-release darifenacin 3.75, 7.5 or 15 mg once daily (qd) in patients with OAB symptoms for ≥6 months (2,3). In the extension phase, all patients received darifenacin 7.5 mg qd for two weeks, regardless of previous treatment, and subsequently darifenacin at doses of 7.5 or 15 mg qd, adjusted according to individual needs. Tolerability and safety were evaluated from adverse events and discontinuations.

Results

716 patients (mean age 57.3 years [range: 19–89], 609 [85.1%] female) were included in the safety population and 475 (66.3%) completed the 24-month open-label study, resulting in a total of 1089.9 subject-years of darifenacin exposure. Overall, 64 patients (8.9%) discontinued due to adverse events. Treatment compliance (defined as 80–120% of doses taken) was >85%.

The most frequently reported all-causality adverse events in the 2-year extension study are shown in Table 1. The most common events, dry mouth and constipation, were well tolerated, with less than 2% and 3% patients discontinuing treatment due to these events, respectively; other adverse events were infrequently considered treatment-related by the investigator (Table).

Evaluation of cardiovascular and nervous system adverse events found that few could be considered to be related to treatment (treatment-related incidences all ≤0.4%). Only hypertension was reported by >1% of patients as an all-causality event, but was considered to be treatment-related for only 0.4% of patients. Similarly, the most common nervous system adverse events were depression, dizziness and insomnia, reported by 2.9, 2.1 and 1.7% of patients, respectively, as all-causality events but only by 0, 0.3% and 0.1% as treatment-related events, respectively. Similarly, over the 24-month study 84 patients experienced serious adverse events, but only 2 were assessed as potentially related to treatment by the investigator (1 abnormal liver function test; 1 coronary artery disease).

Table. Adverse events during treatment with darifenacin 7.5 or 15 mg qd in 2-year open-label extension study

	Incidence of adverse events (%)	
Adverse event	**All-causality events**	**Treatment-related events**
Most common events*		
Dry mouth	23.3	23.2
Constipation	20.9	19.8
Urinary tract infection	11.5	1.1
Respiratory disorder	10.6	0.3
Dyspepsia	9.1	5.2
Accidental injury	8.0	0.1
Flu syndrome	6.8	0
Headache	5.9	2.0
Hypertension	5.4	0.4

*reported by >5% of patients

Interpretation of results

Darifenacin was well tolerated during this study with fewer than 9% of patients withdrawing due to adverse events, and high persistence with therapy over the 24-month duration (66.3%).

The most frequently reported adverse events were the class effects of dry mouth (23.3%) and constipation (20.9%), both of which could be considered manageable and well tolerated, as evidenced by the low rate of discontinuations (less than 2% and 3%, respectively). These events were comparable to, or lower than, that previously reported rates in a pooled analysis of 12-week randomized, double-blind trials (1), or the two feeder studies (2,3). Furthermore, there were few treatment-related cardiovascular, nervous system or serious adverse events.

The high proportion of patients persisting with treatment in the 2-year extension study is likely to reflect the high and sustained efficacy (reported separately), good long-term tolerability (no increase in common AEs relative to feeder studies) and safety (nervous system/cardiac events), which together have the potential to improve patient satisfaction with treatment and encourage compliance and persistence with treatment.

Concluding message

This long-term study of the safety and tolerability of darifenacin 7.5 and 15 mg qd shows that the M_3 selective receptor antagonist demonstrates good clinical tolerability for over 2 years in the treatment of patients with OAB. Class effects of dry mouth and constipation were manageable and well tolerated, and treatment-related cardiovascular or nervous system events were uncommon. This good tolerability profile, accompanied by high and sustained efficacy, encourages persistence and compliance with treatment, making darifenacin a prudent choice of treatment for OAB.

References

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