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Title: EFFICACY AND TOLERABILITY OF ONCE-DAILY TOLTERODINE FOR WOMEN WITH OVERACTIVE BLADDER

Aims of Study:

Overactive bladder (OAB) is more common in women, with symptoms occurring in around 3 times as many women as men (1). Tolterodine, a muscarinic receptor antagonist with a bladder-selective profile, is effective and well tolerated in the treatment of OAB (2-4). Since the chronic nature of the condition necessitates long-term treatment, once-daily (qd) administration of tolterodine may optimise convenience and compliance. A new extended-release (ER) capsule formulation of tolterodine combines highly effective symptom relief with minimal side effects.This study evaluated the efficacy and tolerability of tolterodine ER qd, *versus* placebo and the existing immediate-release (IR) twice-daily (bid) tablet formulation, in women with OAB.

Methods:

A subpopulation analysis was performed on the female cohort of 1529 patients with OAB enrolled into a multinational, randomized, double-blind, active- and placebo-controlled clinical trial of tolterodine ER conducted at 167 centers in Europe (n=89), North America (n=74) and Australia (n=4) (5). A total of 1235 female patients were enrolled and randomized to oral therapy with tolterodine ER 4 mg qd (n=417), tolterodine IR 2 mg bid (n=408) or placebo (n=410) for 12 weeks. About half of patients in each group were pad users and/or had received previous treatment for OAB (of whom 38% had experienced poor efficacy). Efficacy was assessed using micturition charts, while tolerability was determined from an analysis of adverse events, laboratory parameters and withdrawals. Clinical effectiveness was calculated by multiplying the percentage reduction in incontinence episodes (efficacy) by the percentage of patients with no dry mouth (tolerability).

Results:

Tolterodine ER was significantly more effective in reducing weekly number of urge incontinence episodes compared with placebo (p=0.0001) and tolterodine IR (p=0.036). The median reduction in incontinence episodes was 71% for tolterodine ER, compared with reductions of 57% and 33%, respectively, for tolterodine IR and placebo. Tolterodine ER was 24% more effective than tolterodine IR in reducing urge incontinence episodes. Tolterodine ER also produced significantly (p=0.0001) greater mean reductions in micturition frequency (18%) and pad usage (37.5%) compared with placebo (reductions of 11% and 12%, respectively). There was also a significantly (p=0.0001) greater mean increase in volume voided per

micturition (27%) with tolterodine ER than with placebo (10%). Tolterodine IR was associated with a similar degree of improvement in micturition frequency, pad usage and volume voided to that for the ER formulation.

Dry mouth (any severity) was the most common adverse event (ER, 25%; IR, 31%; placebo, 8%). The incidence of other adverse events was low and comparable across treatment groups. Withdrawal rates were comparable

for all three treatment groups. There were no safety concerns.

The clinical effectiveness for tolterodine IR and ER was 39% and 53% respectively implying a 35% greater clinical effectiveness for the extended release preparation.

Conclusions:

Tolterodine ER 4 mg qd is effective and well tolerated in the treatment of women with OAB, with superior efficacy for reducing incontinence episodes and a lower frequency of dry mouth relative to the existing IR twice daily formulation and this is reflected in a 35% increase in clinical effectiveness. This in combination with the convenience of once-daily with tolterodine ER, may facilitate higher levels of patient satisfaction and improved quality of life in women with OAB compared with existing treatment options.

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