PDL NEW DRUG REVIEW

Proprietary Name: Tudorza®
Common Name: aclidinium bromide inhalation powder
PDL Category: Antiasthmatics- Anticholinergics

Comparable Products	Preferred Drug List Status
Atrovent	Preferred
Spiriva	Preferred

Summary

Indications and Usage: For the long-term, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. This is a pregnancy category C medication. The safety and efficacy of use in children under the age of 18 years have not been established.

Drug Interactions: There have been no formal drug-interaction studies with Tudorza®; however, there is a potential for an additive interaction if used concomitantly with other anticholinergic-containing medications.

Dosage Forms: Inhalation, breath-actuated multi-dose dry powder; 400mcg aclidinium per actuation, delivering 375mcg from the mouthpiece.

Recommended Dosage: One inhalation twice daily. Use in those with hepatic impairment has not been studied. Dose adjustments are not required in those with renal impairment.

Tudorza® is not indicated for acute use, for the initial treatment of acute episodes of bronchospasm (ie. rescue therapy).

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions = reported % incidence for drug minus reported % incidence for placebo.* The most commonly reported adverse events with Tudorza® includes headache (1.6%), nasopharyngitis (1.6%), cough (0.8%), diarrhea (1.3%), sinusitis (0.9%), rhinitis (0.4%), toothache (0.3%), fall (0.6%), vomiting (0.6%).

Tudorza® should be used with caution in those with narrow-angle glaucoma and in those with urinary retention. Tudorza® may worsen these conditions. Thus, patients should be educated to contact a physician immediately if signs or symptoms of either of these conditions develop.

Results of three long-term safety trials did not find any new safety findings as compared to the original acute phase placebo-controlled trials.

Contraindications: There are currently no contraindications listed in the prescribing information.

Manufacturer: Forest Pharmaceuticals, Inc.

Analysis: Aclidinium, the active ingredient of Tudorza®, is an anticholinergic that has specific affinity for muscarinic receptors. It is a long-acting antimuscarinic agent that has similar affinity for the subtype muscarinic receptors M_1 to M_5. Effects are seen with inhibition of the M_3 subtype muscarinic receptor on smooth muscle, thus leading to bronchodilation.

Three confirmatory studies were done with aclidinium to assess for the safety and efficacy as treatment for adults with a clinical diagnosis of COPD (N=1276 total). These multicenter, randomized, placebo-controlled studies compared aclidinium with placebo to assess for the primary outcome of comparing bronchodilation, as measured by the change from baseline in morning pre-dose FEV1 at weeks. Results suggest that there was statistically significantly greater bronchodilation seen with aclidinium as compared with placebo in all three studies. The mean treatment differences in Study 1, 2, and 3 were 0.12, 0.07, and 0.11, respectively.

A small (N=30) randomized, double-dummy, double-blind, placebo- and active-controlled study by Fuhr et al[2] assessed the safety and efficacy of aclidinium with placebo and the active-comparator of tiotropium. The primary outcome was the mean change from baseline in FEV1 at day 15 of treatment. Results suggest that aclidinium was superior to placebo for the change from baseline in FEV1 AUC 0-12 hours, with a treatment difference of 221ml ($p<0.0001$). A significant difference vs placebo was also seen with tiotropium, with a treatment difference of 244ml vs placebo ($p<0.0001$). The average use of relief medication significant decreased from baseline with aclidinium (-1.48 puffs/day) and tiotropium (-0.79 puffs/day) as compared with placebo (-0.53 puffs/day). Another secondary outcome was assessing for reduced breathlessness, cough, and nighttime symptoms, and results suggest that aclidinium significantly reduced these effects as compared with placebo but tiotropium did not vs placebo. The authors concluded that aclidinium provided significant bronchodilation as compared with placebo and was comparable to tiotropium; however, greater improvements at night were seen with aclidinium.

A systematic review by Suppli[3] included ten randomized controlled trials (N=3922) to assess for the safety and efficacy of using aclidinium bromide for the treatment of adults with COPD as compared with placebo or other long-acting bronchodilators. Of the included studies, 3 studies compared aclidinium with tiotropium (and placebo), 6 studies compared aclidinium with placebo, and one study compared aclidinium with formoterol. Compared with placebo, results suggest that aclidinium was safe, well-tolerated, and had a fast onset of action. When aclidinium was compared with the other long-acting bronchodilators, at least comparable clinically important improvements were seen between treatments, such as improvements in FEV1, use of rescue medication, and day-time dyspnea scores.

There is no other evidence at this time to support that Tudorza® is more efficacious or safer than the currently available, more cost effective medications. Therefore, it is recommended that Tudorza® remain non-preferred and be available to the few who are unable to tolerate any preferred medications.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☐ **Preferred with Conditions**

References

[1] Tudorza [package insert]. St Louis, MO: Forest Pharmaceuticals, Inc; 2012.

[2] Fuhr R, Magnussen H, Sarem K, et al. Efficacy of aclidinium bromide 400mcg twice daily compared with placebo and tiotropium in patients with moderate to severe COPD. *Chest*. 2012; 141 (3): 745-52.

[3] Supple Ulrik C. Aclidinium bromide: Clinical benefit in patients with moderate to severe COPD. *Open Respir Med J*. 2012; 6:150-4.