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FIVE-YEAR POST-AUTHORISATION SAFETY STUDY OF INHALED MANNITOL IN THE UK

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Introduction: Inhaled mannitol (Bronchitol®) is an inhaled hyperosmotic medicinal product which in CF changes the viscoelastic properties of mucus, increases hydration of the periciliary fluid layer and contributes to increased mucus through mucociliary activity and cough provocation. Inhaled mannitol received a licence for use in adults from the European Medicines Agency (EMA) in 2012 with the recommendation to perform a post-authorisation study to assess long-term safety.

Methods: Using data from the UK CF Registry, a safety study was designed to monitor the use of mannitol in adults with CF. Reports were submitted to the EMA (6 monthly for first 3 years then yearly) over the 5-year period July 2012 - June 2017. All patients recorded as using mannitol in the UK were followed up and matched to similar unexposed patients using annual review data from the year prior to initiating mannitol. A propensity score model was used for matching using age, BMI, percent predicted FEV_1, medication use, hemoptysis history and presence of chronic infections. The main outcomes were hemoptysis and bronchospasm; secondary outcomes included sepsis, abscess, cough fracture and changes in microbial infections. Outcomes were compared between exposed and matched unexposed groups using logistic regression models, adjusted for baseline factors. Reasons for stopping mannitol were also recorded.

Results: 446 adults without transplant were started on mannitol during 5-year study period with 131 subsequently discontinuing treatment (median exposure 15.7 months). The full unexposed population was 5484 subjects from which 947 were selected as matches using the propensity score model. The exposed and matched unexposed groups were similar in age, infection status, and rate of decline in FEV_1 (median 1.7% vs 1.8% per year). The exposed group had lower BMI (mean 21.75 vs 22.58; $p<0.001$) and baseline FEV1 (mean 59.2% vs 63.6%; $p<0.001$) and more days of IV antibiotic use in the year prior to exposure (mean 31 vs 24; $p<0.001$) and the history of hemoptysis was higher (8.84% vs 5.6%; $p=0.02$). Despite these baseline differences there was no significant difference in the main outcome measures of hemoptysis (11.7% vs 8.9%; $p=0.397$) and bronchospasm (defined by introduction of inhaled corticosteroids) 12.9% vs 13.0%, $p=0.397$). No events of cough fracture, pulmonary abscess or septicaemia were reported. Incidence rates (per 100 patient years) of new infections: PA 4.3 vs 4.6, SA 6.3 vs 6.8, *Aspergillus* 6.9 vs 4.8 (all not statistically significant), NTM 7.0 vs 7.0. The median annual rate of decline in FEV_1 slowed in both groups: 1.5% vs 1.6%.

Conclusion: The long-term safety data generated from this 5-year realworld study complements the extensive safety data from a broad clinical trial program with no new safety signals identified. This study confirms that there was no increase in hemoptysis or use of inhaled corticosteroids in the exposed population and no differences in other safety outcomes, including the rate of acquisition of new infections. This is despite the fact that the exposed population appeared sicker at baseline with higher IV antibiotic use and lower FEV_1.