HTA - - Health Technology Assessment Report

Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 Through 11 Years of Age with Cystic Fibrosis Heterozygous for F508del and a Minimal Function Mutation: A Phase 3B, Randomized, Placebo-Controlled Study.

Code: PM35816621 **Year:** 2022 **Date:** 15 Jun 2011 **Author:** Mall MA

List of included studies (2)

Bilton 2011; Aitken 2011; Elkins

Participants

CF patients aged 6 years and above

Interventions

mannitol dry powder for inhalation, alone or in combination with rhDNase, compared with inhaled mucolytics (rhDNase), nebulised hypertonic saline, or best supportive care

Outcome measures

clinical effectiveness (exacerbations, FEV1) and cost effectiveness

Main results

Results show that in adult rhDNase users, there are no significant differences in exacerbations between mannitol and best supportive care (incidence: RR=1.00 (95% CI: 0.61, 1.66); rate ratio per year: 1.14 (95% CI: 0.75, 1.73)); but mannitol leads to a significant improvement in change in FEV1 (MD=91.77 (95% CI: 30.85, 152.69)) when compared with best supportive care. In adults who are ineligible, intolerant or inadequately responsive to rhDNase, there are no significant differences in exacerbations between mannitol and best supportive care (incidence: RR=0.44 (95% CI: 0.18, 1.10); rate ratio per year: 0.50 (95% CI: 0.18, 1.40)); while mannitol leads to a significant improvement in change in FEV1 (MD =162.32 (95% CI: 51.77, 272.87)) when compared with best supportive care. In order to compare mannitol with hypertonic saline, the manufacturer performed a feasibility study to determine whether mannitol could be compared with hypertonic saline via indirect comparison. â€œBased on this feasibility study, an indirect comparison of Bronchitol and hypertonic saline was not felt to be an appropriate analysis in this situation.â€• The Evidence Review Group (ERG) agrees with most objections of the manufacturer regarding heterogeneity between studies. Nevertheless, given the fact that hypertonic saline was mentioned explicitly in the NICE scope, the ERG would like to present the results of an indirect comparison based on current best available evidence. However, it should also be stressed that some data had to be guessed from graphs, making the analyses even more unreliable. Results of the indirect comparison showed that mannitol is superior to hypertonic saline in terms of change in FEV1 in adult rhDNase users (MD = 23.77 (-64.95, 112.49)), although the difference is not statistically significant. In adults who are ineligible, intolerant, or inadequately responsive to rhDNase, there is no significant difference between mannitol and hypertonic saline in terms of change in FEV1 (MD = 94.32 (-33.67, 222.31)). In terms of exacerbations, hypertonic saline seems superior in adult rhDNase users; although, an indirect comparison is not possible because different outcomes are reported for the different studies. Regarding the cost-effectiveness analysis the ERG concludes that, in line with good practice in modeling, the manufacturer model generally reflects the natural disease course since it combines individual patient data with regression models and patient level simulation to reflect the heterogeneity in the disease process. It is also, in most ways, in line with the NICE reference case. However, in terms of rhDNAse use the patient populations defined, the comparisons made, and the data used (especially in the base case analyses) were not according to the scope or good modeling principles. For this reason the ERG conducted its own analyses based on the electronic model as submitted by the manufacturer and with any mistakes corrected. These analyses showed that for rhDNase users the ICER is Â£82,508/QALY with a zero probability to be below a threshold of Â£30,000/QALY. For the rhDNase unsuitable patients the ICER is Â£29,883/QALY with probabilities of being below the Â£20,000 and Â£30,000 of respectively 5% and 50%. Scenario analyses show that relaxing the assumption that mannitol treatment efficacy is lifelong also has a major negative impact on the cost-effectiveness estimate.

Authors' conclusions

The industry submission provides evidence from two RCTs comparing mannitol 400mg with mannitol 50mg over 26 weeks in people

with CF, aged >= 6 years. Data from these two trials would allow for a comparison of mannitol with best supportive care in both populations (adult rhDNase users and adults with cystic fibrosis who are ineligible, intolerant, or inadequately responsive to rhDNase). However, in the Manifacturer studies only lung function is reported for one of the relevant populations for this appraisal: adult rhDNase users. In response to the clarification letter, the ERG received data for both populations, for change in FEV1 (graphs only) and exacerbations. No other data were provided, despite our request for all relevant data for the relevant populations.

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See also

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Keywords

bronchitol; Inhalation OR nebulised; Mannitol; pharmacological_intervention; Powders; Airway clearance drugs -expectorants-mucolytic- mucociliary-; Respiratory System Agents;