Submission to PBS Post-Market Review of Pharmaceutical Benefits Scheme Medicines Used to Treat Asthma in Children with regards to item three of the terms of reference.

Oral salbutamol syrup

We contend that oral salbutamol syrup is being used to treat asthma in children and that there is no evidence to support this practice. The PBS indication for oral salbutamol syrup is for patients that are unable to coordinate inhalation devices. The availability of paediatric masks and spacers eliminates this coordination problem.

Salbutamol exhibits molecular chirality, and is administered as a racemic mixture[1]. This is critically significant, as the bronchodilatory and anti-inflammatory effects of salbutamol are attributed exclusively to the *R*-enantiomer, while the *S*-enantiomer is proinflammatory and exacerbates airway resistance[2]. Oral salbutamol is subject to extensive "first pass metabolism" due to sulphate conjugation by sulphotransferase (SULT) 1A3, predominately in the small intestine and liver[3]. The SULT 1A3 has genetic polymorphisms, which may cause disparity in the bioavailability of orally administered salbutamol between individuals[4]. The bioavailability of *(R)*-salbutamol reportedly varies from 9.4 to 23.8 % for single-dose oral and racemic salbutamol delivered without a spacer, respectively[5], while at steady state the bioavailability of *(R)*-salbutamol is 30 % for orally administered salbutamol[6]. Inhaled salbutamol avoids this "first-pass" effect by being delivered directly to the target organ..

Clinical trial data also does not support the use of oral salbutamol in the treatment of paediatric asthma. In 2011 a Quality Use of Medicines pharmacy student, during a placement at Mater Children's Emergency, conducted a search for evidence of effectiveness of oral salbutamol. The search included PubMed, Embase, Google Scholar, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Australian New Zealand Clinical Trials Registry, and ClinicalTrials.gov, and the bibliographies of found articles. The search yielded six relevant publications of oral and inhaled salbutamol use in the treatment of asthma in children. http://bestbets.org/bets/bet.php?id=2283

In two studies nebulised salbutamol demonstrated statistically greater ($p < 0.05$) improvement in FEV_1[7] and PEFR[8] compared with salbutamol tablets. While maximum improvement in PEFR and FEV_1 was less distinct in comparisons between salbutamol aerosol[9], or inhaled powder[8, 10]. The therapeutic effect of oral salbutamol took two hours to peak [10]. In contrast, the bronchodilatory effect of inhaled salbutamol peaked after 30 minutes[10]. One study of salbutamol use in exercise-induced asthma concluded that the maximum effect of oral salbutamol on FEV_1, which was reached after two hours, was comparable with that reached by inhaled salbutamol after 40 minutes[11]. These studies did not utilise spacers or paediatric masks, which would likely have improved the efficiency of inhaled administration. Oral salbutamol was also associated with an increased incidence of tremor[10], hyperactivity[12], and increased pulse rate[10].

In the treatment of asthma in children, oral salbutamol is surpassed by inhaled formulations in measures of both effectiveness and tolerability. It is our opinion, therefore, that oral salbutamol, marketed in Australia as *Ventolin Sugar Free Syrup*, should be removed from the PBS schedule.

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