Reviewer’s report

Title: Tachykinin receptors antagonism for asthma: a systematic review

Version: 2 Date: 3 February 2011

Reviewer: Brendan J Canning

Reviewer’s report:

The authors have reviewed the results of clinical studies evaluating the efficacy of neurokinin receptor antagonists in asthma.

Minor essential revisions.

1) A key part of the author’s interpretation of the results and their assertion that neurokinin receptor antagonists deserve further evaluation in asthma is their conclusion that the published literature shows that this class of drugs reduces airways hyperresponsiveness. This is clearly overstated. In fact, the literature shows that the NK2 receptor antagonists SR48968, DNK333, AVE5883, CS-003 and MEN11420 produce statistically significant or trends toward significant shifts in the concentration response curves to NKA, an NK2 receptor agonist. It is inappropriate to interpret these results as evidence for an effect on airways hyperresponsiveness, which is typically assessed by methacholine challenge, and to some extent histamine, AMP and hypertonic saline challenges. Surely the authors would agree that histamine receptor antagonists provide little or no benefit in asthma and have no effect on responsiveness to methacholine, but would still likely produce a shift in a histamine concentration response curve in patients. Rather, what these studies show is two-fold: First, that these drugs are indeed NK2 receptor antagonists, and secondly, given the very modest shifts in the NKA concentration response curves, nearly all of these drugs were underdosed in these studies. The doses of ipratropium and tiotropium used in COPD or of montelukast in asthma would produce 100-fold shifts in the methacholine and leukotriene concentration response curves, respectively.

2) Based on what data did the authors conclude that the drugs studied had an effect on lung function? This assertion should be tempered or removed entirely.

3) Additional limitations that the authors should mention is that each of the 7 studies used a different drug, most of these studies failed to document adequate dosing (given that they couldn't even shift an NKA concentration response curve), and nearly every study targeted a different combination of the NK1, NK2 and NK3 receptors. These receptors have very different effects on airway and vascular smooth muscle, inflammatory cells, CNS reflexes and epithelial cells.

4) A diagram or table describing the known actions of NK1, NK2 and NK3 receptors on human airway cells would be helpful.

Level of interest: An article whose findings are important to those with closely
related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.