Omalizumab for the treatment of severe persistent allergic asthma

Assessment Group's commentary on Additional Cost-Effectiveness Analyses submitted by the manufacturer

18/01/2013

1 Introduction

The manufacturer (Novartis) presented additional cost-effectiveness analyses (using the Assessment Group's model) in response to the Appraisal Consultation Document (ACD). These analyses relate to the key remaining areas of uncertainty for the Appraisal Committee on asthma-related mortality rates, proportion of children likely to receive omalizumab, and the most appropriate subgroup population to UK clinical practice. On the assumption that subgroup 1 (maintenance oral corticosteroids (OCS) and hospitalisation for asthma in the previous year) is not favoured by the Appraisal Committee, the manufacturer presents alternative assumptions for subgroup 2 (maintenance OCS only and not necessarily having been hospitalised in the year prior to treatment) and subgroup 3 (maintenance OCS or ≥4 courses of OCS, and not necessarily having been hospitalised in the year prior to treatment).

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2 Methods used in the manufacturer's additional analyses

2.1 Summary of the methods used in the manufacturer's additional analyses

The alternative scenarios proposed by the manufacturer relate to the mortality rates for 'very severe' asthma and the proportion of children on omalizumab. For asthma-related mortality, the manufacturer presents cost-effectiveness results using three alternative assumptions:

1. Watson et al. rates inflated by 15%;
2. de Vries et al. rate inflated by 15%;
3. A mid-point mortality rate between Watson et al. and de Vries et al., both inflated by 15%.

The mid-point mortality rate was calculated for the age categories in Watson et al. To arrive at this average rate, the manufacturer assumes that the mortality risk reported in Watson et al. and de Vries et al. are equivalent measures, which can be averaged in a simple weighted calculation. However, since the rate reported in de Vries et al. does not vary by age, while the rate reported in Watson et al. does, the manufacturer first weights the inflated Watson et al. rates by the proportion of patients in each age category to obtain an average asthma-related mortality rate of 1.45% for Watson et al. This is then averaged with the inflated mortality rate from de Vries et al. of 0.46% to obtain a 'mid-point' rate of 0.955%. The Watson et al. rates are then deflated by this mid-point rate to obtain weighted average asthma-related mortality rates by age.

The manufacturer presented two alternative scenarios for the proportion of children in the overall population who are likely to receive omalizumab:

1. An upper estimate of 7.3% based on the relative proportion of children aged 6-11 years to adults and adolescents ≥12 years in England and Wales (Office for National Statistics mid-2011 census data);
2. An estimate of 4.75% based on the mid-point between the original base-case estimate of 2.2% and the upper estimate of 7.3%.

The various proportions of patients by age and the mortality rates employed in the scenarios are used to calculate the weighted ICER for the overall population in subgroups 2 and 3. The cost-effectiveness results are also presented with and without the PAS.

2.2 Critique of the methods used by the manufacturer

There are a number of concerns with the methods used by the manufacturer to implement their revised assumptions. The first concern relates to the calculation of the mid-point asthma-related mortality rates by age. The manufacturer assumed that the mortality risk reported in Watson et al. and de Vries et al. are essentially the same measure of risk. However, as discussed in the Assessment Group's report (see section 7.2.2.), the mortality risk from Watson et al. is a conditional probability referring to death following a hospitalisation for acute severe asthma, whereas the risk reported in de Vries et al. is a mortality rate for patients at BTS/SIGN step 5 treatment. As a result, these two quantities (conditional probability and rate) must be converted into the same measurable quantity before averaging across the risk. In addition, the manufacturer averaged over the proportion of patients in the overall population for the different age categories of Watson et al. (2.2% for ages 6-11 years, 6.5% for ages 12-16 years, 48.9% for ages 17-44 years, and 42.4% for

ages ≥45 years) in order to obtain an average mid-point mortality risk by age. This mortality risk was then used in the model to calculate the ICER for each age category. The ICER results for the different age cohorts was then subsequently weighted again (i.e. double weighting) by the proportion of patients in each age category in order to obtain the weighted ICER for the overall population consisting of children and adults and adolescents.

A second concern remains about the appropriateness of combining the ICER results for the two separate populations (children aged 6-11 years and adults and adolescents ≥12 years) into a single overall weighted ICER, where the estimate of cost-effectiveness in the separate populations is distinctively different.

On a more minor note, the Assessment Group is unclear about the source of the 7.3% estimate for the proportion of children aged between 6 and 11 years in England and Wales. According to the 2011 census data (http://www.ons.gov.uk/ons/dcp171778_277794.pdf), there are 3,732,999 children aged between 6 and 11 years in the population of 55,730,635, which corresponds to 6.70%.

The Assessment Group has addressed each of the concerns above by implementing what they consider to be the most appropriate approach within the model. In addition, the manufacturer noted a minor inaccuracy in the Assessment Group's economic model (see Section C. Comments on the Evaluation Report - point 2, page 21 of the manufacturer's response to the ACD), which has now been corrected. For these reasons, revised cost-effectiveness estimates are presented in the following section and reported in Table 1 for the same alternative scenarios presented by the manufacturer.

3 Results

Table 1 presents the revised cost-effectiveness results for subgroups 2 and 3 for the three alternative mortality estimates and over a range of proportions of patients aged 6-11 years, with and without the PAS. Without the PAS, the ICER ranges from £30,554 (adults and adolescents only, i.e. 0% proportion of children aged 6-11 years) to £50,057 (children aged 6-11 years), while with the PAS, the ICER ranges from £21,032 (adults and adolescents only) to £33,393 (children aged 6-11 years). Overall, the lowest ICER of £21,032 is for subgroup 3 in adults and adolescents only using the Watson et al. mortality risk inflated by 15% and with the PAS.

Table 1 – Cost-effectiveness results with and without patient access scheme (PAS) for each of the scenarios over a range of proportion of patients aged 6-11 years

Subgroup population	Mortality Assumption	Proportion of Patients Aged 6-11 Years									
		0.0%		2.2%		4.75%		7.3%		100%	
		ICER (w/o PAS)	ICER (w/ PAS)	ICER (w/o PAS)	ICER (w/ PAS)	ICER (w/o PAS)	ICER (w/ PAS)	ICER (w/o PAS)	ICER (w/ PAS)	ICER (w/o PAS)	ICER (w/ PAS)
2 (Maintenance OCS)	Watson +15%	£31,457	£21,659	£31,874	£21,922	£32,349	£22,222	£32,822	£22,520	£50,057	£33,393
	'Midpoint' +15%	£33,955	£23,457	£34,223	£23,626	£34,527	£23,817	£34,830	£24,008	£45,880	£30,955
	De Vries +15%	£42,331	£28,697	£42,334	£28,696	£42,340	£28,694	£42,346	£28,693	£42,551	£28,648
3 (Maintenance OCS or >=4 courses of OCS in the previous year	Watson +15%	£30,554	£21,032	£30,963	£21,291	£31,428	£21,587	£31,892	£21,882	£48,796	£32,615
	'Midpoint' +15%	£33,345	£22,842	£33,616	£23,011	£33,924	£23,203	£34,231	£23,395	£45,397	£30,372
	De Vries +15%	£41,597	£28,129	£41,606	£28,130	£41,617	£28,131	£41,628	£28,133	£42,024	£28,191

4 Discussion

The key driver of cost-effectiveness is the asthma-related mortality risk. Without the PAS, and despite an increase in the mortality risk by 15%, the ICERs remain above the upper threshold of £30,000 per additional QALY for all subgroup populations. With the PAS, the ICER falls to £23,457 and £22,842 in subgroups 2 and 3, respectively, for adults and adolescents only, using the 'mid-point' inflated mortality rate. The corresponding values for children are £30,955 and £30,372, respectively; but note that these cost-effectiveness estimates for children are based on effectiveness data from trials conducted in the adult and adolescent population. An area of concern remains about the appropriateness of combining the ICER results for the two separate populations (children aged 6-11 years and adults and adolescents ≥12 years), where the estimate of cost-effectiveness is distinctively different.