1. Executive Summary

Background

Asthma is a chronic inflammatory disorder of the airways. It affects 5.4 million people in the UK, of whom approximately 1.1 million are children (Asthma UK, 2011). In 2009, there were nearly 80,000 emergency hospital admissions and 1,131 deaths due to asthma (Asthma UK, 2011). In many cases of asthma there is a significant allergic component, predominantly mediated by overproduction of immunoglobulin E (IgE) in response to environmental allergens e.g. house dust mites, pollen and animal fur (GINA 2010). Despite optimised treatment with standard pharmacological therapies, control is not always possible in patients with more severe asthma (Bateman et al. 2004). These patients are seriously debilitated by their condition (Asthma UK 2011).

Omalizumab

Xolair ® (omalizumab) is a humanised anti-IgE monoclonal antibody that inhibits the activity of IgE, a key mediator of allergic reactions. It was licensed in the EU in October 2005 as add-on therapy in adult and adolescent patients (aged ≥12 years) with severe persistent allergic asthma that is uncontrolled by existing treatments (***section 2.1***). In July 2009, the EU licence for omalizumab was extended to cover the treatment of children aged 6-<12 years.

Omalizumab is available as a single-use pre-filled syringe (PFS) containing 150 mg or 75 mg omalizumab (as solution for injection). The UK price (excl. VAT) is £256.15 for the 150 mg PFS and £128.07 for the 75 mg PFS. The PFS formulation replaced the previous lyophilised powder formulation in September 2011 and reduces administration time from approximately 30 minutes to 10 minutes (***section 2.2.8.2***). Each patient receives 75-600 mg of omalizumab in 1-4 subcutaneous injections every 2 or 4 weeks. Dose and dosing frequency are determined by baseline serum total IgE and body weight. "Expanded dosing" above 375 mg per administration and/or dosing for some lower weight patients with IgE of >700-1500 IU/ml was included in the EU SmPC in a January 2010 update. However, this submission primarily makes a case for "***standard dose***" omalizumab (as per TA133 & TA201) and not for ***"expanded dose" (section 2.2.8.1)***.

The SmPC requires that treatment effectiveness is assessed by the treating physician after 16 weeks before further injections are administered. For patients responding to therapy, treatment is continuous from this point as discontinuation of omalizumab generally results in a return to elevated serum IgE levels and associated asthma symptoms.

In UK clinical practice, omalizumab therapy is reserved for severe asthma patents at BTS/SIGN step 5 (or late step 4) and is initiated and monitored by a specialist respiratory physician. In this population, patients often require frequent bursts or continuous use of oral corticosteroids (OCS) which have well documented tolerability concerns (Manson et al. 2009). It is estimated that 1,256 patients are currently receiving omalizumab in England & Wales, of whom approximately 30 are children aged 6-<12 years. This illustrates responsible use of omalizumab in UK clinical practice to date (***section 2.2.6***).

Omalizumab and NICE

TA133 (November 2007) recommends omalizumab, within its licensed indication, as an add-on to optimised standard therapy for patients aged ≥12 years who meet specific criteria with respect to hospitalisations and A&E contacts for asthma in the previous year. TA133 appropriately recommends omalizumab for high risk patients with the most severe asthma. However, issues have been reported in clinical practice with the nature and extent of the "hospitalisation/A&E" restrictions (***section 2.2.5***). TA201 (October 2010) did not recommend the use of omalizumab in children aged 6-<12 years.

Clinical Effectiveness

Randomised Controlled Trials (RCTs)

Four RCTs were identified by systematic review as including populations fully aligned with the EU licence for omalizumab: three in patients aged ≥12 years (INNOVATE, EXALT, ETOPA EUP) and one in patients aged 6-<12 years (IA-05 EUP). Only the open-label EXALT study provides new RCT data vs. TA133 and TA201; no new double-blind RCTs have become available since previous appraisals.

Overall, in patients aged ≥12 years, omalizumab enabled significant reductions in exacerbation rates and unscheduled healthcare resource utilisation, and significant improvements in quality of life/asthma symptoms (see table 1.1). In patients aged 6-<12 years, significantly reduced exacerbation rates were observed.

Table 1.1 –Results on Key Outcome Measures - RCTs of Omalizumab in EU Licensed Indication Populations

	Adults & Adolescents Aged ≥12 years						Children Aged 6-<12 Years	
	INNOVATE (2306) 28 Week Double Blind RCT Humbert et al. (2005)		EXALT (2425) 32 Week Open-Label RCT Bousquet et al. (2011)		ETOPA (IA-04) EU Subgroup 52 Week Open-Label RCT Niven et al. (2008)		IA-05 EU Subgroup 52 Week Double-Blind RCT Kulus et al. (2010)	
	Omalizumab n=209	ST n=210	Omalizumab n=272	ST n=190	Omalizumab n=115	ST n=49	Omalizumab n=159	ST N=76
CS exacerbation rate	0.68*	0.91*	0.55	0.98	1.26	3.06	0.73	1.44
	26% reduction RR 0.738 (0.552,0.998) p=0.042		43% reduction RR 0.570 (0.417, 0.778) p<0.001		59% reduction RR 0.410 (0.288, 0.583) p<0.001		50% reduction RR 0.504 (0.35, 0.725) P<0.001	
CSS exacerbation rate	0.24	0.48	0.24	0.42	NR	NR	0.27	0.50
	50% reduction RR 0.499 (0.321, 0.777) p=0.002		44% reduction RR 0.562 (0.341, 0.924) p=0.023		NR		46% reduction RR 0.545 (0.274, 1.084) p=0.084	
Total emergency visit rate[#]	0.24	0.43	0.35	0.83	0.64	0.74	0.46	0.48
	44% reduction RR 0.561 (0.325, 0.968) p=0.038		60% reduction RR 0.400 (0.244, 0.654) p<0.001		NR		4% reduction RR 0.955 (0.598, 1.524) p=0.847	
AQLQ**	0.91	0.46	1.06	-0.07	1.32	0.17	0.78	0.70
	p<0.001		p<0.001		p<0.001		p=0.566	
Asthma symptom score	-0.66	-0.40	NR	NR	-6.7 (Wasserfallen)	0.5 (Wasserfallen)	-1.41	-1.12
	p=0.039		NR		p<0.05		p=0.434	

CS = clinically significant; CSS = clinically significant severe; Emergency visits = hospitalisations, A&E visits and unscheduled doctor visits; AQLQ = Asthma Quality of Life Questionnaire; ST = standard therapy. * Adjusted *post hoc* for imbalance in baseline exacerbation history; [#] Rate calculated from reported values in IA-04 EUP; ** Mini-AQLQ for IA-04, PAQLQ for IA-05 EUP.

For studies where physician's global evaluation of treatment effectiveness (GETE) was measured (INNOVATE, EXALT and IA-05), additional analyses are presented for omalizumab responders. For example, the rate of clinically significant exacerbations in the 56.5% of omalizumab patients in INNOVATE who were responders was 0.35 (vs. 0.68 for all omalizumab and 0.91 for active control). Given that only responders continue with therapy after 16 weeks, this illustrates the additional treatment effect experienced by this patient group. Increased effect sizes for omalizumab responders were also demonstrated on other outcome measures across included RCTs (***section 3.5.2***).

Non-RCTs

Two non-RCTs were identified by systematic review as including populations completely aligned with the EU licensed indication for omalizumab. Improvements across a variety of clinical outcomes were seen in these studies conducted in "real world" settings (***section 3.8***):-

- **PERSIST (Brusselle et al. 2009):** prospective observational study in Belgium (n=158). 98.1% of patients had an exacerbation in the 12 months prior to omalizumab vs. 34.4% post-treatment (p<0.001). An improvement of 1.79 AQLQ points vs. baseline (3.24) was seen (p<0.001).
- **Cazzola et al. (2010):** prospective observational study of omalizumab in Italy (n=142). Exacerbation rate reduced by 79% from 4.87 in the year pre-omalizumab to 1.00 in the year post.

Data from over 30 other non-RCTs of omalizumab in severe and/or uncontrolled asthma, where precise alignment with all licensed indication criteria is less clear, also show significant benefits for omalizumab in "real world" practice. One large UK non-RCT is of particular interest (***section 3.8.5***):-

- **APEX (Barnes et al. 2011a & 2011b; Niven et al. 2011):** retrospective UK observational study of omalizumab (n=136). 53% reduction in exacerbation rate (3.67 in year pre-omalizumab vs. 1.73 in year post, p<0.001), plus significant AQLQ improvement (mean AQLQ score = 3.13 pre- vs. 4.99 post-, p<0.001). Hospital admissions and A&E visits were reduced by 61% and 70% respectively (p<0.001). Total OCS dose fell by 34% (p<0.001) and 49% of patients stopped OCS.

Subgroups

In TA133, NICE based its recommendation on analysis of a subgroup of patients from INNOVATE who were hospitalised for asthma in the prior year (this subgroup was also submitted for TA201). Although likely to be underpowered, p*ost hoc* analyses of the "hospitalisation" and "maintenance OCS" subgroups from INNOVATE, EXALT, APEX and IA-05 EUP show evidence of clinical effectiveness in these high-risk populations (***sections 3.5.3 & 3.8.5***)

Safety & Tolerability

Data from the included RCTs and adverse event information from the SmPC show that omalizumab is generally well tolerated. The most common adverse events observed were RTIs, nasopharyngitis, headache and cough. There were very few statistically significant differences between the treatment groups in all of the adverse events evaluated, with no consistent differences observed.

Cost-Effectiveness unequivocally

An economic evaluation was conducted using a combined and updated version of the health economic model submitted to NICE for TA133 and TA201. Clinical trial data were used to estimate the cost effectiveness of "***standard dose"*** omalizumab as add-on therapy to standard therapy (ST) alone. Briefly, a Markov model extrapolates omalizumab treatment effects for 10 years and follows patients over a lifetime time horizon. The model addresses the impact of omalizumab on the main outcomes of interest i.e. symptomatic events (clinically significant and severe asthma exacerbations) and day-to-day asthma symptoms. Key assumptions include that (1) only omalizumab patients identified as responders continue therapy after 16 weeks and (2) an asthma-related mortality rate from the literature can be applied to patients experiencing a severe asthma exacerbation (a systematic review identified no new mortality evidence of relevance since TA133 or TA201) (***see section 4.3.2***).

Base case ICERs (cost per QALY gained) for omalizumab plus ST vs. ST alone are **£32,076** for patients aged ≥12 years based on INNOVATE and **£80,747** for children aged 6-<12 years based on IA-05 EUP. Results are summarised in table 1.2 along with supporting analysis from EXALT (the most relevant open-label RCT) & APEX (the most relevant non-RCT to UK clinical practice), plus high-risk subgroup analysis:-

Table 1.2 – Incremental Cost-Effectiveness Ratios (ICERs) – Cost per QALY Gained (Base Case Results in Bold)

Scenario	Full population	"Hospitalisation" Subgroup	"Continuous OCS" Subgroup
Adults and Adolescents Aged 12 Years and Over			
INNOVATE – double-blind RCT	**£32,076**	£27,928	£26,320
EXALT – open-label RCT	£61,687	£35,198	£37,604
APEX – UK observational study	£29,773	£30,407	£29,685
Children aged 6-<12 Years			
IA-05 EUP – double-blind RCT	**£80,747**	£65,100	N/A

As per TA133, ICERs for most adult and adolescent scenarios are close to or below £30,000 per QALY, with ICERs for "high risk" subgroups tending to be lower than ICERs for full study populations. Exploratory sensitivity analysis suggests that ICERs in "maintenance OCS" subgroups can be reduced further if accounting for OCS-sparing effects of omalizumab (***section 4.9***). As per TA201, ICERs for patients aged 6-<12 years remain 2-3-fold higher than for patients aged ≥12 years, driven by the lack of utility difference from 9-11 years and lower asthma-related mortality.

One way sensitivity analysis of the base case ICER for adults and adolescents showed the main model drivers to be model time horizon, exacerbation rate, asthma-related mortality rate, day-to-day utilities, omalizumab drug costs and the discount rate for health effects. The paediatric base case is less sensitive to changes in model time horizon and exacerbation rates, but is very sensitive to changes in omalizumab treatment duration and utilities for day-to-day symptoms. Probabilistic sensitivity analysis of the adult & adolescent base case provided an ICER of **£33,268** (95% CI £22,031 – £54,107). For the paediatric base case, the probabilistic ICER was **£88,998** (95% CI £61,135 – £259,659).

Budget Impact

From a base of 1,256 omalizumab patients in England & Wales (current usage), it is estimated that an additional 329 patients will start therapy in 2012 (8 aged 6-<12 years) rising cumulatively to 653 patients in 2016 (16 aged 6-<12 years). This results in 271 omalizumab responders continuing on therapy in year 1, rising cumulatively to 538 in year 5. We estimate the net incremental cost of omalizumab to be limited at **£2,891,527 in 2012 (12.8% increase vs. 2011)** rising to **£5,282,638 in 2016 (+21.2%).** It is estimated that children aged 6-<12 years will contribute just 2.4% to this budget impact (***section 5***).

Summary

This submission demonstrates the clinical and cost-effectiveness of omalizumab in patients with severe persistent allergic asthma who remain uncontrolled despite current therapies. These benefits are seen in RCTs, "real world" populations reflective of clinical practice and high risk subpopulations. The patients for whom omalizumab is indicated have no alternative therapeutic options, are at high risk of asthma-related morbidity and mortality and are heavy users of healthcare resources.

For TA 133, NICE acknowledged that severity of illness, stakeholder input and significant innovation were 'special circumstances' that enabled it to recommend omalizumab despite a most plausible ICER which, in NICE's opinion, was slightly greater than £30,000 per QALY (Rawlins et al. 2010). We believe that ***"standard dose"*** omalizumab continues to represent a cost-effective use of NHS resources in adults and adolescents aged 12 years and over, whilst having a low net incremental budget impact over the next 5 years. Strong arguments exist to relax current hospitalisation-based subgroup restrictions in TA 133 and to reconsider the previous lack of recommendation for patients aged 6-<12 years (TA 201) given the extremely small number of eligible children.