

**ALVESCO<sup>®</sup> ▼**  
**ciclesonide**

**For the treatment of persistent asthma in adult and  
adolescent patients aged 12 years and over**

Corticosteroids for the treatment of chronic asthma in adults  
and children aged 12 years and over

*Response to the assessment report produced by the Peninsula  
Technology Assessment group and Southampton Health Technology  
Assessments Centre*

**ALTANA Pharma – a Nycomed company**

**28 February 2007**

Having had the opportunity to review the assessment report, *ICS and LABAs for the treatment of chronic asthma in adults and children aged 12 years and over: Systematic review and economic analysis*, carried out on behalf of NICE, we would like to draw the Appraisal Committee's attention to the following points regarding Alvesco<sup>®</sup> (ciclesonide, ALTANA Pharma – a Nycomed company).

### **Size of evidence base for ciclesonide**

In the assessment report, the reviewers expressed concerns regarding the size of the evidence base for newer inhaled corticosteroids (ICSs), including ciclesonide, compared with that for older compounds.

[REDACTED]

The active controlled studies showed that ciclesonide administered once daily was comparable to equivalent doses of fluticasone propionate (FP; 1:1), budesonide (BUD; 1:2) and beclometasone dipropionate (BDP; 1:2) given twice daily, for improving lung function, reducing the incidence of asthma symptoms and reducing the use of rescue medication in patients with mild-to-severe, persistent asthma.<sup>4-16</sup> In addition, ciclesonide was shown to reduce the need for oral steroids in patients with severe steroid-dependent asthma and to be as effective as short courses of oral steroids during induced acute asthma exacerbations.<sup>17</sup>

### **Comparative studies of ciclesonide versus FP, BUD and BDP**

Another concern expressed by the reviewers was the comparability between the ciclesonide and comparator doses used in the active controlled studies. We would respectfully draw your attention to section 5.2 of our original application, which summarises the results of 22 randomised, controlled studies comparing ciclesonide with FP, BUD and BDP, showing a consistent comparability of 1:1 between ciclesonide and FP, 1:2 between ciclesonide and BUD, and 1:2 between ciclesonide and BDP.

#### *Ciclesonide versus FP*

[REDACTED]

[REDACTED] A safety study (Bernstein *et al*)<sup>25</sup> showed that treatment of patients with moderate-to-severe asthma with ciclesonide 160 µg twice daily

or 320 µg twice daily resulted in an incidence of oropharyngeal side-effects similar to placebo and less than FP 440 µg twice daily.

*Ciclesonide versus BUD*

[REDACTED]

*Ciclesonide versus BDP*

In study by Adachi *et al*,<sup>31</sup> a daily ciclesonide dose of 640 µg was found to be superior to BDP 800 µg in maintaining morning peak expiratory flow (PEF) and reducing use of rescue medication and asthma scores. In the same study, Ciclesonide 320 µg daily was as effective as BDP 800 µg.

Please note that the 80 µg, 160 µg, 320 µg, 640 µg and 1,280 µg doses of ciclesonide are ex-actuator doses delivered from the mouthpiece of the pressurised MDI (pMDI) device, in accordance with the European Union (EU) directives for inhaled formulations.<sup>32</sup> These are equivalent to metered doses of 100 µg, 200 µg, 400 µg, 800 µg and 1,600 µg respectively.

**Safety and tolerability of ciclesonide**

[REDACTED]

*Ciclesonide high-dose licence extension*

The recommended dose of ciclesonide is 160 µg once daily, which leads to asthma control in the majority of patients. However, in light of the very favourable safety and tolerability data for ciclesonide outlined above, the European Medicines Agency (EMA) has recently granted a licence extension for ciclesonide in the EU, under which daily doses of up to 640 µg can be administered for up to 12 weeks in patients who need increased anti-inflammatory treatment.

### **Once-daily administration of ciclesonide**

We were surprised to note that the review did not discuss the matter of once-daily versus twice-daily administration of ICSs, since it has been shown that the complexity of a chronic treatment regimen may have a negative impact on patient adherence.<sup>34</sup> Indeed, a retrospective case control study showed significant improvements in treatment compliance in a population of 222 adult asthma patients following a switch from a twice-daily ICS to a once-daily ICS.<sup>35</sup> A comprehensive programme of randomised, controlled studies has demonstrated the clinical efficacy of ciclesonide administered once daily, and the current UK product licence for ciclesonide is based on this regimen. Once-daily administration of ciclesonide, either in the morning or in the evening, is likely to be more convenient for the patient than twice daily administration. This may help to improve treatment compliance – and thus overall asthma control – compared with twice-daily regimens.

### **Cost-effectiveness**

In the assessment report, the reviewers estimated the mean annual cost per patient at £87. This, however, was based on the pack price of ciclesonide 80 µg (£0.238 per puff) as opposed to the pack price of ciclesonide 160 µg (£0.28 per puff), which results in a range of mean annual costs between £87 and £102, dependent on the dose used, as shown in the appendix to this response document.

The reviewers noted that the low cost of ciclesonide was strongly dependent on the simplistic, assumed dose-equivalence ratio of 1:2 between ciclesonide and BDP. This issue has been discussed above, along with further reference to the clinical evidence on which the justification for a cost-minimisation analysis was based. Furthermore, the reviewers' finding that the safety profile across ICSs was essentially similar fails to appreciate the likelihood that the evidence for effectiveness of medication in everyday clinical practice may be compromised relative to findings from clinical trials.

[REDACTED]

In section 6.4.1, the reviewers highlight the nature of the research questions relating to the cost-effectiveness assessment. The ciclesonide cost-minimisation analysis clearly helps us to answer the first of these questions: 'At low doses (200–800 µg BDP per day or equivalent), which is the most cost-effective of the five ICSs? (Step 2 of the guidelines)' The rationale for including the cost comparison between ciclesonide and combination therapy was to highlight the cost differential of potentially inappropriate management of patients at Step 2.

### **References**

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## Appendix. Costs of inhaled corticosteroid therapies for asthma in the UK

Brand name	Generic name	Device name	Strength (amount delivered per actuation (µg))	Reference	Pack size (number of actuations)	NHS pack price (£)	Price/puff (£)	Daily treatment cost for Alvesco 160 µg equivalent dose (£)	Cost/30 days (£)	Cost/365 days (£)
<b>BDP 400 µg daily</b>										
Beclazone	Beclometasone	Easi-Breathe	50	MIMS Dec 2006	200	4.34	0.0217	0.17	5.21	63.36
Beclazone	Beclometasone	Easi-Breathe	100	MIMS Dec 2006	200	10.30	0.0515	0.21	6.18	75.19
Beclazone	Beclometasone	Inhaler	50	MIMS Dec 2006	200	1.76	0.0088	0.07	2.11	25.70
Beclazone	Beclometasone	Inhaler	100	MIMS Dec 2006	200	2.76	0.0138	0.06	1.66	20.15
Beclazone	Beclometasone	Inhaler	200	MIMS Dec 2006	200	8.11	0.0406	0.08	2.43	29.60
<b>BDP 400 µg daily</b>										
Becodisks	Beclometasone	Diskhaler	100	MIMS Dec 2006	120	12.00	0.1000	0.40	12.00	146.00
Becodisks	Beclometasone	Diskhaler	200	MIMS Dec 2006	120	22.87	0.1906	0.38	11.44	139.13
Becodisks	Beclometasone	Diskhaler	400	MIMS Dec 2006	120	45.14	0.3762	0.38	11.29	137.30
Beclometasone	Beclometasone	Inhaler	50	Drug Tariff Feb 2007	200	4.44	0.0222	0.18	5.33	64.82
Beclometasone	Beclometasone	Inhaler	100	Drug Tariff Feb 2007	200	6.05	0.0303	0.12	3.63	44.17
Asmabec	Beclometasone	Clickhaler	50	MIMS Dec 2006	200	6.68	0.0334	0.27	8.02	97.53
Asmabec	Beclometasone	Clickhaler	100	MIMS Dec 2006	200	9.81	0.0491	0.20	5.89	71.61
<b>BDP 400 µg daily</b>										
Becotide	Beclometasone	Inhaler	50	MIMS Dec 2006	200	1.79	0.0090	0.07	2.15	26.13
Becotide	Beclometasone	Inhaler	100	MIMS Dec 2006	200	2.79	0.0140	0.06	1.67	20.37
Becotide	Beclometasone	Inhaler	200	MIMS Dec 2006	200	8.14	0.0407	0.08	2.44	29.71
<b>BDP 200 µg daily</b>										
Qvar	Beclometasone	Inhaler	50	MIMS Dec 2006	200	7.87	0.0394	0.16	4.72	57.45
Qvar	Beclometasone	Inhaler	100	MIMS Dec 2006	200	17.21	0.0861	0.17	5.16	62.82
Qvar	Beclometasone	Autohaler	50	MIMS Dec 2006	200	7.87	0.0394	0.16	4.72	57.45
Qvar	Beclometasone	Autohaler	100	MIMS Dec 2006	200	17.21	0.0861	0.17	5.16	62.82
Qvar	Beclometasone	Easi-Breathe	50	MIMS Dec 2006	200	7.74	0.0387	0.15	4.64	56.50
Qvar	Beclometasone	Easi-Breathe	100	MIMS Dec 2006	200	16.95	0.0848	0.17	5.09	61.87
<b>BDP 400 µg daily</b>										
Pulvinal	Beclometasone	Pulvinal	100	MIMS Dec 2006	100	5.58	0.0558	0.22	6.70	81.47
Pulvinal	Beclometasone	Pulvinal	200	MIMS Dec 2006	100	10.29	0.1029	0.21	6.17	75.12
Pulvinal	Beclometasone	Pulvinal	400	MIMS Dec 2006	100	20.41	0.2041	0.20	6.12	74.50
<b>BUD 400 µg daily</b>										
Pulmicort	Budesonide	Turbohaler	100	MIMS Dec 2006	200	18.50	0.0925	0.37	11.10	135.05
Pulmicort	Budesonide	Turbohaler	200	MIMS Dec 2006	100	18.50	0.1850	0.37	11.10	135.05
Pulmicort	Budesonide	Turbohaler	400	MIMS Dec 2006	50	18.50	0.3700	0.37	11.10	135.05
Pulmicort	Budesonide	Inhaler	200	MIMS Dec 2006	200	20.90	0.1045	0.21	6.27	76.29
<b>FP 200 µg daily</b>										
Flixotide	Fluticasone	Diskhaler	50	MIMS Dec 2006	60	8.17	0.1362	0.54	16.34	198.80
Flixotide	Fluticasone	Diskhaler	100	MIMS Dec 2006	60	12.71	0.2118	0.42	12.71	154.64
Flixotide	Fluticasone	Accuhaler	50	MIMS Dec 2006	60	6.38	0.1063	0.43	12.76	155.25
Flixotide	Fluticasone	Accuhaler	100	MIMS Dec 2006	60	8.93	0.1488	0.30	8.93	108.65
Flixotide	Fluticasone	Evohaler	50	MIMS Dec 2006	120	5.44	0.0453	0.18	5.44	66.19
<b>MF 200 µg daily</b>										
Asmanex	Mometasone	Twisthaler	200	MIMS Dec 2006	30	16.00	0.5333	0.53	16.00	194.67
Asmanex	Mometasone	Twisthaler	200	MIMS Dec 2006	60	24.00	0.4000	0.40	12.00	146.00
<b>Ciclesonide 160 µg daily</b>										
Alvesco	Ciclesonide	Inhaler	160	MIMS Dec 2006	120	33.60	0.2800	0.28	8.40	102.20
Alvesco	Ciclesonide	Inhaler	160	MIMS Dec 2006	60	16.80	0.2800	0.28	8.40	102.20
Alvesco	Ciclesonide	Inhaler	80	MIMS Dec 2006	120	28.56	0.2380	0.48	14.28	173.74
<b>FP 200 µg daily</b>										
Seretide	Salmeterol/Fluticasone	Accuhaler	100	MIMS Dec 2006	60	31.19	0.5198	1.04	31.19	379.48
Seretide	Salmeterol/Fluticasone	Evohaler	50	MIMS Dec 2006	120	18.14	0.1512	0.60	18.14	220.70
<b>BUD 400 µg daily</b>										
Symbicort	Budesonide/Formoterol	Turbohaler	200	MIMS Dec 2006	120	38.00	0.3167	0.63	19.00	231.17
Symbicort	Budesonide/Formoterol	Turbohaler	100	MIMS Dec 2006	120	33.00	0.2750	1.10	33.00	401.50
Symbicort	Budesonide/Formoterol	Turbohaler	400	MIMS Dec 2006	60	38.00	0.6333	0.63	19.00	231.17
<b>BDP 400 µg daily</b>										
Aerobec	Beclometasone	Autohaler	50	MIMS Dec 2006	200	4.04	0.0202	0.16	4.85	58.98
Aerobec	Beclometasone	Autohaler	100	MIMS Dec 2006	200	7.66	0.0383	0.15	4.60	55.92
Filair	Beclometasone	Inhaler	50	MIMS Dec 2006	200	3.85	0.0193	0.15	4.62	56.21
Filair	Beclometasone	Inhaler	100	MIMS Dec 2006	200	7.32	0.0366	0.15	4.39	53.44
Easyhaler BDP	Beclometasone	Easyhaler	200	MIMS Dec 2006	200	15.60	0.0780	0.16	4.68	56.94
<b>BUD 400 µg daily</b>										
Easyhaler BUD	Budesonide	Easyhaler	100	MIMS Dec 2006	200	9.25	0.0463	0.19	5.55	67.53
Easyhaler BUD	Budesonide	Easyhaler	200	MIMS Dec 2006	200	18.50	0.0925	0.19	5.55	67.53
Easyhaler BUD	Budesonide	Easyhaler	400	MIMS Dec 2006	100	18.50	0.1850	0.19	5.55	67.53
Novolizer	Budesonide	Novolizer	200	MIMS Dec 2006	100	14.86	0.1486	0.30	8.92	108.48
Clenil Modulite	Beclometasone	CFC-MDI	50	MIMS Dec 2006	200	3.85	0.0193	0.15	4.62	56.21
Clenil Modulite	Beclometasone	CFC-MDI	100	MIMS Dec 2006	200	7.72	0.0386	0.15	4.63	56.36
Clenil Modulite	Beclometasone	CFC-MDI	200	MIMS Dec 2006	200	16.83	0.0842	0.17	5.05	61.43
Clenil Modulite	Beclometasone	CFC-MDI	250	MIMS Dec 2006	200	16.95	0.0848	0.17	5.09	61.87