Scottish Medicines Consortium

indacaterol 150 and 300 micrograms inhalation powder hard capsules (Onbrez Breezhaler®) (No.619/10)

Novartis Pharmaceuticals Ltd

04 June 2010 *(Issued 09 July 2010)*

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

indacaterol (Onbrez Breezhaler®) is accepted for use within NHS Scotland.

Indication under review: maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD).

Indacaterol has been found to be statistically superior to placebo and other long-acting bronchodilators in improving lung function (FEV_1) after 12 weeks.

Another long-acting $beta_2$ agonist is available at lower cost.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

For maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD).

Dosing information

The inhalation of the contents of one 150 microgram capsule once daily using the Onbrez Breezhaler® inhaler. The dose should only be increased on medical advice to a maximum of 300 micrograms once daily.

Product availability date

01 July 2010

Summary of evidence on comparative efficacy

Chronic obstructive pulmonary disease (COPD) is characterised by airflow obstruction that is usually progressive, not fully reversible and does not change markedly over several months. Indacaterol is a long-acting $beta_2$-adrenergic agonist which when inhaled acts locally as a bronchodilator.

A number of phase III double-blind clinical studies have been performed to support the efficacy of indacaterol in patients with COPD. These include a 12-week comparison with placebo, two 26-week comparisons (one with salmeterol and one with open-label tiotropium) and one 52-week comparison with formoterol, although all primary outcomes were measured at 12 weeks regardless of the length of study. None of these studies have been published in full as yet.

The studies enrolled patients at least 40 years of age with moderate to severe COPD, as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. They had a current or former smoking history of at least 20 pack years, post-bronchodilator forced expiratory volume in 1 second (FEV_1) ≥30% to <80% of predicted normal values and post-bronchodilator FEV_1/(forced vital capacity)FVC <70%. Randomisation was stratified by smoking status (current or ex-smoker). In each study, the primary endpoint was change in FEV_1 at 12 weeks between indacaterol and placebo. Comparisons between indacaterol and salmeterol or open-label tiotropium were secondary objectives and comparison between indacaterol and formoterol was an exploratory objective.

Trough FEV_1 (L) at 12 weeks (ITT population, LOCF)

Study	Indacaterol 150mcg od	Indacaterol 300mcg od	Salmeterol 50mcg bd	Tiotropium 18mcg od	Formoterol 12mcg bd	Placebo
12-week comparison with placebo						
Trough FEV_1 at week 12: LS mean (SE)	(n=201) 1.48 (0.018)	-	-	-	-	(n=189) 1.35 (0.019)
Difference versus placebo: LS mean (95% CI); p-value	0.13 (0.09 - 0.18) p<0.001					

26-week comparison with salmeterol and placebo						
Trough FEV_1 at week 12: LS mean (SE)	(n=320) 1.45 (0.018)		(n=317) 1.39 (0.018)	-	-	(n=316) 1.28 (0.019)
Difference versus placebo: LS mean (95% CI); p-value	0.17 (0.13 - 0.20) p<0.001		0.11 (0.07 - 0.14) p<0.001			
Difference versus salmeterol: LS mean (95% CI); p-value	0.06 (0.02 to 0.10) p<0.001					
26-week comparison with open-label tiotropium and placebo						
Trough FEV_1 at week 12: LS mean (SE)	(n=416) 1.46 (0.015)	(n=416) 1.46 (0.015)		(n=415) 1.42 (0.015)		(n=418) 1.28 (0.015)
Difference versus placebo: LS mean; p-value	0.18 p<0.001	0.18 p<0.001				
Difference versus tiotropium: LS mean; p-value	0.05 p=0.004	0.04 p=0.01				
52-week comparison with formoterol and placebo						
Trough FEV_1 at week 12: LS mean (SE)	-	(n=389) 1.48 (0.012)			(n=379) 1.38 (0.013)	(n=371) 1.31 (0.013)
Difference versus placebo: LS mean; p-value	-	0.17 (0.13 - 0.20) p<0.001			0.07 (0.04 - 0.10) p<0.001	
Difference versus formoterol: LS mean; p-value	-	0.10 (0.07 - 0.13) p<0.001				

FEV_1 = forced expiratory volume in 1 second; LS mean = least squares mean; SE = standard error; CI = confidence interval.

Results of other secondary endpoints (time to first exacerbation and days of poor COPD control) all showed inconsistent results for indacaterol. Pooled analysis over 6-months, found that the frequency of COPD exacerbations was significantly lower with indacaterol than placebo: 0.68 (95% confidence interval [CI]: 0.47 - 0.98) for indacaterol 150 micrograms versus placebo and 0.74 (95% CI: 0.56 - 0.96) for indacaterol 300 micrograms versus placebo.

Symptom relief was assessed by measuring dyspnoea using the Transition Dyspnoea Index (TDI) score and health status using the St George's Respiratory Questionnaire (SGRQ). The TDI is a sum of three domains (functional impairment, magnitude of task and magnitude of effort) with a score range of -9 to 9, where negative scores indicate deterioration. This was assessed in the three studies with an active control with results demonstrating statistically significant and clinically relevant (defined as an improvement of at least one unit) difference versus placebo. The differences versus active comparator were smaller and not clinically relevant. The SGRQ is a self-administered 50-item survey encompassing three components (symptoms, activity and social or psychological impacts with scores ranging from 0 [best] to 100 [worst]). The results demonstrated that indacaterol was statistically superior to placebo but only in two studies was the difference clinically significant (defined as an improvement of at least 4 units). The differences between indacaterol and the active controls were smaller and not clinically relevant.

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

The safety profile of indacaterol was as expected of a long-acting beta$_2$-adrenergic agonist. The most notable adverse event was post-inhalation cough reported in 30% of indacaterol patients. This had an onset of less than 15 seconds after inhalation, was generally mild and did not lead to patients discontinuing from the studies. However the incidence did not seem to decline over time. Other frequently reported adverse events were COPD (including exacerbations), upper respiratory tract infections, nasopharyngitis, headache and muscle spasms.

Summary of clinical effectiveness issues

The studies supporting the efficacy of indacaterol primarily compared effects on lung function (assessed by FEV_1) of indacaterol and placebo, with secondary endpoints comparing indacaterol with active control. Indacaterol resulted in mean changes from baseline relative to placebo of 130 to 180ml and these results were above the 120ml level considered to be clinically relevant. The differences between indacaterol and active comparators were smaller (40 to 100ml) and although statistically significant were not considered clinically relevant. These outcome data are short-term, measured at 12 weeks, and longer-term efficacy data are lacking.

However the aim of COPD treatment is to reduce exacerbation rates and slow the decline in health status and not to improve lung function per se. Therefore the secondary, patient-focussed endpoints are clinically relevant. A key secondary endpoint, a company derived "days of poor control" described by the European Medicines Agency (EMA) as non-validated, produced inconsistent results. There was inconsistency in the effect on exacerbation rates although pooled 6-month analysis favoured indacaterol over placebo. Indacaterol was found to be statistically superior to placebo in terms of TDI and SGRQ scores but the differences were not consistently clinically relevant. Responder analysis found that significantly higher proportions of indacaterol patients achieved the minimally clinically important difference for both SGRQ and TDI scores compared to placebo.

Indacaterol is the first long-acting beta$_2$-adrenergic agonist available for once-daily inhalation. The Onbrez Breezhaler is a single dose dry powder inhaler and patients will need to become familiar with its use.

Patients enrolled in the studies had moderate to severe COPD as defined by the GOLD guidelines. However, these patients (FEV_1 ≥30% and <80%), when defined using the severity assessment used by the National Institute for Health and Clinical Excellence (NICE), have mild to moderate COPD.

The NICE clinical guideline on the management of COPD, recommends that inhaled corticosteroids should be prescribed only for patients with an FEV <50% predicted, who are having two or more exacerbations that require treatment with antibiotics or oral corticosteroids in a 12-month period. The other long-acting beta$_2$-adrenergic agonists (salmeterol and formoterol) are also available as combination products containing inhaled corticosteroids. These are generally less expensive than their components prescribed in separate inhalers and inhaled corticosteroids are not themselves licensed for monotherapy in COPD. The indacaterol clinical data support monotherapy and there are no data for use in combination with inhaled corticosteroids.

Summary of comparative health economic evidence

The manufacturer presented a cost-minimisation analysis comparing indacaterol with either salmeterol or tiotropium for maintenance bronchodilator treatment of airflow obstruction in adult patients with COPD. The time horizon for the analysis was one year. Clinical data to support the assumption of equivalent efficacy were based on a comparative study of indacaterol and salmeterol, and a number of placebo controlled studies where comparative efficacy with salmeterol and tiotropium was explored as a secondary endpoint. The analysis was simple and included only drug acquisition costs with all other resource use assumed to be equal. Compared with salmeterol, the manufacturer claimed that indacaterol was at least as effective at equivalent cost. In the secondary comparison with tiotropium, the manufacturer claimed that indacaterol was at least as effective and would result in savings of £51 per patient per year.

The comparators used in the analysis were salmeterol and tiotropium and SMC experts confirmed that these drugs are used in Scotland. The manufacturer stated that formoterol was not an appropriate comparator as it is not widely used in Scotland. However, SMC experts have indicated that there is some use of formoterol in practice. In addition, formoterol is available at a lower cost than indacaterol.

The clinical data showed that indacaterol and salmeterol had comparable efficacy in terms of improvement in FEV_1, with one study comparing the efficacy of indacaterol and salmeterol as a primary endpoint. In the comparison with tiotropium, the clinical data to support the assumption of equivalent efficacy were based on secondary endpoints only.

Based on drug acquisition costs alone indacaterol appears to be cost-neutral compared with salmeterol and cost-saving compared with tiotropium. As such, the economic case, compared with these products, has been demonstrated. The economic case for indacaterol compared with formoterol has not been presented.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The National Institute for Health and Clinical Excellence (NICE) published a clinical guideline on the management of COPD in adults in primary and secondary care in February 2004. This guideline recommends initial treatment with a short-acting bronchodilator when required. In patients who remain symptomatic a long-acting bronchodilator (long-acting $beta_2$-adrenergic agonists or tiotropium) or a short-acting anticholinergic is recommended. Long-acting bronchodilators should also be used in patients who have two or more exacerbations per year. The choice of drug(s) should take into account the patient's response to a trial of the drug, the drug's side effects, patient preference and cost. In addition, inhaled corticosteroids should be prescribed for patients with an FEV <50% predicted, who are having two or more exacerbations that require treatment with antibiotics or oral corticosteroids in a 12-month period. The aim of treatment is to reduce exacerbation rates and slow the decline in health status and not to improve lung function per se. The NICE COPD guidance is currently under review with expected publication in June 2010.

Additional information: comparators

Other long-acting beta$_2$-adrenergic agonists (salmeterol and formoterol) and the long-acting anticholinergic, tiotropium. Salmeterol and formoterol are also available as combination inhalers with corticosteroids for COPD.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£) Cost per course (£)
Long-acting bronchodilators		
Indacaterol	**150 to 300 micrograms once daily**	**355**
Salmeterol	50 to 100 micrograms twice daily	355 to 853
Tiotropium (Spiriva Handihaler)	18 micrograms once daily	390*
Tiotropium (Spiriva Respimat)	5 micrograms once daily	440
Formoterol	12 to 24 micrograms twice daily	144 to 602
Long-acting beta$_2$-adrenergic agonists plus corticosteroids		
Fluticasone 500micrograms/ salmeterol 50micrograms (Seretide 500 Accuhaler)	One blister twice daily	496
Budesonide 400micrograms/ formoterol 12 micrograms (Symbicort 400/12 Turbohaler)	One puff twice daily	461
Budesonide 200micrograms/ formoterol 6 micrograms (Symbicort 200/6 Turbohaler)	Two puffs twice daily	461

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis 29 March 2010 except costs for long-acting beta$_2$-adrenergic agonists plus corticosteroids which were from eVadis on 28 April 2010.

* cost includes one device

Additional information: budget impact

The manufacturer estimated that there would be savings of £48k in year 1 rising to £111k in year 5 based on patients using indacaterol instead of tiotropium. Using indacaterol instead of salmeterol would be cost neutral for NHS Scotland. It was estimated there would be 1,910 patients treated with indacaterol in year 1 assuming a share of the long-acting bronchodilator market of 1.85%, rising to 3,742 in year 5 assuming a market share of 3.41%. These figures were based on 960 patients receiving indacaterol instead of salmeterol in year 1 rising to 1,553 in year 5 and 950 patients receiving indacaterol instead of tiotropium in year 1 rising to 2,189 in year 5.

Long-acting $beta_2$-adrenergic agonists are often co-prescribed with inhaled corticosteroids. Combination inhalers containing other long-acting $beta_2$-adrenergic agonists together with inhaled corticosteroids are less expensive than the individual components, therefore use of indacaterol may not be cost saving if it displaces combination inhalers. Similarly, there may be a net budget increase if indacaterol displaces low dose formoterol in this indication.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 14 May 2010.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/*

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

Novartis. Study SPP100A 2336 ; A 26-week treatment, multi center, randomized, double blind, double dummy, placebo controlled, parallel group study to assess the efficacy and safety of indacaterol (150 µg o.d.) in patients with chronic obstructive pulmonary disease, using salmeterol (50 µg b.i.d.) as an active control.

European Medicines Agency (EMA) European Public Assessment Report (EPAR) for indacaterol (Onbrez Breezhaler®), EMEA/H/C/001114 www.ema.europa.eu