Indacaterol (Onbrez Breezhaler) for chronic obstructive pulmonary disease

April 2009

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Indacaterol (Onbrez Breezhaler) for chronic obstructive pulmonary disease

Target group
- Adults with chronic obstructive pulmonary disease (COPD) – maintenance therapy.

Technology description
Indacaterol is a long-acting inhaled selective beta2 agonist bronchodilator, administered at 150µg or 300µg once-daily as a dry powder inhalation using the Onbrez Breezhaler inhalation device.

Innovation and/or advantages
Indacaterol provides bronchodilation for up to 24 hours with once daily dosing rather than the twice daily dosing of current selective beta2 agonists.

Developer
Novartis Pharmaceuticals UK Ltd.

Availability, launch or marketing dates, and licensing plans:
In phase III clinical trials.

NHS or Government priority area
This topic is relevant to The National Service Framework for Chronic Obstructive Pulmonary Disease (in development).

Relevant guidance
- NICE service guideline. Assisted-discharge service for patients with COPD. 20063.
- Clinical Knowledge Summaries. Chronic obstructive pulmonary disease. Care guideline. 20074.
Clinical need and burden of disease

COPD is a condition characterised by airflow obstruction that is not fully reversible. The airflow obstruction is due to a combination of airway and parenchymal damage, and is usually progressive. COPD is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Other factors, particularly occupational exposures, may also contribute to its development. Significant airflow obstruction may be present before the individual is aware of it. Common symptoms are breathlessness, cough, sputum, wheeze and chest tightness.

COPD is a leading cause of morbidity and mortality in the UK. The number of patients on Quality and Outcomes Framework (QOF) disease registers with COPD was around 800,000 in the period 2007/08 with an unadjusted prevalence of 1.5% of all patients registered with a general practitioner in England.

In 2006/07 there were 115,598 admissions to hospital with a primary diagnosis of COPD and 195,468 finished consultant episodes (ICD J40-J44; J47). Of the admissions, 105,266 (91%) were emergencies, which represented 0.8% of all emergency medical admissions to hospital. COPD accounted for 920,167 in-patient bed days, which represented almost 2% of all NHS in-patient bed days. There were 24,204 registered deaths from COPD in England and Wales in 2006, 90% of these being in the 65 and over age group.

Existing comparators and treatments

The NICE guideline recommends the following treatment and support options for management of patients with stable COPD:
- Smoking cessation
- Inhaled bronchodilator therapy:
  - Short-acting beta2 agonist, e.g. salbutamol.
  - Short-acting antimuscarinic, e.g. ipratropium.
  - Long-acting beta2 agonist, e.g. salmeterol.
  - Long-acting antimuscarinic, e.g. tiotropium.
- Theophylline - slow-release formulation.
- Corticosteroids:
  - Inhaled corticosteroid, e.g. beclometasone dipropionate – not licensed for use alone in COPD.
  - Oral corticosteroid, e.g. prednisolone – not recommended.
- Combination therapy of the above.

Efficacy and safety

Completed, published trials:

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00098228: indacaterol vs placebo with tiotropium extension; phase II.</th>
<th>NCT00557466: indacaterol vs placebo; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Novartis Pharmaceuticals.</td>
<td>Novartis Pharmaceuticals.</td>
</tr>
<tr>
<td>Status</td>
<td>Completed; published12.</td>
<td>Completed; published13.</td>
</tr>
<tr>
<td>Location</td>
<td>USA</td>
<td>EU, Turkey, South Africa, South America</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo controlled, double-blind.</td>
<td>Randomised, placebo controlled, double-blind.</td>
</tr>
<tr>
<td>Participants</td>
<td>n= 635; adults aged ≥ 40; moderate to severe</td>
<td>n=163 randomised, 155 completed; adults</td>
</tr>
</tbody>
</table>

Airflow obstruction is defined as a reduced FEV1 (forced expiratory volume in 1 second) and a reduced FEV1/FVC ratio (where FVC is forced vital capacity), such that FEV1 is less than 80% predicted and FEV1/FVC is less than 0.7.
and schedule severe COPD; 20 pack years smoking history; post-bronchodilator FEV₁ ≥40% of predicted normal value; pre-bronchodilator FEV₁/FEV <70%. Randomised to indacaterol 50, 100, 200 or 400µg or placebo via multi-dose or indacaterol 400µg via single-dose inhaler for 7 days. A subset from each treatment group entered open-label extension with tiotropium 18µg for 8 days.

aged ≥ 40; moderate to severe COPD; 10 pack years smoking history; FEV₁/FVC <70%. Randomised to indacaterol 400µg or 800µg, or placebo for 28 days.

Follow-up 7 days core period; 8 days open label. 28 days.

Primary outcomes FEV₁ AUC (area under curve) at 22-24h post-dose on day 1. FEV₁ pre- and 30 min post-dose on days 1, 14 and 28.

Secondary outcomes 22h-24h post-dose (trough) FEV₁ on days 1 and 7 and days 1 and 8 of the open-label extension.

Key results All doses of indacaterol superior to placebo ($p \leq 0.01$) for primary outcome; 200µg and 400µg dose most effective; indacaterol FEV₁ levels compared favourably with day 8 improvement with tiotropium.

Adjusted mean ±SE FEV₁ indacaterol-placebo differences: day 28, 260±61ml and 200±61ml for 400 and 800µg, respectively (all $p<0.01$ vs placebo). Pre-dose (trough) adjusted mean ±SE FEV₁ indacaterol-placebo differences: day 28, 220±49 ml and 210±49ml for indacaterol 400 and 800mg, respectively (all $p<0.0001$ vs placebo).

Adverse effects - Mild to moderate AEs reported by 35%, 51% and 25% in indacaterol 400µg, 800µg and placebo groups respectively.

Completed, unpublished trials:

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT00393458: indacaterol vs formoterol; phase III.</th>
<th>NCT00463567: indacaterol vs formoterol or tiotropium, phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Novartis Pharmaceuticals.</td>
<td>Novartis Pharmaceuticals.</td>
</tr>
<tr>
<td>Status</td>
<td>Completed, unpublished.</td>
<td>Completed (ongoing open-label extension), unpublished.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (inc. UK), USA and other countries.</td>
<td>USA, EU, Asia.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, double-blind, placebo-controlled.</td>
<td>Randomised, dose-ranging stage 1, then partially-blind, placebo-controlled stage 2.</td>
</tr>
<tr>
<td>Participants and schedule</td>
<td>n=1,716; adults aged ≥ 40 years; COPD; 20 pack years smoking history; pre-bronchodilator FEV₁&lt; 65% of predicted normal value and at least 0.75L; pre-bronchodilator FEV₁/FVC &lt; 70%. Randomised to: 1. indacaterol 300µg once daily + placebo to formoterol 2. indacaterol 600µg twice daily + placebo to formoterol 3. formoterol 12µg + placebo to indacaterol, or 4. placebo to indacaterol + placebo to formoterol for 52 weeks.</td>
<td>n=805; adults aged ≥ 40 years; COPD; 20 pack years smoking history; post bronchodilator FEV₁ &lt; 80% and ≥ 30% of predicted normal value; post-bronchodilator FEV₁/FVC &lt;70%. Randomised in stage 1 to: 1. indacaterol 75µg 2. indacaterol 150µg 3. indacaterol 300µg, or 4. indacaterol 600µg Randomised in stage 2 to: 1. indacaterol 150µg + placebo to formoterol 2. indacaterol 300µg + placebo to formoterol</td>
</tr>
</tbody>
</table>
### Follow-up
- 52 weeks.

### Primary outcomes
- Trough FEV1 at 12 weeks.

### Secondary outcomes
- Percentage of COPD ‘days of poor control’ over 52 weeks; time to first COPD exacerbation; St George’s Respiratory Questionnaire (SGRQ) score after 12 weeks.

### Expected reporting date

### Trial
- **NCT00624286**: indacaterol vs placebo; phase III.
- **NCT00622635**: indacaterol vs placebo vs salmeterol; phase III.
- **NCT00615030**: indacaterol vs salmeterol; phase III.

### Sponsor
- Novartis Pharmaceuticals.

### Status
- Completed, unpublished.

### Location
- EU, USA, New Zealand. EU, USA.

### Design
- Randomised, double-blind, placebo controlled.
- Randomised, partially blind, placebo-controlled, 3-period crossover.
- Randomised, double-blind, controlled, 4 treatments, 3 period incomplete crossover.

### Participants and schedule
- **n=290, 232 completed; adults aged ≥40 years; moderate to severe COPD; 20 pack years smoking history; post-bronchodilator FEV1 <80% and ≥30% of predicted normal value; post-bronchodilator FEV1/FVC <70%. Randomised to indacaterol 150μg or placebo for 12 weeks.**
- **n=54; adults aged ≥40 years; moderate to severe COPD; 20 pack years smoking history; post-bronchodilator FEV1 <80% and ≥30% of predicted normal value; post-bronchodilator FEV1/FVC <70%. Randomised to each of:**
  1. indacaterol 300μg
  2. placebo
  3. salmeterol 50μg twice daily (open label) for 14 days per treatment.
- **n=78; adults aged ≥40 years; COPD; 20 pack years smoking history; post-bronchodilator FEV1 <80% and ≥30% of predicted normal value; post-bronchodilator FEV1/FVC <70%. Randomised to 3 of:**
  1. indacaterol 300μg a.m
  2. indacaterol 300μg p.m
  3. salmeterol 50μg twice daily
  4. placebo to indacaterol + placebo to salmeterol

### Follow-up
- 12 week treatment period.
- 10 weeks (6 weeks active treatment periods, 4 weeks washout)
- 10 weeks (6 weeks active treatment periods, 4 weeks washout)

### Primary outcomes
- 24h post-dose (trough) FEV1 at 12 weeks.
- Trough FEV1 on day 14 of each treatment period.
- Trough FEV1 of indacaterol (300μg p.m. dose) vs placebo.

### Secondary outcomes
- FEV1 other time points;
- Day 1 and 14: FEV1
- Trough FEV1 of morning
### Outcomes

- peak expiratory flow (PEF); time to first COPD exacerbation; health-related quality of life (QoL) measure: SGRQ.
- standardised AUC from 5min to 23h 45min post-dose.
- Day 1: trough FEV1; peak FEV1 during 4h post morning dosing; time to peak FEV1.
- and evening indacaterol vs placebo.

### Expected Reporting Date

- European Respiratory Society (September 2009).

### Ongoing Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Location</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00567996: indacaterol vs salmeterol</td>
<td>Novartis Pharmaceuticals.</td>
<td>EU, USA, Canada and other countries.</td>
<td>Randomised, double-blind, placebo-controlled, 3 period incomplete crossover design.</td>
</tr>
<tr>
<td>NCT00615459: indacaterol vs tiotropium; phase III.</td>
<td>Novartis Pharmaceuticals.</td>
<td>EU, USA.</td>
<td>Randomised, double-blind, placebo-controlled.</td>
</tr>
</tbody>
</table>

### Participants and Schedule

- **Participants and schedule**
  - **Trial 1:**
    - n=972; adults aged ≥ 40 years; COPD; 20 pack years smoking history; post bronchodilator FEV1 <80% and ≥30% of predicted normal value; post-bronchodilator FEV1/FVC <70%.
    - Randomised to:
      1. indacaterol 150µg + placebo to salmeterol
      2. salmeterol 50µg twice daily with placebo to indacaterol, or
      3. placebo to indacaterol + placebo to salmeterol for 26 weeks.
  - **Trial 2:**
    - n=75; adults aged ≥ 40 years; COPD; 20 pack years smoking history; post bronchodilator FEV1 <80% and ≥30% of predicted normal value; post-bronchodilator FEV1/FVC <70%.
    - Randomised to 3 of:
      1. indacaterol 150µg with placebo to tiotropium
      2. indacaterol 300µg with placebo to tiotropium
      3. tiotropium 18µg with placebo to indacaterol, or
      4. placebo to indacaterol + placebo to tiotropium for 14 days per treatment.

### Follow-up

- **Trial 1:** 26 weeks.
- **Trial 2:** 10 weeks (6 weeks active treatment periods, 4 weeks washout).

### Primary Outcomes

- **Trial 1:** 24h post dose trough FEV1 at 12 weeks.
- **Trial 2:** Trough FEV1 after 14 days.

### Secondary Outcomes

- **Trial 1:** Days of poor control; SGRQ score; health related QoL; standardised AUC for FEV1; FEV1 and FVC, trough FEV1; time to first COPD exacerbation and COPD exacerbation rate.
- **Trial 2:** 24h post dose trough FEV1, days to peak effect; AUC for FEV1 on day 1 and day 14.

### Expected Reporting Date

- American College of Chest Physicians (November 2009).

### Estimated Cost and Cost Impact

The cost of indacaterol is not yet known. The annual costs of other licensed bronchodilators for COPD are:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Annual cost £</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol (Serevent Accuhaler)</td>
<td>50µg twice daily</td>
<td>£356</td>
</tr>
<tr>
<td>Tiotropium (Spiriva HandiHaler)</td>
<td>18µg once daily</td>
<td>£451</td>
</tr>
</tbody>
</table>
Potential or intended impact – speculative

Patients

- Reduced morbidity
- Reduced mortality or increased length of survival
- Improved quality of life for patients and/or carers: with once daily dosing
- Quicker, earlier or more accurate diagnosis or identification of disease
- Other: None identified

Services

- Increased use
- Service reorganisation required
- Staff or training required
- Decreased use
- Other: None identified

Costs

- Increased unit cost compared to alternative
- Increased costs: more patients coming for treatment
- Increased costs: capital investment needed
- New costs:
- Savings:
- Other: Unknown comparative cost

References
