

acridinium 322 micrograms inhalation powder (Eklira Genuair®)

SMC No. (810/12)

Almirall S.A.

05 October 2012

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

acridinium (Eklira Genuair®) is accepted for use within NHS Scotland.

Indication under review: as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

In two phase III studies, acridinium was statistically superior to placebo in improving lung function (forced expiratory volume in 1 second [FEV₁]) after 12 weeks and 24 weeks.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

As a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

Dosing Information

One inhalation of 322 micrograms twice daily.

Product availability date

September 2012.

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. Acclidinium is a long-acting muscarinic antagonist which antagonises M_3 receptors on airways smooth muscle to induce bronchodilation.

The evidence to support the efficacy of acclidinium in COPD comes from the results of two similarly designed phase III studies, one of 24 week duration (ATTAIN)¹ and one of 12 week duration (ACCORD I).² Both studies enrolled patients aged ≥ 40 years who were current or former cigarette smokers (smoking history of ≥ 10 pack-years) and had a diagnosis of COPD according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. Eligible patients had post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio of $< 70\%$, and ATTAIN required $FEV_1 < 80\%$ of predicted (at least moderately severe COPD), while ACCORD I required $FEV_1 \geq 30\%$ and $< 80\%$ of predicted (moderate to severe COPD). Patients were randomised equally to receive acclidinium 200 micrograms, acclidinium 400 micrograms or placebo twice daily for 24 or 12 weeks. The 400 micrograms metered dose of acclidinium (bromide) used in the clinical studies is equivalent to the delivered dose of 322 micrograms acclidinium stated in the summary of product characteristics. The intent to treat population comprised 819 patients in ATTAIN and 560 in ACCORD I. During the studies, patients were allowed to use salbutamol/albuterol as needed (but discontinued ≥ 6 hours before study visits) and to continue to use the following concomitant medicines provided they had been at stable doses for ≥ 4 weeks before screening: inhaled corticosteroids, systemic corticosteroids (equivalent to prednisone ≤ 10 mg/day or 20mg on alternate days) and theophylline.

The primary endpoint was change from baseline in trough (morning pre-dose) FEV_1 for acclidinium versus placebo measured at 24 weeks in the ATTAIN study and at 12 weeks in the ACCORD I study. Results are presented for the licensed dose of acclidinium (400 micrograms twice daily) and placebo.

In ATTAIN, the change from baseline in trough FEV_1 at week 24 was significantly greater with acclidinium compared with placebo, with a mean improvement of 128mL (95% confidence interval [CI]: 85 to 170), $p < 0.0001$.¹ Baseline trough FEV_1 values were 1.51L and 1.50L in the acclidinium and placebo groups respectively. The clinical study report states that at 24 weeks the mean changes from baseline were 55mL and -73mL respectively.³ In ACCORD I, the change from baseline in trough FEV_1 at week 12 was significantly greater with acclidinium than placebo with a mean improvement of 124mL (95% CI: 83 to 164), $p < 0.0001$.² Baseline trough FEV_1 values were 1.33L and 1.38L in the acclidinium and placebo groups respectively.² The clinical study report states that at 12 weeks the mean changes from baseline were 99mL and -25mL respectively.⁴

Secondary endpoints included the change from baseline in peak FEV₁, the St George's Respiratory Questionnaire (SGRQ) and the Transition Dyspnoea Index (TDI) score. In both studies there was a significant improvement in peak FEV₁ in the aclidinium group versus placebo: a mean improvement of 209mL at week 24 in ATTAIN and of 192mL at week 12 in ACCORD I. 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 aclidinium was statistically superior to placebo in both studies with a mean improvement over placebo of 4.6 in ATTAIN and 2.5 in ACCORD I.^{1,2} The proportion of patients achieving a clinically significant difference (defined as an improvement of at least 4 units) was significant at week 24 in ATTAIN (57% of aclidinium versus 41% of placebo patients) but not at week 12 in ACCORD I (44% versus 36% respectively).⁴ The TDI assesses symptom relief. It 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. In both studies, there was a statistically significant improvement in mean TDI focal score of 1.0 in the aclidinium group compared with baseline over placebo at study endpoint. An improvement of ≥1 unit in TDI focal score is considered clinically significant and this was reported in significantly more aclidinium than placebo patients (57% versus 46%, respectively in ATTAIN) and 48% versus 33% respectively, in ACCORD I).^{1,2}

In both studies, the use of rescue medication with salbutamol/albuterol was significantly reduced in the aclidinium group by 0.90 to 0.95 puffs/day compared with placebo. There was a numerical, but not statistical, reduction in moderate to severe COPD exacerbations (requiring antibiotics or corticosteroids or hospitalisation) with aclidinium versus placebo in both studies. In ATTAIN, the annualised rate of moderate or severe COPD exacerbations was 0.34 versus 0.47 per patient per year respectively (rate ratio: 0.72 [95% CI: 0.51 to 1.02] p=0.06). In ACCORD I, there was a 34% reduction in the rate of moderate or severe COPD exacerbations compared with placebo. A pooled analysis found an annual rate of 0.31 with aclidinium versus 0.44 with placebo (p=0.0149).

Summary of evidence on comparative safety

There are no comparative safety data available for aclidinium. During the clinical studies, the most frequently reported adverse events were headache (6.6%) and nasopharyngitis (5.5%). In both the ATTAIN and ACCORD I studies, the incidence of anticholinergic adverse events was similar or lower (<2%) with aclidinium than with placebo.^{1,2}

Summary of clinical effectiveness issues

Aclidinium is a new long-acting muscarinic antagonist (LAMA) for the treatment of COPD. Two clinical studies primarily compared lung function (assessed by FEV₁) of aclidinium and placebo and results demonstrated significant improvements. The European Medicines Agency (EMA) recommends that there should be co-primary endpoints assessing lung function and symptom-based outcomes. Patient-orientated outcomes (SGRQ, TDI, COPD exacerbations) were assessed as secondary endpoints. The ATTAIN study was sufficiently powered to detect differences in the secondary endpoints.

The EMA notes that there is no general agreement on the degree of change in lung function that is considered to be clinically relevant. Acclidinium resulted in mean changes from baseline relative to placebo of 124 to 128mL, which are marginally higher than the 120ml level considered to be clinically relevant by some sources.

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. The reduction in moderate to severe COPD exacerbations was not significantly different between acclidinium and placebo in either study but, in a pooled analysis, the difference achieved statistical significance.

The EMA also suggests that randomisation should be stratified according to smoking status. This was not done in the ATTAIN and ACCORD I studies but baseline characteristics suggest similar proportions in each group.

Study patients had moderate to severe COPD so there is a lack of phase III data in patients with mild or very severe disease. The duration of the studies, 12 and 24 weeks, is relatively short for a chronic disease. However, unpublished safety data to one year suggest that the bronchodilator effect is maintained.

There are no relevant clinical data comparing acclidinium with an active comparator, particularly tiotropium. The results of an ongoing 6-week comparison with tiotropium are awaited. An indirect comparison of acclidinium versus tiotropium was presented. This was a network meta-analysis (NMA) applying Bayesian indirect treatment comparison models. Indirect evidence only was included from two acclidinium and 16 tiotropium studies and the common reference comparator was placebo. The primary outcome of the indirect comparison was the difference in change from baseline trough FEV₁ at 24 weeks which suggested non-inferiority between acclidinium and tiotropium. Analyses of secondary outcomes of TDI and SGRQ also suggested non-inferiority. SMC noted that there were differences between the studies and that the studies used different lengths of follow-up.

Since the studies excluded patients with certain cardiovascular conditions, acclidinium should be used with caution in such patients (see summary of product characteristics for details).

Acclidinium requires twice daily dosing compared with once daily tiotropium. Acclidinium is administered via a new inhaler device (Genuair®) and patients will require training to ensure satisfactory technique. It is a multi-dose, breath-actuated dry powder inhaler which is disposable after all doses have been used.

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis comparing acclidinium with tiotropium in patients matching the licensed indication. Tiotropium was selected as the only currently licensed LAMA and because it is widely prescribed in Scotland; it was thus was an appropriate comparator. A one year time horizon was used for the analysis.

The evidence on efficacy came from an indirect comparison of the clinical studies of acclidinium compared to studies of tiotropium; these supported a claim of non-inferiority so the cost-minimisation analysis was appropriate. The only costs considered were the medicine plus delivery device. For tiotropium, one delivery device per annum was assumed in the base case.

The submission reported the annual cost with aclidinium would be £343 versus £386 with tiotropium. Given this finding, the economic case was demonstrated.

The economics case described above was based on the price of the main comparator at the time of the submission. The price of the comparator has subsequently changed (see “Cost of relevant comparators” section of this guidance document for the relevant price) but the SMC is satisfied that this has not altered the conclusion that the economic case for aclidinium has been demonstrated.

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 clinical guideline 101 on the management of COPD in adults in primary and secondary care in June 2010. This guideline recommends:

- initial treatment with a short-acting bronchodilator when required.
- once-daily LAMA should be offered in preference to four-times-daily short-acting muscarinic antagonist (SAMA) to people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as required, and in whom a decision has been made to commence regular maintenance bronchodilator therapy with a muscarinic antagonist.
- in patients with stable COPD and $FEV_1 \geq 50\%$ predicted who remain breathless or have exacerbations either a long-acting beta-agonist (LABA) or LAMA is recommended.
- if these patients still remain breathless or have exacerbations consider LABA+ inhaled corticosteroid (ICS) in a combination inhaler or LAMA in addition to LABA where ICS is declined or not tolerated.
- in patients with stable COPD $FEV_1 < 50\%$ predicted who remain breathless or have exacerbations on short-acting bronchodilators either LABA+ICS in a combination inhaler, or LAMA is recommended.
- if patients still remain breathless or have exacerbations despite taking LABA+ICS, irrespective of their FEV_1 a LAMA in addition to LABA+ICS should be considered.

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.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) published revised guidelines “Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease” in 2011. This guideline recommends the following first and second choice options according to the patient's COPD:

- for patients with low risk and fewer symptoms: first choice - shorting-acting bronchodilators as required or SAMA; second choice - LAMA or LABA or SAMA + SABA
- for patients with low risk and more symptoms: first choice - LAMA or LABA; second choice -LAMA + LABA
- for patients with high risk and fewer symptoms: first choice - LAMA or ICS + LABA; second choice - LAMA + LABA
- for patients with high risk and more symptoms: first choice - LAMA or ICS + LABA; second choice - ICS + LAMA or ICS + LABA +LAMA or ICS +LABA + phosphodiesterase inhibitor or LAMA + LABA or LAMA + phosphodiesterase inhibitor

These guidelines predates the availability of aclidinium.

Additional information: comparators

The main comparator is tiotropium, which is the only other LAMA available. Other long-acting bronchodilators include the LABAs, salmeterol and formoterol.

Cost of relevant comparators

| Drug | Dose Regimen | Cost per year (£) |
|---------------------------------|------------------------------------------|-------------------|
| Aclidinium | 322micrograms inhaled twice daily | 343 |
| Tiotropium (Spiriva Respimat) | 5 micrograms inhaled once daily | 426 |
| Tiotropium (Spiriva Handihaler) | 18 micrograms inhaled once daily | 403* |

Doses are for general comparison and do not imply therapeutic equivalence. Costs are taken from eMIMS September 2012. * cost for tiotropium (Spiriva Handihaler) includes one device.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 49,805 in year 1 rising to 51,098 in year 5 with an estimated uptake rate of 3% in year 1 and 20% in year 5. The gross impact on the medicines budget was estimated to be £505k in year 1 and £3.51m in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to result in savings of £63k in year 1 and £434k in year 5.

References

The undernoted references were supplied with the submission.

1. Jones PW, Singh D, Bateman ED et al. Efficacy and safety of twice-daily aclidinium bromide in COPD patients: The ATTAIN study. Eur Respir J 2012 Mar 22.
2. Kerwin EM, D'Urzo AD, Gelb AF, L et al. Efficacy and safety of a 12-week treatment with twice-daily aclidinium bromide in COPD Patients (ACCORD COPD I) 4. COPD 2012; 9:1-12.
3. Data on file. Efficacy and safety of aclidinium bromide at two dose levels versus placebo when administered to patients with moderate to severe chronic obstructive pulmonary disease (COPD). 12 April 2011.
4. Data on file. Efficacy and safety of aclidinium bromide at two dose levels (200µg twice daily, 400µg twice daily) vs placebo when administered to patients with moderate to severe chronic obstructive pulmonary disease (COPD). 21 January 2011.

This assessment is based on data submitted by the applicant company up to and including 13 August 2012.

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.

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.