Scottish Medicines Consortium

erdosteine 300mg capsules (Erdotin®) No. (415/07)

Edmond Pharma Sr.l/Galen Ltd.

5 October 2007

The Scottish Medicines Consortium 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

erdosteine (Erdotin®) is not recommended for use within NHS Scotland as an expectorant for the symptomatic treatment of acute exacerbations of chronic bronchitis in adults.

Evidence for the clinical efficacy of erdosteine is limited and was obtained from studies that do not reflect current practice for the management of chronic obstructive pulmonary disease (COPD) in NHS Scotland. The manufacturer did not present a sufficiently robust clinical or economic case for erdosteine to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

As an expectorant for the symptomatic treatment of acute exacerbations of chronic bronchitis in adults.

Dosing information

300mg twice daily for a maximum of 10 days

Product availability date

15 November 2006

Summary of evidence on comparative efficacy

Erdosteine is a mucolytic agent that reduces the viscosity of mucus and purulent sputum, thereby easing expectoration. After activation by metabolism to produce free thiol groups it opens the disulphide bonds of bronchial mucoproteins. It has also shown anti-oxidant properties and inhibits bacterial adhesion to epithelial cells.

Chronic bronchitis is now considered a component of chronic obstructive pulmonary disorder (COPD). Chronic bronchitis is characterised by persistent cough and sputum production, while COPD is characterised by airflow limitation that is not fully reversible. These features commonly overlap but the terms are not synonymous.

There are no trials comparing erdosteine with mucolytics licensed for use in COPD in the United Kingdom. However, a number of trials are available comparing it with mucolytics licensed in other countries. The largest comparative trial was double-blind and recruited 195 patients aged 35-80 who had chronic bronchitis for at least 3 months a year over 2 years, an FEV_1/VC ratio at least 10% below theoretical, a body temperature $\geq$38° and a requirement for antibiotics. They were randomised to receive erdosteine 300mg twice daily or n-acetylcysteine 200mg three times daily. All patients also received amoxicillin 500mg three times a day.

In two trials erdosteine 300mg or placebo twice daily were added to antibiotic therapy in patients with an exacerbation of chronic bronchitis. In these trials the primary end-point was a global clinical measure of efficacy incorporating 6 functional signs of chronic bronchitis (sputum appearance, sputum viscosity, difficulty of expectoration, catarrh, cough, dyspnoea), as opposed to the single measure (difficulty in expectoration) which was the primary efficacy outcome in the comparative trial above.

In the first of these trials, the antibiotic was amoxicillin 500mg three times a day and the primary end-point was scored from 0 to 18 where 0 indicates no symptoms and 18 indicates the presence of all 6 symptoms at their highest severity score. 237 patients were randomised and received study drug, while 226 were included in a primary per-protocol analysis. At the 7 to 10 day final assessment the global clinical efficacy score was 4.9 (standard deviation $\pm$2.7) in the erdosteine treatment group compared to 7.4 $\pm$2.8 in the placebo group, representing reductions of 60% and 41% from baselines of 12 and 13 respectively. The between-group difference was significant.

In the second trial, comparing the addition of erdosteine or placebo to ciprofloxacin 500mg twice a day, 200 patients were randomised, completed the study and were included in the primary analysis. The global clinical scoring system, which used the same clinical

parameters, was not explained clearly. However the reduction at day 8 (mean±SD) was significantly greater in the erdosteine treatment group than placebo (3.0±0.50 versus 2.3±0.31), as was the proportion of patients with improvement in the global score (97% compared with 82%).

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

Summary of evidence on comparative safety

The main adverse events associated with erdosteine are gastric disorders, itching and headache, and in the largest comparative trial gastrointestinal effects occurred equally in both erdosteine and n-acetylcysteine groups.

Summary of clinical effectiveness issues

Most trials investigating erdosteine in acute exacerbations of chronic bronchitis were published before 1996 and recruited patients whose condition was defined as chronic bronchitis rather than COPD. Comparative trials are limited to mucolytics unlicensed in the United Kingdom (UK), therefore their relevance to UK-licensed mucolytics is uncertain. Indirect comparisons with licensed agents are presented but have serious limitations, such as differences in study population, sample size and objectives.

A number of guidelines are cited that refer to the use of mucolytics in patients with chronic obstructive pulmonary disorder with the objective of reducing the incidence of exacerbations. However, most of these provide no support for mucolytics in the treatment of acute exacerbations, despite giving distinct advice for management of this phase of the disease. In COPD, mucolytics licensed for chronic use should be stopped if there are no benefits after a 4-week trial.

In most trials, both erdosteine and comparators have been added to antibiotic therapy. Mucolytics have been shown to enhance penetration of antibiotics into sputum, and this and other synergistic effects may contribute to their effect in COPD.

Most trials excluded or limited concomitant COPD medications such as corticosteroids and anticholinergics which are likely to be administered during an exacerbation in clinical practice. Thus, they do not provide robust evidence as to whether any benefits of mucolytic therapy exceed those of standard care in current clinical practice in NHS Scotland.

Clinical experts expressed reservations about the limited clinical evidence base for erdosteine.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis comparing erdosteine plus standard care with standard care alone, carbocisteine plus standard care and mecysteine plus standard care, for the treatment of patients with an acute exacerbation of COPD (AECOPD). A decision tree was used to estimate the costs of the different interventions and a function from a literature study was the basis of the QALY gain associated with erdosteine treatment. The manufacturer estimated that treatment with erdosteine dominated standard care, based on estimated savings of £3.47 and a QALY gain of 0.00004 per patient. Erdosteine was

estimated to be cost-saving compared to carbocisteine and mecysteine based on indirect comparisons.

Utility values used in the model appear to be relatively conservative in comparison with comparable health states in the literature. However, these utility values did not distinguish between the severities of COPD. The resource use estimates used in the analysis were based on clinical opinion rather than data from the trial. However, these estimates were made by GPs working in Scotland and resource use was estimated according to patient response rather than according to the type of treatment the patient received. The manufacturer carried out a thorough sensitivity analysis on all the parameters included in the model.

There were a number of concerns with the data used in the economic evaluation:

- Comparator – clinical experts have indicated that a number of medicines excluded from the clinical trial now form part of standard care for the treatment of AECOPD. It is therefore difficult to estimate what the incremental benefit of erdosteine would be compared to current medicines used as standard care. Clinical experts suggested that they would be unlikely to use erdosteine in this indication until further evidence on its benefit over standard care had been demonstrated.
- A number of issues were identified with the indirect comparisons carried out to demonstrate equivalent efficacy between erdosteine and the other two licensed mucolytics.

Due to problems with the clinical data used in the economic evaluation, it is difficult to estimate what the incremental benefit of erdosteine would be compared to current medicines used as standard care for AECOPD. Therefore, the manufacturer did not present a sufficiently robust economic case to gain acceptance by SMC.

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 produced guidance on COPD in adults in primary and secondary care in 2004. Mucolytic therapies are recommended in chronic cough associated with COPD that is productive of sputum but are not one of the options discussed in the section dealing with acute exacerbations of COPD.

Additional information: previous SMC advice

After review of a full submission, the Scottish Medicines Consortium (SMC) issued advice in October 2003 that moxifloxacin is recommended for restricted use in NHS Scotland:

Moxifloxacin (Avelox®), a new fluoroquinolone antibiotic, for the treatment of acute exacerbations of chronic bronchitis, should be restricted to patients who fail to respond to conventional therapy or in whom this is contra-indicated. Its use should be in accordance with British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) guidance.

Additional information: comparators

Carbocisteine and mecysteine.

Cost of relevant comparators

Drug	Dose regimen	Cost per 10 days* (£)
Erdosteine capsules	**300mg twice daily**	**5.00**
Mecysteine hydrochloride tablets	200mg four times daily for 2 days then 200mg three times daily**	11.00
Carbocisteine capsules	750mg three times daily**	8.30
Carbocisteine oral liquid	750mg three times daily**	8.80

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on August 6th 2007

* Erdosteine is licensed for up to 10 days in the treatment of acute exacerbations. Carbocisteine and mecysteine are not restricted to use during acute exacerbations of COPD only. For consistency with erdosteine they have been costed for 10 days, however these agents might be continued into chronic use.

** For consistency with erdosteine it has been assumed that all comparator mucolytics have been initiated at starting doses during an exacerbation.

Additional information: budget impact

The manufacturer estimated the budget impact of erdosteine based on the assumption that it would replace other mucolytics in some patients and that it would also be used in a proportion of patients who would currently receive standard care. The net budget impact was estimated at £21k in year 1 rising to £119k in year 5, based on 7,791 and 32,223 patients treated, respectively.

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

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 13 September 2007.

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.

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.

Arnaud A. Clinical study of efficacy and tolerability of erdosteine in the treatment of chronic obstructive bronchitis with super infection. Controlled double blind study vs. n-acetylcysteine. Clinical study report 5.3.5.1.16. 1991.

Marchioni CF, Polu JM, Taytard A, Hanard T, Noseda G, Mancini C. Evaluation of efficacy and safety of erdosteine in patients affected by chronic bronchitis during an infective exacerbation phase and receiving amoxycillin as basic treatment (ECOBES, European Chronic Obstructive Bronchitis Erdosteine Study). Int J Clin Pharmacol Ther 1995;33(11):612-8.

Mohanty K, Thiappanna G, Singh V, Mancini C. Evaluation of efficacy and safety of erdosteine in patients affected by exacerbation of chronic bronchitis and receiving ciprofloxacin as basic treatment. J Clin Research 2001;4(35-39).