Commissioning Support
N-Acetylcysteine
(Aceteff®, generic N-acetylcysteine, NACSYS®)

For the treatment of hypersecretion of mucus in respiratory disorders

Commissioning guidance:

Commissioners may wish to bear the following in mind when considering the commissioning of N-acetylcysteine products licensed as mucolytic treatments:

- In a situation where a licensed product has become available for a previously unlicensed indication, the MHRA advise that the licensed product should be used where possible. Use of unlicensed medicines should only continue in cases of special clinical need at the discretion of the prescriber.[1,2]
- Treatment duration is specified for one N-acetylcysteine formulation (200 mg oral powder); the duration of treatment is dependent on the nature and severity of the illness, and should be decided by the clinician initiating treatment. There is no such restriction in the NACSYS Summary of Product Characteristics (SPC). Local specialist opinion also recommends that treatment should be reviewed regularly and stopped if no symptomatic benefit has been achieved.
- Given the considerable cost differential between licensed products, prescribing by brand is advisable; selecting the brand with the lowest acquisition cost.

Efficacy

- Results from four systematic reviews showed that N-acetylcysteine was more effective than placebo in preventing exacerbations in people with chronic bronchitis or chronic obstructive pulmonary disease (COPD); see efficacy section below.
- There were no published direct comparisons of N-acetylcysteine with another mucolytic treatment. Indirect comparison in the Cochrane review (four carbocisteine trials were included) found that effect sizes relating to numbers of exacerbations per participant per month were not affected by type of mucolytic or dose.
- There were also no comparisons of mucolytic treatments with other therapies for the prevention of exacerbations e.g. long-acting bronchodilator plus inhaled corticosteroids.
- Mucolytics are included in the NICE guidance on COPD and in the GOLD guidelines. The NICE guideline development group expressed a concern that mucolytics should not routinely be used to prevent exacerbations in people with stable COPD in preference to other treatments that may be more effective[7].

Safety

- Adverse events were mild, and mostly gastrointestinal in nature.
- Stey *et al*.[11] reported that 10.2% of N-acetylcysteine-treated participants had dyspepsia diarrhoea or heartburn, compared with 10.9% of placebo-treated participants.
- There were no significant differences between N-acetylcysteine and placebo for the numbers of patients reporting adverse events, or withdrawing due to an adverse event.[11]

Cost

Across the NHS England West Midlands region, the average prevalence of diagnosed COPD is 1.86% and there are 74,366 patients in COPD disease registers.[12] According to a study in the Netherlands, about 13% of patients with COPD may have excessive sputum production and chronic cough requiring treatment with a mucolytic.[13]

The current prices (per patient per 30 days) of N-acetylcysteine products are listed below (MIMs August 2018):

- Aceteff® 600 mg effervescent tablet £ 89.50
- Generic 200 mg oral powder £ 337.50
- NACSYS® 600 mg effervescent tablet £ 5.50

Patient factors

- The use of N-acetylcysteine may be of benefit in terms of reducing pill burden in some patients. Two of the newly licensed formulations (Aceteff® and NACSYS®) are taken once daily unlike carbocisteine, where the recommended dose is 2 capsules three times daily, decreasing to 1 capsule four times daily once a satisfactory response has been obtained.

Description of technology

N-Acetylcysteine is a long-established treatment for paracetamol overdose (via intravenous infusion) and as an ocular lubricant. In 2017, three N-acetylcysteine products were launched in the UK as mucolytic treatments in people with respiratory disorders and hypersecretion of mucus:

Aceteff® is licensed for use as adjunctive therapy in respiratory tract disorders associated with excessive viscous mucus secretions in adults and adolescents

14 years of age and over. The recommended dose is one 600 mg tablet daily dissolved in a glass of water[3].

A generic N-acetylcysteine formulation is licensed as an adjuvant in the therapy of respiratory disorders associated with thick, viscous, mucus hypersecretion. It is formulated as a 200 mg powder for oral solution; one sachet to be dissolved in water, three times daily[4].

NACSYS® is licensed for use in adults only as a mucolytic agent in respiratory disorders e.g. bronchitis, emphysema, mucoviscidoses and bronchiectasis. The recommended dose is one 600mg effervescent tablet daily in half a glass of water.[5]

Background

According to the 2018-updated guideline from the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is a common, preventable and treatable disease. It is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases[6].

Mucus hypersecretion and chronic cough are two of the key presenting symptoms in people with COPD, and mucus hypersecretion may contribute to the development of COPD; studies have shown an association between mucus hypersecretion and increased FEV_1 decline. Chronic bronchitis has also been associated with an increased risk in the total number as well as severity of exacerbations.[6]

The British Lung Foundation statistics on COPD estimate that 1.2 million people are living with diagnosed COPD. Along with lung cancer and pneumonia, COPD is one of the three leading contributors to respiratory mortality in the UK. In 2012, 29,776 people died from COPD (5.3% of the total number of UK deaths, and 26.1% of deaths from lung disease).

The GOLD guideline states that in COPD patients not receiving inhaled corticosteroids, regular treatment with mucolytics such as carbocisteine and N-acetylcysteine may reduce exacerbations and modestly improve health status. A third mucolytic agent, erdosteine, is also available for the symptomatic treatment of acute exacerbations of chronic bronchitis for a maximum of 10 days[6].

Current NICE guidance for the treatment of COPD advises that mucolytic agents should be considered in people with COPD and chronic cough that produces sputum.

Clinical evidence for efficacy and safety

A literature search for systematic reviews and meta-analyses evaluating use of N-acetylcysteine in all respiratory disorders, found that only reviews involving COPD and chronic bronchitis evaluated the 600 mg once-daily dose specified in the licensed indications for the products under review, and these are described below.

A 2015 Cochrane review[8] assessed whether treatment with mucolytics reduced frequency of exacerbations and/or days of disability in people with chronic bronchitis or COPD compared with placebo. The review included 34 trials, 19 of which evaluated N-acetylcysteine (carbocisteine [4 trials], ambroxol [3] + eight other mucolytics with 1 trial each). The review found that mucolytic-treated patients were more likely to be exacerbation free during the study period than with placebo treatment (odds ratio 1.75, 95% CI 1.57 to 1.94; number needed to treat [NNT] 8, 95% CI 7 to 10). In addition, mucolytic use was associated with a lower rate of exacerbations, fewer days of disability per participant per month, and a lower rate of hospitalisations compared with placebo although there was a lot of heterogeneity between the trials (lack of consistently positive or negative trial outcomes). Part of the heterogeneity was believed to arise from changing practice in the treatment of COPD over the time range that the trials were published (1971 to 2014).

Three other systematic reviews also reported significantly lower rates of exacerbations with N-acetylcysteine treatment *vs*. placebo in participants with COPD, chronic bronchopulmonary disease or chronic bronchitis[9-11]. In addition to these analyses of exacerbation rates, Sutherland *et al*.[10] evaluated N-acetylcysteine treatment with or without use of inhaled corticosteroids (ICS) and found a larger effect (change in rate of exacerbations) in the absence of ICS[10]. Stey et al[11] also reported that a higher percentage of participants treated with N-acetylcysteine gave positive ratings relating to symptom improvement than those receiving placebo (61.4% *vs*. 34.6%; Relative risk 1.78 [95% CI 1.54 to 2.05];NNT 3.7 [95% CI 3.0 to 4.9]).

References

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