Asthma: fluticasone furoate/vilanterol (Relvar Ellipta) combination inhaler

Evidence summary
Published: 3 March 2014
nice.org.uk/guidance/esnm34

Key points from the evidence

The content of this evidence summary was up-to-date in March 2014. See summaries of product characteristics (SPCs), British national formulary (BNF), BNF for children (BNFc) or the MHRA or NICE websites for up-to-date information.

Summary

Relvar Ellipta is a combination inhaler containing 2 active ingredients not previously available for the treatment of asthma: fluticasone furoate (an inhaled corticosteroid [ICS]) and vilanterol (a long-acting beta-2 agonist [LABA]). There are no published studies that compare fluticasone furoate/vilanterol with a currently available ICS/LABA combination inhaler or currently available ICS monotherapy for a patient-orientated primary outcome such as exacerbation rate.
**Effectiveness**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- No statistically significant difference was found between fluticasone furoate/vilanterol 92/22 micrograms once daily and fluticasone propionate/salmeterol 250/50 micrograms twice daily for the 0–24 hour weighted mean forced expired volume in 1 second (FEV₁) week-24 change from baseline (1 randomised controlled trial [RCT]; n=806).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>- A statistically significant reduction (from 15.9% to 12.8%; ( p = 0.036 )) was found in the adjusted probability of having a severe asthma exacerbation by 52 weeks with fluticasone furoate/vilanterol 92/22 micrograms once daily compared with fluticasone furoate 92 micrograms once daily (1 RCT; n=2020).</td>
<td></td>
</tr>
</tbody>
</table>

**Safety**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Systemic effects may occur with any ICS; particularly at high doses prescribed for long periods. Because fluticasone furoate is a new ICS more information about its effect on cortisol suppression relative to other inhaled corticosteroids is needed.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>- Cardiovascular events, particularly tachycardia, are known risks associated with LABAs. The summary of product characteristics states that fluticasone furoate/vilanterol should be used with caution in people with severe cardiovascular disease.</td>
<td></td>
</tr>
</tbody>
</table>

**Patient factors**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Administration is once-daily using a multi-dose dry powder inhalation device (the Ellipta device).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>- Two strengths are available for the treatment of asthma. The lower strength delivers fluticasone furoate 92 micrograms once daily (approximately equivalent to fluticasone propionate 250 micrograms twice daily). Because a lower strength is not available, the ability to step down treatment is limited.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>- In clinical trials the most commonly reported adverse reactions were headache and nasopharyngitis.</td>
<td></td>
</tr>
</tbody>
</table>

**Resource implications**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- The cost of fluticasone furoate/vilanterol 92/22 micrograms is £27.80 for 30 days of treatment. The cost of fluticasone furoate/vilanterol 184/22 micrograms is £38.87 for 30 days of treatment.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>- The cost of other available ICS/LABA combination inhalers ranges from £29.26 to £76.00 for 30 days of treatment.</td>
<td></td>
</tr>
</tbody>
</table>
Key points

Relvar Ellipta is licensed for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (LABA and ICS) is appropriate, that is patients not adequately controlled with ICS and ‘as needed’ inhaled short-acting beta-2 agonists. It is not licensed for use in patients who are already adequately controlled on both an ICS and a LABA, unlike the other 4 ICS/LABA combination inhalers that are licensed in the UK for the treatment of asthma (summaries of product characteristics: Seretide, Flutiform, Symbicort and Fostair).

For the treatment of asthma, 2 strengths of the Relvar Ellipta combination inhaler (with different doses of fluticasone furoate and the same dose of vilanterol) are available:

- fluticasone furoate 92 micrograms plus vilanterol 22 micrograms (delivered dose leaving mouthpiece) and
- fluticasone furoate 184 micrograms plus vilanterol 22 micrograms (delivered dose leaving mouthpiece).

In patients with asthma, fluticasone furoate 92 micrograms once a day is approximately equivalent to fluticasone propionate 250 micrograms twice a day and fluticasone furoate 184 micrograms once a day is approximately equivalent to fluticasone propionate 500 micrograms twice a day (summaries of product characteristics).

The British guideline on the management of asthma (SIGN guideline 101) published jointly by the Scottish Intercollegiate Guidelines Network and British Thoracic Society and accredited by NICE indicates that 250 micrograms fluticasone propionate twice a day is approximately equivalent to 1000 micrograms beclometasone dipropionate per day and 500 micrograms fluticasone propionate twice a day is approximately equivalent to 2000 micrograms beclometasone dipropionate per day.

For adults and young people aged over 12 years, the British guideline on the management of asthma recommends a trial of ICS plus LABA when asthma is uncontrolled by an ICS alone (step 3: initial add-on therapy). The guideline states that the first choice as add-on therapy to ICS is a LABA, which should be considered before going above a dose of 400 micrograms beclometasone dipropionate equivalents per day and certainly before going above 800 micrograms beclometasone dipropionate equivalents per day.

This evidence review is based on the 2 randomised controlled trials (RCTs) that provide the best published evidence for fluticasone furoate/vilanterol for treating asthma.
Woodcock et al. (2013) (n=806) found that there was no statistically significant difference between fluticasone furoate/vilanterol 92/22 micrograms once daily and fluticasone propionate/salmeterol 250/50 micrograms twice daily for the 0–24 hour weighted mean FEV₁ week-24 change from baseline. The study was designed to show superiority of fluticasone furoate/vilanterol and powered to detect a difference of 80 ml in the serial weighted mean FEV₁ between the 2 groups. At entry to the study (prior to a 4-week run-in period on ICS alone), 69% of participants were already using an ICS plus LABA (equivalent to step 3 or 4 of the British guideline on the management of asthma). Caution is needed in extrapolating the results of this study to people with less severe asthma.

Bateman et al. (2013) (n=2020) found that there was a statistically significant reduction from 15.9% to 12.8% in the risk of having a severe asthma exacerbation by 52 weeks with fluticasone furoate/vilanterol 92/22 micrograms once daily compared with fluticasone furoate 92 micrograms once daily. At entry to the study 60% of participants were already using an ICS plus LABA (equivalent to step 3 or 4 of the British guideline on the management of asthma).

There are limited published efficacy data available for the higher strength inhaler. O’Byrne et al. (2013) compared fluticasone furoate/vilanterol 184/22 micrograms once daily with fluticasone furoate 184 micrograms once daily and fluticasone propionate 500 micrograms twice daily. The co-primary outcome measures for this study were both disease orientated; the change from baseline in trough FEV₁ and weighted mean 0–24 hour serial FEV₁. The study found that fluticasone furoate/vilanterol statistically significantly improved both primary outcome measures compared with fluticasone furoate and fluticasone propionate.

In Woodcock et al. (2013) rates of serious adverse events and adverse events leading to withdrawal from the study were similar between fluticasone furoate/vilanterol 92/22 micrograms once daily and fluticasone propionate/salmeterol 250/50 micrograms twice daily, although no statistical analysis was provided. In a 52-week safety study (Busse et al. 2013) oral/oropharyngeal candidiasis was more common with both strengths of fluticasone furoate/vilanterol once daily compared with fluticasone propionate 500 micrograms twice daily (6% and 7% compared with 3% respectively; no statistical analysis presented). Extrasystoles (bigeminy or trigeminy on Holter recording) were more common in the fluticasone furoate/vilanterol 184/22 micrograms group (7%) compared with the 92/22 microgram strength inhaler group (2%) or the fluticasone propionate group (3%).

According to the summaries of product characteristics during clinical trials, the most commonly reported (1/10 or more) adverse reactions were headache and nasopharyngitis. Other common adverse reactions reported (1/100 or more to less than 1/10) include candidiasis of the mouth and
throat, upper respiratory tract infections, bronchitis, dysphonia, pyrexia, abdominal pain, arthralgia, back pain and oropharyngeal pain.

Local decision-makers will need to consider the available evidence on efficacy and safety, as well as the licensed indications, cost and individual patient factors, when making decisions about using Relvar Ellipta or another ICS/LABA combination inhaler.

**Key evidence**

Bateman E, O’Byrne PM, Busse WW et al. (2013) *Once-daily fluticasone furoate/vilanterol reduces risk of severe exacerbations in asthma versus fluticasone furoate alone,* Thorax doi:10.1136/thoraxjnl-2013-203600

Woodcock A, Bleecker ER, Lotvall J et al. (2013) *Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma,* Chest 144: 1222–9

Busse WW, O’Byrne PM, Bleecker ER et al. (2013) *Safety and tolerability of the novel inhaled corticosteroid fluticasone furoate in combination with the β₂ agonist vilanterol administered once daily for 52 weeks in patients ≥12 years old with asthma: a randomised trial,* Thorax 68: 513–20

**About this evidence summary**

‘Evidence summaries: new medicines’ provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.

**Relevance to NICE guidance programmes**

The fluticasone furoate/vilanterol combination inhaler was not considered appropriate for a NICE technology appraisal and is not currently planned into any other work programme.

Inhaled corticosteroids for the treatment of chronic asthma in children under the age of 12 years (NICE technology appraisal guidance 131) and Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over (NICE technology appraisal guidance 138) considered inhaled corticosteroids (ICS) for the maintenance treatment of asthma, both as a single agent and in combination with a long-acting beta-2 agonist (LABA).
Introduction

The British guideline on the management of asthma (SIGN guideline 101), published jointly by the Scottish Intercollegiate Guidelines Network and the British Thoracic Society and accredited by NICE, advocates the following stepwise approach for the treatment of asthma. Inhaled corticosteroids (ICS) are the first-choice regular preventer therapy for children and adults. If asthma is not adequately controlled by an ICS alone (at step 2), add-on therapy may be needed (step 3). No exact dose of inhaled steroid can be deemed the correct dose at which to add another therapy; an absolute threshold for introduction of add-on therapy in all patients cannot be defined.

For adults and young people aged over 12 years, the British guideline on the management of asthma recommends an ICS and a long-acting beta-2 agonist (LABA) when add-on therapy is needed. However, before starting a new drug or stepping up treatment, adherence to existing therapies, inhaler technique and appropriate elimination of trigger factors should be confirmed.

If poor control persists after the options at step 3 have been tried (including increasing the dose of ICS to 800 micrograms of beclometasone dipropionate or equivalent), high-dose ICS treatment (up to 2000 micrograms of beclometasone dipropionate or equivalent) or the addition of a fourth drug should be considered (step 4).

Cochrane reviews of regular treatment of chronic asthma with 2 LABAs, formoterol and salmeterol, found that adding a LABA to an ICS can improve lung function and asthma symptoms, and reduce asthma exacerbations. However, the reviews found that the use of LABAs (formoterol and salmeterol) is associated with an increase in the risk of serious adverse events which does not appear to be completely abolished when an ICS is used concurrently.

After assessing the risks and benefits of LABAs in asthma, the Medicines and Healthcare products Regulatory Agency concluded in a Drug Safety Update that the benefits of using a LABA with an ICS outweigh any apparent risks. The Commission on Human Medicines has issued advice for prescribers on the use and safety of LABAs for treating chronic asthma.

Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over (NICE technology appraisal guidance 138) recommends a combination inhaler, within its marketing authorisation, as an option if treatment with an ICS and a LABA is considered appropriate. NICE recommends that the decision to use a combination inhaler or the 2 agents in separate inhalers should be made on an individual basis, taking into consideration therapeutic need and the likelihood of treatment adherence. If a combination inhaler is chosen, then the least costly device that is suitable for the individual is recommended.
Product overview

Drug action

Relvar Ellipta is a combination inhaler containing 2 active ingredients not previously available for the treatment of asthma: fluticasone furoate (an inhaled corticosteroid [ICS]) and vilanterol (a long-acting beta-2 agonist [LABA]). These are administered using the multi-dose, dry-powder Ellipta inhalation device (summaries of product characteristics).

Licensed therapeutic indication

Fluticasone furoate/vilanterol (Relvar Ellipta) received a European marketing authorisation in November 2013. It is licensed for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (LABA and ICS) is appropriate, that is patients not adequately controlled with ICS and 'as needed' inhaled short-acting beta-2 agonists (summaries of product characteristics).

Fluticasone furoate/vilanterol is also licensed for the symptomatic treatment of chronic obstructive pulmonary disease (COPD) in adults with a FEV1 (forced expired volume in 1 second) of less than 70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy. NICE has published an evidence summary: new medicine on the use of fluticasone furoate/vilanterol in COPD. Two strengths of Relvar Ellipta combination inhaler are available. For the COPD indication, only the fluticasone furoate/vilanterol 92/22 microgram strength inhaler is licensed.

Relvar Ellipta was launched in the UK in January 2014.

Course and cost

For the asthma indication, 2 strengths of the Relvar Ellipta combination inhaler (with different doses of fluticasone furoate and the same dose of vilanterol) are available:

- fluticasone furoate 92 micrograms plus vilanterol (as trifenatate) 22 micrograms (the delivered dose leaving the mouthpiece) and
- fluticasone furoate 184 micrograms plus vilanterol (as trifenatate) 22 micrograms (the delivered dose leaving the mouthpiece).
The dose for both strengths is 1 inhalation once a day. The summaries of product characteristics state that a starting dose of Relvar Ellipta 92/22 micrograms should be considered for adults and adolescents 12 years and over who require a low to mid dose of ICS in combination with a LABA. If patients are inadequately controlled on Relvar Ellipta 92/22 micrograms, the dose can be increased to 184/22 micrograms, which may provide additional improvement in asthma control. Patients should be regularly reassessed by a healthcare professional so that the strength of fluticasone furoate/vilanterol they are receiving remains optimal and is only changed on medical advice. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. Relvar Ellipta 184/22 micrograms should be considered for adults and adolescents 12 years and over who require a higher dose of ICS in combination with a LABA. Patients with asthma should be given the strength of Relvar Ellipta containing the appropriate fluticasone furoate dosage for the severity of their disease.

In people with asthma, fluticasone furoate 92 micrograms once a day is approximately equivalent to fluticasone propionate 250 micrograms twice a day and fluticasone furoate 184 micrograms once a day is approximately equivalent to fluticasone propionate 500 micrograms twice a day (summaries of product characteristics).

The British guideline on the management of asthma indicates that 250 micrograms fluticasone propionate twice a day is approximately equivalent to 1000 micrograms beclometasone dipropionate per day and 500 micrograms fluticasone propionate twice a day is approximately equivalent to 2000 micrograms beclometasone dipropionate per day.

The Ellipta device contains 30 inhalations for 30 days of treatment. The cost of the fluticasone furoate/vilanterol 92/22 microgram strength inhaler is £27.80. The cost of the fluticasone furoate/vilanterol 184/22 microgram strength inhaler is £38.87 (MIMS; January 2014).

Evidence review

This evidence review is based on the 2 randomised controlled trials (RCTs) that provide the best published evidence for fluticasone furoate/vilanterol for treating asthma. Woodcock et al. (2013) compared fluticasone furoate/vilanterol 92/22 micrograms once daily with fluticasone propionate/salmeterol 250/50 micrograms twice daily in patients aged 12 years and over with persistent asthma uncontrolled on a medium dose of inhaled corticosteroid. The primary outcome measure was the 0–24 hour serial weighted mean FEV₁ (forced expired volume in 1 second) after 24 weeks of treatment. Bateman et al. (2013) compared fluticasone furoate/vilanterol 92/22 micrograms once daily with fluticasone furoate 92 micrograms once daily for the primary outcome measure of time to first severe asthma exacerbation in patients aged 12 years and over with asthma and 1 or
more recorded exacerbations within the previous year. A 52-week safety study (Busse et al. 2013) assessed the safety and tolerability of fluticasone furoate/vilanterol in patients with asthma aged 12 years and over and is discussed in the safety section.

The European public assessment report (EPAR) for Relvar Ellipta describes and discusses 3 studies in detail: the Bateman et al. (2013) study and 2 other studies not included in detail in this evidence summary. One of these studies (O’Byrne et al. 2013) compared fluticasone furoate/vilanterol 184/22 micrograms once daily with fluticasone furoate 184 micrograms once daily and fluticasone propionate 500 micrograms twice daily over a 24-week period. The co-primary outcome measures for this study were the change from baseline in trough FEV₁ and weighted mean 0–24 hour serial FEV₁. This study is briefly discussed in the clinical effectiveness section. The other study (NCT01165138) compared fluticasone furoate/vilanterol 92/22 micrograms once daily with fluticasone furoate 92 micrograms once daily and placebo over a 12-week period. The co-primary outcome measures for this study were the change from baseline in trough FEV₁ and weighted mean 0–24 hour serial FEV₁.

The studies reviewed in this evidence summary were chosen as they provide the best published evidence for fluticasone furoate/vilanterol for treating asthma. Bateman et al. (2013) has a patient-orientated primary outcome and Woodcock et al. (2013) provides comparison with a currently available ICS/LABA combination inhaler.

An ongoing, open-label study (NCT01706198) is investigating the effectiveness and safety of fluticasone furoate/vilanterol compared with existing asthma maintenance treatment (inhaled corticosteroid [ICS] alone or ICS/LABA [long-acting beta-2 agonist]). The primary outcome measure is the percentage of participants who have an Asthma Control Test score of 20 or more at week 24. The estimated completion date for the study is currently under review by the manufacturers (GlaxoSmithKline: personal communication February 2014).

Woodcock et al. (2013)

- Design: 24-week randomised, double-blind, double-dummy, parallel group study. Allocation was concealed. There was a 4-week run-in period in which the participants’ current asthma medication was replaced with fluticasone propionate 250 micrograms twice daily and salbutamol.

- Population: 806 adults and young people aged 12 years or older (mean age 43 years; 61% female) with asthma who had been taking ICS for at least 12 weeks with a stable medium dose (defined as fluticasone propionate 250 micrograms twice a day or equivalent) for at least 4 weeks. Participants had to have a minimum reversibility of FEV₁ of 12% and 200 ml after
salbutamol inhalation at screening. At baseline (prior to the 4-week run-in period on ICS alone) 31% were taking ICS and 69% were taking ICS/LABA. Current smokers with a smoking history of at least 10 pack-years and participants who had had an asthma exacerbation that needed oral corticosteroids or hospitalisation within the previous 12 weeks were excluded from the study. The study involved 65 participating centres in 6 countries.

- Intervention and comparison: participants were randomised in approximately equal numbers to fluticasone furoate/vilanterol 100/25 micrograms (delivered dose 92/22 micrograms) once daily or fluticasone propionate/salmeterol 250/50 micrograms twice a day.

- Outcomes: The primary efficacy outcome was change from baseline in 0–24 hour serial weighted mean FEV₁ after 24 weeks of treatment. The study was designed to detect a difference of 80 ml between fluticasone furoate/vilanterol and fluticasone propionate/salmeterol. Secondary and additional outcomes included change from baseline in the mean score of the Asthma Quality of Life +12 Questionnaire (AQLQ+12) and change from baseline in the mean score of the Asthma Control Test. Adverse events could be reported throughout the study. Other safety assessments included severe asthma exacerbations and 24-hour urinary cortisol excretion.

Table 1 Summary of Woodcock et al. (2013)

<table>
<thead>
<tr>
<th>Efficacy (ITT population)</th>
<th>Fluticasone furoate/vilanterol 92/22 micrograms once daily</th>
<th>Fluticasone propionate/salmeterol 250/50 micrograms twice daily</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–24 hour wm FEV₁ week-24 change from baseline</td>
<td>341 ml</td>
<td>377 ml</td>
<td>No statistically significant difference between groups Adjusted mean treatment difference: −37 ml (95% CI −88 to 15 ml) p=0.162</td>
</tr>
<tr>
<td>Selected secondary and additional outcomes:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean baseline score: 5.35</td>
<td>Mean baseline score: 5.37</td>
<td>No statistically significant difference between groups 0.09 (95% CI −0.03 to 0.21)</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>---------------------------</td>
<td>---------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>AQLQ+12 week-24 change from baseline</td>
<td>LS mean change from baseline: 0.46 (SE 0.043)</td>
<td>LS mean change from baseline: 0.37 (SE 0.043)</td>
<td></td>
</tr>
<tr>
<td>ACTb week-24 change from baseline</td>
<td>Mean baseline score: 18.9</td>
<td>Mean baseline score: 18.8</td>
<td>No statistically significant difference between groups 0.2 (95% CI −0.2 to 0.7)</td>
</tr>
<tr>
<td></td>
<td>LS mean change from baseline: 2.3 (SE 0.16)</td>
<td>LS mean change from baseline: 2.0 (SE 0.16)</td>
<td></td>
</tr>
<tr>
<td>Safety (ITT population)</td>
<td>403</td>
<td>403</td>
<td></td>
</tr>
<tr>
<td>Patients reporting serious adverse events</td>
<td>1.0% (4/403)</td>
<td>1.2% (5/403)</td>
<td>No statistical analysis presented</td>
</tr>
<tr>
<td>Adverse events leading to discontinuation or withdrawal</td>
<td>1.5% (6/403)</td>
<td>2.0% (8/403)</td>
<td>No statistical analysis presented</td>
</tr>
<tr>
<td>Asthma exacerbations</td>
<td>2%</td>
<td>3%</td>
<td>No statistical analysis presented</td>
</tr>
</tbody>
</table>
| 24-hour UC excretion week-24 ratio to baseline | 1.11                      | 1.21                      | Increased in both groups from baseline. No statistically significant difference between groups: adjusted treatment ratio 0.85; 95% CI 0.72 to 1.02; p=0.075.
a The AQLQ+12 is a modified version of the AQLQ valid for use in adults and young people from 12 to 70 years of age. The AQLQ contains 32 questions. Each question is on a 7-point scale (from 1 severely impaired to 7 not impaired at all). The overall AQLQ score is the mean of all 32 responses.

b The Asthma Control Test is a patient self-assessment tool of asthma control. A score of less than 20 indicates that asthma may not have been controlled over the past 4 weeks, a score of 20 to 24 indicates reasonable asthma control over the past 4 weeks and a score of 25 indicates that asthma has been under control over the past 4 weeks.

Bateman et al. (2013)

- Design: randomised, double-blind, parallel group study of variable duration (from a minimum of 24 weeks to a maximum of 78 weeks). The mean study duration was reported as 52.0 to 52.7 weeks. Allocation was concealed. There was a 2-week run-in period during which baseline safety evaluations and measures of asthma status were conducted.

- Population: 2019 adults and young people aged 12 years or older (mean age 42 years; 67% female) with asthma who had had 1 or more asthma exacerbations that needed systemic corticosteroids or a hospital visit in the previous year and who were taking ICS (at a dose of at least fluticasone propionate 200 micrograms a day or equivalent) or ICS plus a long-acting beta-2 agonist (at an ICS dose of fluticasone propionate 200 to 500 micrograms a day or equivalent) for 12 weeks or more before study entry with a stable dose for the previous 4 weeks. Participants had to have a minimum reversibility of FEV₁ of 12% and 200 ml after salbutamol inhalation at screening. At baseline 39.5% were taking ICS and 60.5% were taking ICS/LABA. The study involved 167 centres in 11 countries.

- Intervention and comparison: participants were randomised in approximately equal numbers to fluticasone furoate/vilanterol 100/25 micrograms (delivered dose 92/22 micrograms) once daily and fluticasone furoate 100 micrograms (delivered dose 92 micrograms) once daily.

- Outcomes: the primary outcome was time to first severe asthma exacerbation. A severe asthma exacerbation was defined as a deterioration of asthma needing the use of systemic corticosteroids for at least 3 days or inpatient hospitalisation or hospital visit owing to asthma needing systemic corticosteroids. The study was designed to finish after 330 severe asthma exacerbations had occurred. Secondary outcomes included the rate of severe asthma exacerbations per patient per year. Safety outcomes relating to severe asthma exacerbations
included the number of hospitalisations, accident and emergency or urgent care visits, unscheduled healthcare provider visits and intubations for an asthma event.

Table 2 Summary of Bateman et al. (2013)

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Fluticasone furoate/vilanterol 92/22 micrograms once daily</th>
<th>Fluticasone furoate 92 micrograms once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised</td>
<td>1009</td>
<td>1011</td>
</tr>
<tr>
<td>Efficacy (ITT population)</td>
<td>1009</td>
<td>1010</td>
</tr>
</tbody>
</table>

**Primary outcome:**

Time to first severe asthma exacerbation – adjusted probability of a severe asthma exacerbation by 52 weeks

- Fluticasone furoate/vilanterol 92/22 micrograms once daily: 12.8% (95% CI 10.7% to 14.9%)
- Fluticasone furoate 92 micrograms once daily: 15.9% (95% CI 13.5% to 18.2%)
- HR 0.795 (95% CI 0.642 to 0.985); p=0.036

**Selected secondary and additional outcomes:**

- Rate of severe asthma exacerbations per patient per year: 0.14, 0.19
  - Rate reduction 25% (95% CI 5% to 40%); p=0.014

- Number of participants who had 1 or more on-treatment severe asthma exacerbations: 154 (15%), 186 (18%)
  - No statistical analysis presented

**Safety (ITT population):**

- Patients reporting serious adverse events: 4.1% (41/1009), 2.9% (29/1010)
  - No statistical analysis presented

- Adverse events leading to discontinuation or withdrawal: 1.6% (16/1009), 1.9% (19/1010)
  - No statistical analysis presented
Clinical effectiveness

Woodcock et al. (2013) found that there was no statistically significant difference between fluticasone furoate/vilanterol 92/22 micrograms once daily and fluticasone propionate/salmeterol 250/50 micrograms twice daily for the 0–24 hour weighted mean FEV₁ week-24 change from baseline (see table 1). The study was designed to show superiority of fluticasone furoate/vilanterol over fluticasone propionate/salmeterol and powered to detect a difference of 80 ml in the serial weighted mean FEV₁ between the 2 groups. Secondary and additional outcomes for this study included a number of patient-orientated outcomes. It was reported that there was no statistically significant difference between the 2 groups for the mean week-24 change from baseline for the Asthma Control Test or the AQLQ+12. However, because the primary outcome was not statistically significant the secondary outcomes should be regarded as descriptive only.

The Asthma Control Test is a patient self-assessment tool of asthma control. A score of less than 20 indicates that asthma may not have been controlled over the past 4 weeks, a score of 20 to 24 indicates reasonable asthma control over the past 4 weeks and a score of 25 indicates that asthma has been under control over the past 4 weeks. Participants in both groups showed a slight improvement in Asthma Control Test scores at week 24 compared with baseline (from 18.9 to 21.2 with fluticasone furoate/vilanterol and from 18.8 to 20.9 with fluticasone propionate/salmeterol). The British guideline on the management of asthma states that the minimally clinically important difference for the Asthma Control Test has not been defined.

The AQLQ+12 is a modified version of the AQLQ valid for use in adults and young people aged 12 to 70 years. The AQLQ contains 32 questions that are answered on a scale ranging from 1 (severe impairment) to 7 (no impairment). The overall AQLQ score is the mean of all 32 responses. The British guideline on the management of asthma states that the minimal important difference for the AQLQ is 0.5 and this is also suggested by the authors of the study. There was an improvement in this score of less than 0.5 in both groups (0.46 for fluticasone furoate/vilanterol and 0.37 for fluticasone propionate/salmeterol).

Bateman et al. (2013) found that there was a statistically significant reduction from 15.9% to 12.8% (adjusted probability) in the risk of having a severe asthma exacerbation by 52 weeks with
fluticasone furoate/vilanterol 92/22 micrograms once daily compared with fluticasone furoate 92 micrograms once daily. This is a reduction of approximately 20% in relative terms. A total of 340 participants had 471 severe exacerbations (154 participants in the fluticasone furoate/vilanterol group had 200 exacerbations and 186 participants in the fluticasone furoate group had 271 exacerbations). There was a statistically significant reduction from 0.19 to 0.14 in the rate of severe exacerbations per patient per year with fluticasone furoate/vilanterol compared with fluticasone furoate. The rate of severe exacerbations was low in both groups despite the fact that all participants were required to have had a severe asthma exacerbation during the 12 months before randomisation. Some participants in the study may have received a step-up in ICS dose after randomisation and some may have received a similar dose. It is unclear whether the mean ICS dose before randomisation was similar between the 2 groups (see Evidence strengths and limitations).

O’Byrne et al. 2013 (n=586) compared fluticasone furoate/vilanterol 184/22 micrograms once daily with fluticasone furoate 184 micrograms once daily and fluticasone propionate 500 micrograms twice daily over a 24-week period. The co-primary outcome measures for this study were the change from baseline in trough FEV\textsubscript{1} and weighted mean 0–24 hour serial FEV\textsubscript{1}. Fluticasone furoate/vilanterol statistically significantly improved trough FEV\textsubscript{1} compared with both fluticasone furoate and fluticasone propionate. The difference in mean change from baseline was 193 ml (95% CI 108 to 277 ml; p<0.001) compared with fluticasone furoate and 210 ml (95% CI 127 to 294 ml; p<0.001) compared with fluticasone propionate. There was also a statistically significant improvement in weighted mean 0–24 hour serial FEV\textsubscript{1} with fluticasone furoate/vilanterol compared with both fluticasone furoate and fluticasone propionate. The difference in mean change from baseline was 136 ml compared with fluticasone furoate (95% CI 1 to 270 ml; p=0.048) and 206 ml (95% CI 73 to 339 ml; p=0.003) compared with fluticasone propionate. For the secondary outcome measure of mean change from baseline in percentage of rescue-free 24-hour periods there was a statistically significant difference between fluticasone furoate/vilanterol and fluticasone furoate (11.7%; 95% CI 4.9 to 18.4%; p<0.001). However, there was no statistically significant difference between fluticasone furoate/vilanterol and fluticasone propionate for this outcome measure (6.3%; 95% CI −0.4 to 13.1%; p=0.067).

**Safety**

According to the summaries of product characteristics, during asthma and chronic obstructive pulmonary disease (COPD) clinical trials, the most commonly reported (1/10 or more) adverse reactions with fluticasone furoate/vilanterol were headache and nasopharyngitis. With the exception of pneumonia and fractures, the safety profile was similar in participants with asthma and COPD. During clinical studies, pneumonia and fractures were more frequently commonly seen in participants with COPD. Other common (1/100 or more to less than 1/10) adverse reactions
that have been reported include candidiasis of the mouth and throat, upper respiratory tract infections, bronchitis, dysphonia, pyrexia, abdominal pain, arthralgia, back pain and oropharyngeal pain.

For people with moderate or severe hepatic impairment the summaries of product characteristics advise that the 92/22 microgram strength inhaler should be used and patients should be monitored for systemic corticosteroid-related adverse reactions. The summaries of product characteristics also advise avoiding the use of concomitant strong CYP3A4 inhibitors such as ketoconazole. The summaries of product characteristics include special warnings and precautions for use of fluticasone furoate/vilanterol if there is deterioration of disease; possible systemic corticosteroid effects of fluticasone furoate/vilanterol use; and cardiovascular effects, including advice that fluticasone furoate/vilanterol should be used with caution in people with severe cardiovascular disease.

Busse et al. 2013 was a 52-week randomised, multicentre, double-blind, double-dummy, active comparator, parallel group study. The aim of the study was to assess the safety and tolerability of fluticasone furoate/vilanterol 92/22 micrograms and 184/22 micrograms in participants aged 12 years and over with asthma who were currently using an inhaled corticosteroid with or without additional controller medication. After a 2-week run-in period, 503 participants (mean age 39 years) were randomised 2:2:1 to fluticasone furoate/vilanterol 92/22 micrograms once daily, fluticasone furoate/vilanterol 184/22 micrograms once daily or fluticasone propionate 500 micrograms twice daily. The incidence of adverse events, severe adverse events and severe asthma exacerbations were recorded throughout the study. Statistical analysis was performed on the intention-to-treat population but it was not provided for the majority of outcomes.

The incidence of any on-treatment adverse event was similar across all 3 groups (66% to 73%). Headache and upper respiratory tract infections were the most commonly reported adverse events; with similar rates reported across all 3 groups. Oral/oropharyngeal candidiasis was more common with fluticasone furoate/vilanterol at both strengths than with fluticasone propionate (6 to 7% compared with 3%). No clinically important changes were reported for ophthalmic assessments, QT interval (corrected using Fridericia’s formula), non-fasting glucose or potassium levels. Extrasystoles (bigeminy or trigeminy on Holter recording) were more common in the fluticasone furoate/vilanterol 184/22 micrograms group (7%) compared with the 92/22 microgram strength inhaler group (2%) or the fluticasone propionate group (3%). Non-sustained ventricular tachycardia was seen in 2 participants from each fluticasone furoate/vilanterol group and sustained supraventricular tachycardia was seen in 3 participants in the fluticasone furoate/vilanterol 184/22 microgram group. During the treatment period 3 participants (1%) in the fluticasone furoate/vilanterol 92/22 microgram group, 6 participants (3%) in the fluticasone...
furoate/vilanterol 184/22 microgram group and 3 participants (3%) in the fluticasone propionate group had a severe asthma exacerbation.

In Woodcock et al. (2013) there was no statistically significant difference between fluticasone furoate/vilanterol 92/22 micrograms once daily and fluticasone propionate/salmeterol 250/50 micrograms twice daily in the 24-hour urinary cortisol excretion week-24 ratio to baseline, although it was increased in both groups. In Busse et al. 2013, urinary cortisol measurements were available for 362 participants. Statistically significant cortisol suppression was seen with fluticasone propionate 500 micrograms twice daily compared with both fluticasone furoate/vilanterol groups at week 12 and week 28 but not at week 52. However, using information from the intention-to-treat population the majority of participants had 'normal' or 'no change' from baseline in 24-hour urinary cortisol at any post-baseline visit (76% to 81% in the fluticasone furoate/vilanterol groups and 70% in the fluticasone propionate group). As fluticasone furoate is a new inhaled corticosteroid, more information on its effect on cortisol suppression relative to other inhaled corticosteroids is needed.

In Woodcock et al. (2013) rates of serious adverse events and adverse events leading to withdrawal from the study were similar between fluticasone furoate/vilanterol 92/22 micrograms once daily and fluticasone propionate/salmeterol 250/50 micrograms twice daily, although no statistical analysis was given (see table 1).

In Bateman et al. (2013) rates of adverse events leading to withdrawal from the study and serious asthma-related adverse events were similar between fluticasone furoate/vilanterol 92/22 micrograms once daily and fluticasone furoate 92 micrograms once daily; no statistical analysis was presented (see table 2).

**Evidence strengths and limitations**

Woodcock et al. (2013) was designed as a superiority study and powered to detect a difference of 80 ml in the serial weighted mean FEV₁ between the 2 groups, a disease-orientated outcome. However, the study found no statistically significant difference between fluticasone furoate/vilanterol 92/22 micrograms once daily and fluticasone propionate/salmeterol 250/50 micrograms twice daily.

This study included patient orientated secondary and additional outcomes, including mean week-24 change from baseline for the Asthma Control Test or the AQOL+12 questionnaire. However, because the primary outcome was not statistically significant the secondary outcomes should be regarded as descriptive only.
Whilst Bateman et al. (2013) did look at a patient-orientated primary outcome, time to first severe exacerbation, the study compared fluticasone furoate/vilanterol 92/22 micrograms once daily with fluticasone furoate 92 micrograms alone once daily, which is not available as ICS monotherapy. There are no published studies that compare fluticasone furoate/vilanterol at either strength with a currently available ICS/LABA combination inhaler or currently available ICS monotherapy for a patient-orientated primary outcome such as exacerbation rate.

In Woodcock et al. (2013) participants had to have been taking a stable dose of ICS at a dosage of fluticasone propionate 250 micrograms twice daily or equivalent for at least 4 weeks before study entry, and 69% of the study population were already taking an ICS/LABA combination inhaler. Therefore 69% of participants were at step 3 or 4 of the British guideline on the management of asthma before study entry. Caution is needed in extrapolating the results of this study to people with less severe asthma; for example, people whose asthma is inadequately controlled on regular-dose ICS alone (step 2).

In Bateman et al. (2013) participants had to be using ICS at a daily dose of at least 200 micrograms fluticasone propionate or equivalent and 60% were using an ICS/LABA combination inhaler (with a daily ICS dose of 200 to 500 micrograms fluticasone propionate or equivalent) before study entry. Therefore 60% of participants were at step 3 or 4 of the British guideline on the management of asthma before study entry. Although there was an equal distribution between the 2 groups in the number of participants who were using ICS alone and the number using an ICS/LABA combination inhaler before study entry, it is unclear whether the mean ICS dose before study entry was similar between the 2 groups. This may have caused bias in the results; some participants would have received a step-up in ICS dose after randomisation whereas others would have received a similar dose to that prior to randomisation.

There are limited published efficacy data available for the higher strength inhaler. Woodcock et al. (2013) and Bateman et al. (2013) did not include the fluticasone furoate/vilanterol 184/22 microgram inhaler in their studies. O’Byrne et al. (2013) did compare fluticasone furoate/vilanterol 184/22 micrograms once daily with fluticasone furoate 184 micrograms once daily and fluticasone propionate 500 micrograms twice daily, but for disease-orientated primary outcome measures.
**Context**

**Treatment alternatives**

Four other ICS/LABA (inhaled corticosteroid/long-acting beta-2 agonist) combination inhalers are licensed in the UK for the treatment of asthma:

- fluticasone propionate/salmeterol (Seretide) metered-dose inhaler and dry-powder inhaler
- fluticasone propionate/formoterol (Flutiform) metered-dose inhaler
- budesonide/formoterol (Symbicort) dry-powder inhaler
- beclometasone/formoterol (Fostair) metered-dose inhaler.

The ICS/LABA combination inhalers listed above differ in their licensing status and recommended dosing for use in children and young people aged under 18 years. Please refer to the relevant summaries of product characteristics for full details.

NICE has published an evidence summary: new medicine on the use of fluticasone propionate/formoterol (Flutiform) in asthma.

**Costs of treatment alternatives**

<table>
<thead>
<tr>
<th></th>
<th>Beclometasone dipropionate CFC(^a) equivalent: 400 micrograms</th>
<th>Beclometasone dipropionate CFC(^a) equivalent: 800 to 1000 micrograms</th>
<th>Beclometasone dipropionate CFC(^a) equivalent: 1600 to 2000 micrograms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seretide Accuhaler(^b)</td>
<td>100/50 micrograms 1 inhalation twice a day £18.00 60-dose unit</td>
<td>250/50 micrograms 1 inhalation twice a day £35.00 60-dose unit</td>
<td>500/50 1 inhalation twice a day £40.92 60-dose unit</td>
</tr>
<tr>
<td>Flutiform metered-dose inhaler</td>
<td>50/5 micrograms 2 puffs twice a day</td>
<td>125/5 micrograms 2 puffs twice a day</td>
<td>250/10 micrograms 2 puffs twice a day</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------</td>
<td>-------------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>120-dose unit</td>
<td>£18.00</td>
<td>£29.26</td>
<td>£45.56</td>
</tr>
<tr>
<td>Fostair metered-dose inhaler</td>
<td>100/6 micrograms 1 puff twice a day</td>
<td>100/6 micrograms 2 puffs twice a day</td>
<td>Not available</td>
</tr>
<tr>
<td>120-dose unit</td>
<td>£14.66 for 30 days</td>
<td>£29.32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Based on a 120-dose unit at £29.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symbicort dry-powder inhaler</td>
<td>200/6 micrograms 1 inhalation twice a day</td>
<td>400/12 micrograms 1 inhalation twice a day</td>
<td>400/12 micrograms 2 inhalations twice a day</td>
</tr>
<tr>
<td></td>
<td>£19.00 for 30 days</td>
<td>£38.00</td>
<td>£76.00</td>
</tr>
<tr>
<td></td>
<td>Based on a 120-dose unit at £38.00</td>
<td></td>
<td>2×60-dose units</td>
</tr>
</tbody>
</table>

Please refer to the relevant summaries of product characteristics for full details.


The Ellipta device contains 30 inhalations for 30 days of treatment. The cost of the fluticasone furoate/vilanterol 92/22 microgram strength inhaler is £27.80. The cost of the fluticasone furoate/vilanterol 184/22 microgram strength inhaler is £38.87 (MIMS: January 2014).
Estimated impact for the NHS

Likely place in therapy

Relvar Ellipta is a combination inhaler containing 2 active ingredients not previously available for the treatment of asthma: fluticasone furoate and vilanterol. There are no published studies that compare fluticasone furoate/vilanterol at either strength with a currently available ICS/LABA (inhaled corticosteroid/long-acting beta-2 agonist) combination inhaler or currently available ICS monotherapy for a patient-orientated primary outcome such as exacerbation rate. There are limited published efficacy data available for the higher-strength inhaler. In addition, because fluticasone furoate is a new ICS, more information on its effect on cortisol suppression relative to other ICSs is needed.

Relvar Ellipta is licensed for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (LABA and ICS) is appropriate, that is patients not adequately controlled with ICS and 'as needed' inhaled short-acting beta-2 agonists. It is not licensed for use in patients who are already controlled on both an ICS and a LABA, unlike the other 4 ICS/LABA combination inhalers licensed in the UK for the treatment of asthma (summaries of product characteristics). The initial asthma indication applied for did include this 'substitution' indication for people whose condition is already controlled by an ICS and a LABA. However, the Committee for Medicinal Products for Human Use did not consider this indication acceptable for Relvar Ellipta because no direct comparison between fluticasone furoate/vilanterol and an approved fixed-dose combination of an ICS and a LABA was submitted with the application (European public assessment report).

For adults and young people aged over 12 years, the British guideline on the management of asthma recommends a trial of ICS plus LABA when asthma is uncontrolled by an ICS alone. The British guideline on the management of asthma recommends that consideration should be given to adding a LABA before increasing the dosage to above 400 micrograms beclometasone dipropionate equivalents per day and certainly before increasing the dosage to above 800 micrograms beclometasone dipropionate equivalents per day. The Relvar Ellipta inhaler is available at 2 different strengths of fluticasone furoate: 92 micrograms and 184 micrograms. In people with asthma fluticasone furoate 92 micrograms once a day is approximately equivalent to fluticasone propionate 250 micrograms twice a day and fluticasone furoate 184 micrograms once a day is approximately equivalent to fluticasone propionate 500 micrograms twice a day (summaries of product characteristics). The British guideline on the management of asthma indicates that 250 micrograms fluticasone propionate twice a day is approximately equivalent to
1000 micrograms beclometasone dipropionate per day and 500 micrograms fluticasone propionate twice a day is approximately equivalent to 2000 micrograms beclometasone dipropionate per day.

The British guideline on the management of asthma recommends stepping down therapy once asthma is controlled, but this recommendation is often not implemented, leaving some people overtreated. Regular review as treatment is stepped down is important. The lowest-strength fluticasone furoate/vilanterol inhaler available is fluticasone furoate/vilanterol 92/22 micrograms once a day. As previously stated, in people with asthma fluticasone furoate 92 micrograms once a day is approximately equivalent to fluticasone propionate 250 micrograms twice a day. Because a lower strength is not available, the ability to step down treatment is limited.

Because of their different potencies and dosing frequencies, there is a potential risk of medication errors with fluticasone furoate and fluticasone propionate-containing inhalers.

Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over (NICE technology appraisal guidance 138) recommends that the decision on whether to prescribe a combination device or separate devices should be made on an individual basis, taking into consideration therapeutic need and the likelihood of treatment adherence. If a combination device is chosen the guidance recommends the least costly device that is suitable for the individual, within its marketing authorisation.

Local decision-makers will need to consider the available evidence on efficacy and safety, as well as the licensed indication, cost and individual patient factors, when making decisions about using Relvar Ellipta or another ICS/LABA combination inhaler.

Estimated usage

The manufacturers of Relvar Ellipta (GlaxoSmithKline) estimate that there are currently 935,000 people with asthma who are prescribed ICS monotherapy (plus as-needed short-acting beta-2 agonists). They estimate that 40% of these people have poorly controlled asthma. Therefore, approximately 374,000 people may be eligible for combined ICS/LABA treatment.

References

Bateman E, O’Byrne PM, Busse WW et al. (2013) Once-daily fluticasone furoate/vilanterol reduces risk of severe exacerbations in asthma versus fluticasone furoate alone. Thorax doi:10.1136/thoraxjnl-2013-203600
British Thoracic Society and Scottish Intercollegiate Guidelines Network (2012) British guideline on the management of asthma. SIGN guideline 101

Busse WW, O’Byrne P, Bleecker ER et al. (2013) Safety and tolerability of the novel inhaled corticosteroid fluticasone furoate in combination with the β₂-agonist vilanterol administered once daily for 52 weeks in patients ≥ 12 years old with asthma: a randomised trial. Thorax 68: 513–20


Cates CJ and Lasserson TJ (2010) Regular treatment with formoterol and an inhaled corticosteroid versus regular treatment with salmeterol and an inhaled corticosteroid for chronic asthma: serious adverse events. Cochrane Database of Systematic Reviews issue 1: CD007694

European Medicines Agency (2013): European Public Assessment report: Relvar Ellipta (EMEA/H/C/002673/0000) [online; accessed 9 January 2014]


O’Byrne PM, Bleecker ER, Bateman ED et al. (2103). Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. European Respiratory Journal doi: 10.1183/09031936.00064513

Woodcock A, Bleecker ER, Lotvall J et al. (2013) Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma. Chest. 144: 1222–1229

Changes after publication

12 March 2014:

The text in this evidence summary has been altered to make it clear that Relvar Ellipta is a combination inhaler containing 2 active ingredients not previously available for the treatment of asthma: fluticasone furoate (an inhaled corticosteroid) and vilanterol (a long-acting beta-2 agonist). Fluticasone furoate was previously only available as a nasal spray (Avamys) for the prophylaxis and treatment of allergic rhinitis.

This change does not alter the key messages of the evidence summary.

About this evidence summary

‘Evidence summaries: new medicines’ provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.

For information about the process used to develop this evidence summary, see Evidence summaries: new medicines – integrated process statement.

Copyright

© National Institute for Health and Care Excellence, 2014. All rights reserved. NICE copyright material can be downloaded for private research and study, and may be reproduced for educational and not-for-profit purposes. No reproduction by or for commercial organisations, or for commercial purposes, is allowed without the written permission of NICE.

ISBN: 978-1-4731-0468-6