

# Chronic urticaria: off-label doses of cetirizine

Evidence summary

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## Key points from the evidence

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

## Summary

Overall, 2 small [randomised controlled trials](#) (RCTs) and 2 double-blind [crossover studies](#) (total n=76) suggest that cetirizine 20 mg daily may improve weals and itching in adults with severe chronic urticaria refractory to standard doses of antihistamines. However, symptoms remain in a proportion of people and the studies have many limitations. Nevertheless, cetirizine 20 mg appears to be well tolerated and the benefits may outweigh the risks for some people whose quality of life is significantly impaired by the condition. No data are available from high quality studies on the use of cetirizine at doses higher than 20 mg.

**Regulatory status:** Cetirizine is licensed for the relief of symptoms of chronic idiopathic urticaria at a dose of 10 mg daily in adults. The use of higher doses of cetirizine, as discussed in this evidence summary, is off-label.

Effectiveness	Safety
<ul style="list-style-type: none"> <li>• Four small studies suggest that cetirizine 20 mg daily may improve symptoms in adults with severe chronic urticaria.</li> <li>• In <a href="#">Okubo et al (2013)</a>, itching and weals improved in people who took cetirizine 20 mg daily or olopatadine 5 mg twice daily as a dose increase from cetirizine 10 mg. However, improvements were not statistically significant (n=18).</li> <li>• In <a href="#">Kameyoshi et al (2007)</a>, urticarial symptom scores were statistically significantly improved in people who continued on cetirizine 20 mg daily after a dose increase from 10 mg daily, compared to people who had a dose increase to 20 mg daily for 1–2 weeks and who then were stepped down to 10 mg daily for 1–2 weeks (n = 21; <math>p &lt; 0.01</math>).</li> <li>• In <a href="#">Zuberbier et al (1996)</a>, a double blind crossover study (n=11), a statistically significant reduction was seen in all urticarial symptoms with cetirizine 20 mg compared with placebo (<math>p=0.013</math>).</li> <li>• In <a href="#">Zuberbier et al (1995)</a>, a double blind crossover study (n=24), the only significant difference between cetirizine 10 mg and 20 mg was in improvement of weals (<math>p=0.04</math>); it is not reported which dose was more effective.</li> </ul>	<ul style="list-style-type: none"> <li>• Few adverse effects were reported in the 4 studies in this evidence summary.</li> <li>• According to the summaries of product characteristics (for example, <a href="#">Zirtek</a>), cetirizine 10 mg daily has minor central nervous system adverse effects including somnolence, fatigue, dizziness and dry mouth.</li> </ul>

Patient factors	Resource implications
<ul style="list-style-type: none"><li>Chronic urticaria can significantly reduce quality of life and is sometimes refractory to standard treatment. From the limited evidence available, cetirizine 20 mg appears to be well tolerated. Some people may be prepared to risk adverse effects such as drowsiness in order to reduce symptoms.</li><li>Little information is available on the use of off-label doses of cetirizine in children and young people under 16 years, or adults over 65 years.</li><li>No information is available from RCTs on the use of doses above 20 mg cetirizine.</li></ul>	<ul style="list-style-type: none"><li>According to the <a href="#">Drug Tariff</a> (May 2014), the cost of 30 cetirizine 10 mg tablets is £1.06.</li></ul>

## Introduction and current guidance

Urticaria is a superficial swelling of the skin that results in a red, raised, itchy rash (weals). Acute urticaria may be caused by allergy to foods, drugs, irritants, insect bites and stings, physical stimuli and viral infection. It is usually a self-limiting, one-off episode. By contrast, the cause of many cases of chronic urticaria cannot be identified and it may remit and relapse, triggered by, for example, viral illness, stress, or drugs. In chronic urticaria, symptoms last for more than 6 weeks (recurrence of acute symptoms or persistent symptoms) and may last for months or years ([NICE Clinical knowledge summary: urticaria](#)).

The underlying cause of urticaria should be identified and managed, if possible. People with urticaria who need treatment should be offered a non-sedating antihistamine at the standard licensed dose. People with severe urticaria may also be given a short course of oral corticosteroids. If response to treatment is inadequate, it is common practice to increase the dose of non-sedating antihistamine when the potential benefits are considered to outweigh the risks ([British Society for Allergy and Clinical Immunology guidelines for the management of chronic urticaria and angio-oedema, 2007](#)).

Cetirizine is licensed for the relief of symptoms of chronic idiopathic urticaria at a dose of 10 mg daily in adults. This evidence summary looks at the evidence supporting the off-label use of high doses of cetirizine for chronic urticaria.

[Full text of Introduction and current guidance.](#)

## Product overview

Cetirizine is a non-sedating antihistamine, which is licensed for the relief of symptoms of chronic idiopathic urticaria at a dose of 10 mg daily in adults and young people aged over 12 years. Lower doses are licensed for use in children. Use of higher doses of cetirizine is off-label.

[Full text of Product overview.](#)

## Evidence review

This evidence summary is based on 2 small RCTs and 2 double-blind crossover studies that assessed the safety and efficacy of doses of cetirizine higher than 10 mg for treating chronic urticaria in people with symptoms that are unresponsive to standard doses of antihistamines.

- [Okubo et al \(2013\)](#) was an open-label study in which 51 people with chronic urticaria took cetirizine 10 mg daily for a mean of 10.1 days. People whose urticaria was refractory to cetirizine 10 mg (n=18) in the first treatment period were subsequently randomised to receive cetirizine 20 mg daily or olopatadine (an antihistamine which is only available as an eye drop in the UK) 5 mg twice daily in a second treatment period for a mean of 13.3 days. Of the 33 people whose symptoms responded to cetirizine 10 mg in the first treatment period, 22 continued this treatment. In the second treatment period, the severity of weals improved in all groups: itching improved with cetirizine 20 mg and olopatadine but worsened with cetirizine 10 mg. No changes were statistically significant. Remission was achieved in 81.3% of people who continued cetirizine 10 mg, 66.7% of people in the cetirizine 20 mg group and 42.9% of people in the olopatadine group, with no statistically significant differences between the groups.

- [Kameyoshi et al \(2007\)](#) was an open-label study in which, following a screening period with cetirizine 10 mg daily, 21 people with chronic idiopathic urticaria who had an inadequate response to the 10 mg dose received cetirizine 10 mg twice daily for 1–2 weeks. Subsequently, 1 group continued the 20 mg dosage, whereas the other group reverted to the 10 mg dosage for a further 1–2 weeks. In the first 1- to 2-week period, urticarial symptom scores were statistically significantly lower than in the screening period in both groups ( $p < 0.01$  for weals, duration, itch and total scores). In the group that continued treatment with cetirizine 20 mg, urticarial symptom scores continued to improve in the second treatment period. By contrast, in the group that reverted to 10 mg, the weal, itch and total scores began to increase again, and by the end of the study the weal and itch scores were not significantly different from those seen in the screening period.
- [Zuberbier et al \(1996\)](#) was a double-blind crossover study in 13 adults with confirmed cholinergic urticaria (generally triggered by physical exercise or a hot shower or bath). People were randomised to either placebo or cetirizine 20 mg daily for 3 weeks before switching to the alternative treatment. In the 11 people analysed (2 were excluded because of lack of adherence), a statistically significant reduction was seen with cetirizine compared with placebo for weals ( $p = 0.015$ ), erythema ( $p = 0.033$ ), itching ( $p = 0.006$ ) and all symptoms ( $p = 0.013$ ).
- [Zuberbier et al \(1995\)](#) was a double-blind crossover study in 25 adults with confirmed cholinergic urticaria (triggered by exercise, stress and heat). People were randomised to receive cetirizine 10 mg or 20 mg daily for 3 weeks (double blind), followed by a 3-week washout period on placebo (single blind) and another 3-week period with the alternative dose of cetirizine. One person was excluded because of incorrect inclusion criteria. The difference between the 2 doses of cetirizine was significant for weals only ( $p = 0.04$ ); it is not reported which dose was more effective. The average proportion of days with mild or no symptoms was statistically significantly higher with cetirizine than placebo (placebo 57%, cetirizine 10 mg 74% and cetirizine 20 mg 81%; cetirizine 20 mg compared with placebo,  $p = 0.01$ ).
- Few adverse effects were reported in the studies. According to the summaries of product characteristics for cetirizine (for example, [Zirtek](#)), adverse reactions at rates of 1% or more for cetirizine 10 mg daily in placebo-controlled clinical trials include minor central nervous system adverse effects such as somnolence, fatigue, dizziness and dry mouth.

- The 4 studies outlined in this evidence summary have many limitations that affect their application to clinical practice. For example, they were small (limiting their statistical power) and of short duration (limiting their ability to assess long-term efficacy and adverse effects, particularly because urticaria fluctuates and depends on the presence of trigger factors). In addition, the method of randomisation is not reported in any of the studies and it is unlikely that allocation was concealed. Two studies were placebo-controlled, rather than using an active comparator, and the other 2 studies were not blinded. None of the study analyses were by intention-to-treat. All of these factors may introduce bias.
- The studies generally included adults aged 16–65 years, which limits their applicability to children and young people under 16 years, and adults over 65 years. Two of the studies were undertaken in Japan, which may limit their applicability to the UK population.
- The European Academy of Allergology and Clinical Immunology, Global Allergy and Asthma European Network, European Dermatology Forum and World Allergy Organisation guideline on the management of urticaria (EAACI/GA<sup>2</sup>LEN/EDF/WAO guideline) advises that the standard dose of a non-sedating antihistamine may be increased 4-fold if standard doses are ineffective. In the development of this evidence summary, no evidence from high quality studies was found to support the use of doses of cetirizine higher than 20 mg.

Full text of Evidence review.

## Context and estimated impact for the NHS

According to the Drug Tariff (May 2014), the cost of 30 cetirizine 10 mg tablets is £1.06.

The NHS prescription cost analysis for England 2012 reported that 4,964,700 prescriptions for cetirizine were dispensed in primary care in England in 2011 at a net cost of £6,266,700 (net cost per item £1.26). It is not known how many of these prescription items were for chronic urticaria, or how many were for off-label doses.

Full text of Context and estimated impact for the NHS.

## Information for the public

A [plain English summary](#) is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people with chronic urticaria who are thinking about trying off-label doses of cetirizine.

### About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance**.

## Full evidence summary

### Introduction and current guidance

Urticaria is a superficial swelling of the skin (epidermis and mucous membranes) that results in a red, raised, itchy rash (weals). It can be localised or generalised ([NICE Clinical knowledge summary: urticaria](#)).

Acute urticaria may be caused by allergy to foods, drugs, irritants, insect bites and stings, physical stimuli and viral infection. It is usually a self-limiting, one-off episode. By contrast, the cause of many cases of chronic urticaria cannot be identified and it may remit and relapse, triggered by, for example, viral illness, stress, or drugs. Symptoms last for more than 6 weeks (recurrence of acute symptoms or persistent symptoms) and may last for months or years.

The British Society for Allergy and Clinical Immunology guidelines for the management of chronic urticaria and angio-oedema ([BSACI guidelines](#)) state that the lifetime prevalence



of chronic urticaria is 0.5–1%. Although rarely life-threatening, it significantly reduces quality of life.

The [NICE clinical knowledge summary on urticaria](#) advises that the underlying cause of urticaria should be identified and managed, if possible. People with urticaria who need treatment should be offered a non-sedating antihistamine (for example, cetirizine, fexofenadine or loratadine) at the standard licensed dose, either as required until symptoms settle or regularly for up to 6 weeks. People with severe urticaria may also be given a short course of oral corticosteroids. If response to treatment is inadequate, the following options may be considered:

- In adults, if there are no contraindications, the standard licensed dose of the first choice antihistamine should be doubled (off-label use).
- An alternative non-sedating antihistamine should be tried.
- An additional sedative antihistamine (such as chlorphenamine) should be taken at night.
- A topical antipruritic agent (such as calamine lotion) should be used to relieve itch.

Referral to a dermatologist or immunologist is advised if symptoms are not well controlled on treatment or antihistamines are needed continuously for more than 6 weeks to control symptoms.

The [BSACI guidelines](#) state that it is common practice to increase the dose of non-sedating antihistamine above the normal dose when the potential benefits are considered to outweigh the risk in patients who do not achieve adequate control at standard doses. If higher than standard doses of antihistamines are to be considered, incremental up-dosing is advised.

An upper limit for increasing the dose of non-sedating antihistamine is not specified in the [BSACI guidelines](#). However, the European Academy of Allergology and Clinical Immunology, Global Allergy and Asthma European Network, European Dermatology Forum and World Allergy Organisation guideline on the management of urticaria ([EAACI/GA<sup>2</sup>LEN/EDF/WAO guideline](#)) advises that the standard dose may be increased 4-fold, based on studies using levocetirizine, desloratadine and rupatadine.

Higher, off-label doses of antihistamines are also advised for chronic urticaria in children and young people under 16 years if the response to standard doses is inadequate. The



[EAACI/GA<sup>2</sup>LEN/EDF/WAO guideline](#) advises that a 4-fold (weight-adjusted) dose increase may be used.

The [BSACI guidelines](#) note that cetirizine may be more effective than the other antihistamines in chronic urticaria. However, this is based on a single study of chronic urticaria and studies of suppression of in vivo histamine-induced weal and flare responses, and individual responses and side effects to antihistamines vary. Therefore, no specific antihistamine is advocated in the guidelines.

This evidence summary looks at the evidence supporting the use of high, off-label doses of cetirizine for chronic urticaria.

## Product overview

### Drug action

Cetirizine is a second generation, non-sedating antihistamine, which selectively antagonises peripheral H<sub>1</sub>-receptors and displays anti-allergic properties. It is a human metabolite of the sedating antihistamine, hydroxyzine (see summaries of product characteristics for cetirizine, for example, [Zirtek](#)).

### Regulatory status

Cetirizine is licensed for the relief of symptoms of chronic idiopathic urticaria at a dose of 10 mg daily in adults and young people aged over 12 years, 5 mg twice daily in children aged 6–12 years, and 2.5 mg twice daily in children aged 2–6 years. It is also licensed at these doses for the relief of nasal and ocular symptoms of seasonal and perennial allergic rhinitis (see summaries of product characteristics for cetirizine, for example, [Zirtek](#)).

Use of higher doses of cetirizine is off-label. In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using cetirizine outside its authorised indications.

### Cost

According to the [Drug Tariff](#) (May 2014), the cost of:

- 30 cetirizine 10 mg tablets is £1.06
- 7 cetirizine 10 mg capsules is £2.91
- 200 ml cetirizine 1 mg/ml oral solution is £1.70.

## Evidence review

This evidence summary is based on 2 small [randomised controlled trials](#) (RCTs) and 2 double blind [crossover](#) studies that assessed the safety and efficacy of doses of cetirizine above 10 mg for treating chronic urticaria in people with symptoms that are unresponsive to standard doses of antihistamines. No RCTs or crossover studies were found in children and young people under 16 years.

## Clinical effectiveness

[Okubo et al \(2013\)](#)

This Japanese open-label randomised study compared the efficacy and safety of either doubling the dose of cetirizine or replacing cetirizine with olopatadine (an antihistamine which is only available as eye drops in the UK). The study included 51 people aged 16 years or over (mean 39 years) with urticaria (mean duration 7 months). H<sub>1</sub>-receptor antagonists and other drugs (not specified) that may have affected the results were stopped at least 3 days before the study started.

All participants received cetirizine 10 mg daily for a mean of 10.1 days. People whose urticaria was refractory to cetirizine 10 mg (n=18: weal or itching graded as 'no change' or 'exacerbated', or treatment reported to be 'relatively unsatisfactory' or worse) were subsequently randomised to receive cetirizine 20 mg daily (n=9) or olopatadine 5 mg twice daily (n=9) for a mean of 13.3 days. Of the 33 people whose symptoms responded to cetirizine 10 mg, 22 continued this treatment (10 stopped treatment because their symptoms resolved and 1 because of drowsiness).

Doctors assessed the severity of weals on a scale of 0–3, where 3 is severe. Participants used a visual analogue scale to record itching. Quality of life was also assessed and an overall evaluation was made. Efficacy was evaluated in only 16 people who changed their treatment (2 people in the olopatadine group dropped out) and 16 people who continued cetirizine 10 mg (6 dropped out).

At the start of the second treatment period, the severity of urticaria varied between the groups, although the statistical significance of differences in baseline characteristics at this stage was not reported. The group that continued to take cetirizine 10 mg had less severe weals and itching than those randomised to cetirizine 20 mg, who had less severe symptoms than those randomised to olopatadine. In this treatment period, the severity of weals improved in all groups: itching improved with cetirizine 20 mg and olopatadine but worsened slightly with cetirizine 10 mg. No change in outcome was statistically significant.

Remission was achieved in 81.3% (13/16) of people in the continued cetirizine 10 mg group, 66.7% (6/9) in the cetirizine 20 mg group and 42.9% (3/7) in the olopatadine group, with no statistically significant differences between the groups. Urticaria worsened in 2 people in each of the cetirizine groups and 3 people in the olopatadine group.

Statistically significant improvements in quality of life scores were seen with continued cetirizine 10 mg (n=16). In the cetirizine 20 mg and olopatadine groups, improvements in quality of life did not reach statistical significance. However, only 5 people were evaluated in each of these groups and they had lower quality of life scores at baseline than those in the continued cetirizine 10 mg group.

#### Kameyoshi et al (2007)

This open-label randomised study was undertaken in secondary care in Japan. It evaluated the effect of increasing the dose of cetirizine to 20 mg in 21 people (mean age 40 years) with chronic idiopathic urticaria for more than 1 month who had seen only limited benefits (change in total daily urticarial symptom score less than 1 on a scale of 0–9; mean score 4) with the standard 10 mg dose. All participants had previously been unsatisfactorily treated with an average of 3 H<sub>1</sub>-receptor antagonists, with or without corticosteroids. These treatments were stopped before the screening period.

Participants were randomised to 2 groups. There were no significant differences between the groups in age or mean urticarial symptom scores at baseline. All participants received cetirizine 10 mg twice daily for 1–2 weeks. Subsequently, 1 group (n=11) continued the 20 mg dosage, whereas the other group (n=10) reverted to the 10 mg dosage for a further 1–2 weeks. People assessed their daily urticarial symptom scores and recorded them in diaries. The number of weals, duration of weals and the severity of itch were each assessed on a scale of 0–3, where 3 is severe, to give a total score of 0–9.

In the first 1- to 2-week period, urticarial symptom scores were statistically significantly

lower than in the screening period in both groups ( $p < 0.01$  for weals, duration, itch and total scores; mean total scores about 2.5–3). In the group that continued treatment with cetirizine 20 mg, urticarial symptom scores continued to improve (mean total score about 1.5) in the second 1- to 2-week period. By contrast, in the group that reverted to 10 mg, the weal, itch and total scores began to increase again, and by the end of the study the weal and itch scores were not significantly different from those seen in the screening period.

Zuberbier et al (1996)

This double-blind crossover placebo-controlled study was undertaken in 13 adults (mean age 26.5 years) recruited from 2 dermatology clinics in Germany. It assessed cetirizine 20 mg daily for treating confirmed cholinergic urticaria (generally triggered by physical exercise or a hot shower or bath). For inclusion, participants had attacks of urticaria at least once a week for more than 1 month (mean duration 89 months) and global scores of 3 on provocation of an attack at the time of screening (mean symptoms scores at baseline on a scale of 0–3, where 3 is severe: weals 1.30, erythema 2.00 and itching 2.23). Exclusion criteria included severe chronic disease and use of systemic corticosteroids within 2 months, topical steroids within 2 weeks, other antihistamines within 4 days or anticholinergics within 2 days of study entry.

Participants were randomised to either placebo or cetirizine 20 mg daily. Once they had received a 3-week course of randomised treatment, they were switched to the alternative treatment. Participants recorded trigger factors, symptoms and use of rescue medication (cetirizine 20 mg) in a diary each day. Erythema, weals and itching were assessed on a scale of 0–3. Only the last 2 weeks of the treatment periods were analysed to allow for a washout period. Two people taking placebo were excluded during the first treatment period because of lack of adherence. Only days with trigger factors were included in analyses.

In the 11 people analysed, a statistically significant reduction was seen with cetirizine compared with placebo in weals (mean symptom score 0.23 compared with 0.92 respectively,  $p = 0.015$ ), erythema (mean symptom score 0.29 compared with 0.91 respectively,  $p = 0.033$ ), itching (mean symptom score 0.16 compared with 0.87 respectively,  $p = 0.006$ ) and all symptoms (mean symptom score 0.22 compared with 0.90 respectively,  $p = 0.013$ ). One person taking cetirizine took 1 dose of rescue medication on 1 occasion when 3 trigger factors were present. A second person used 1 dose of rescue medication on day 1 of the cetirizine treatment period and 20 doses throughout the

placebo treatment period.

#### Zuberbier et al (1995)

This study had a similar design to Zuberbier et al (1996). It was a double-blind crossover placebo-controlled study undertaken in 25 adults aged between 18 years and 65 years (mean age 26 years) recruited from 4 dermatology clinics in Germany and Austria. The study assessed cetirizine at doses of 10 mg and 20 mg daily for treating confirmed cholinergic urticaria (triggered by exercise, stress and heat) for more than 1 month (mean duration 5.12 years). Sixteen people had previously tried other antihistamines, usually with unsatisfactory results. Exclusion criteria included liver, cardiac or renal dysfunction and use of corticosteroids within 7 days, antihistamines within 4 days or anticholinergics within 2 days of study entry. Mean baseline scores for weals, erythema and itching were 1.96, 1.96 and 2.12 respectively on a scale of 0–3, where 3 is severe.

People were randomised to receive cetirizine 10 mg or 20 mg daily for 3 weeks (double blind), followed by a 3-week washout period on placebo (single blind) and another 3-week period with the alternative dose of cetirizine. Participants kept a daily diary of their symptoms (weals, erythema and itching on a scale of 0–3) and trigger factors. One person was excluded because of a major protocol violation (wrong inclusion criteria).

Evaluation of participant diaries showed that cetirizine (both groups combined) statistically significantly improved weals and itching ( $p=0.01$  and  $p=0.008$  respectively) compared with placebo. The difference between the 2 doses of cetirizine was significant for weals only ( $p=0.04$ ); it is not reported which dose was more effective. Mean scores for individual doses were not reported. The average proportion of days with mild or no symptoms was statistically significantly higher with cetirizine compared with placebo (placebo 57%, cetirizine 10 mg 74% and cetirizine 20 mg 81%; cetirizine 20 mg compared with placebo,  $p=0.01$ ).

## Safety and tolerability

### Summaries of product characteristics

According to the summaries of product characteristics for cetirizine (for example, Zirtek), adverse reactions of licensed doses seen in placebo-controlled clinical trials at rates of 1% or more include somnolence, fatigue, dizziness and dry mouth. Adverse reactions at rates of 1% or more in children aged from 6 months to 12 years in placebo-controlled clinical

trials include diarrhoea, somnolence, rhinitis and fatigue.

Adverse reactions reported after taking at least 5 times the recommended daily dose include confusion, diarrhoea, dizziness, fatigue, headache, malaise, mydriasis, pruritus, restlessness, sedation, somnolence, stupor, tachycardia, tremor and urinary retention.

#### Okubo et al (2013)

Drowsiness was reported in 3 people in the second period of this study: 2 in the continued cetirizine 10 mg group and 1 in the cetirizine 20 mg group.

#### Kameyoshi et al (2007)

Of the 21 participants, 2 (both in the group that reverted to 10 mg cetirizine) experienced drowsiness in the first 1- to 2-week period, which resolved in the second 1- to 2-week period when the dose was reduced to 10 mg. No other adverse effects were reported in this study.

#### Zuberbier et al (1996)

In this study, none of the 11 participants reported any adverse effects during the cetirizine or placebo treatment periods.

#### Zuberbier et al (1995)

Treatment was generally well tolerated in this study. Of the 25 participants, 1 had diarrhoea in the first week on cetirizine 10 mg, which resolved spontaneously. At this dose, 1 person reported mild, transient loss of appetite in the first treatment week only. One person experienced mild tiredness at the 10 mg but not the 20 mg dose, and 2 people experienced mild or moderate continuous tiredness at the 20 mg but not the 10 mg dose. One person taking placebo asked to change treatment because of severe symptoms.

## **Evidence strengths and limitations**

Well designed and reported clinical trials comparing the efficacy and safety of off-label doses of cetirizine in chronic urticaria are lacking. The 4 studies outlined in this evidence summary have many limitations that affect their application to clinical practice.

The 4 studies were all small. The numbers of participants randomised ranged from 13 to 25: the total number of people evaluated was only 76. This limits the statistical power of the studies to be able to detect differences between treatment groups. The baseline characteristics of participants were poorly reported and it is generally unclear whether there were any significant differences between treatment groups.

The treatment periods in the studies lasted between 1 and 3 weeks. This limits the studies' ability to assess long-term efficacy and adverse effects. Chronic urticaria fluctuates and any improvements in symptoms may have been due to natural variations in the disease. In addition, urticaria can depend on trigger factors, which may not always be present. Longer studies are needed to identify longer-term adverse effects and eliminate the effects of disease variation.

Although all the studies were randomised and controlled, the method of randomisation is not reported in any of them and it is unlikely that allocation was concealed. This means that researchers (unconsciously or otherwise) could have influenced which intervention group each participant was assigned to. The 2 studies by Zuberbier et al. were placebo-controlled, rather than using an active comparator. The other 2 studies (Okubo et al. 2013 and Kameyoshi et al. 2007) were not blinded. Lack of blinding is another source of bias, which may be exacerbated in these studies because participants, aware of which treatment they were taking, also assessed their own symptoms. Analyses were not by intention-to-treat (dropouts were not included), which may also introduce bias.

Symptoms were assessed on severity scales (graded from 0–3) and visual analogue scales. It is not known whether the scales used have been validated in populations with chronic urticaria. In addition, it is unclear whether any statistically significant improvements seen on the symptom scales were clinically important.

Most participants in the studies had chronic urticaria lasting at least 1 month but usually much longer. In the 2 studies by Zuberbier et al., participants had cholinergic urticaria, a specific type of urticaria generally triggered by exercise, heat or stress. Participants' symptoms were generally severe and refractory to treatment with standard doses of antihistamines. None of the studies included children and young people under 16 years: the mean age of participants in 2 of the studies was about 26 years and in the other 2 studies it was about 40 years. This limits their applicability to children and young people, and older adults. Two of the studies (Okubo et al. 2013 and Kameyoshi et al. 2007) were undertaken in Japan, which limits their applicability to the UK population.



Some authors of the Zuberbier et al. studies were employed by UCB Pharma, the manufacturer of a brand of cetirizine (Zirtek).

Overall, these studies suggest that cetirizine 20 mg improves weals and itching in people with severe chronic urticaria refractory to standard doses of antihistamines and is well tolerated. However, symptoms of urticaria remain in a proportion of patients.

The [EAACI/GA<sup>2</sup>LEN/EDF/WAO guideline](#) on the management of urticaria advises that the standard dose of a non-sedating antihistamine may be increased 4-fold if standard doses are ineffective, based on studies using levocetirizine, desloratadine and rupatadine. In the development of this evidence summary, no evidence from RCTs was found supporting the use of doses of cetirizine above 20 mg. An [observational study \(Asero et al 2007\)](#) referenced by the [EAACI/GA<sup>2</sup>LEN/EDF/WAO guideline](#) reported that, of 22 adults with chronic spontaneous urticaria refractory to standard antihistamines, only 1 had satisfactory improvement of symptoms when the dose of cetirizine was increased from 10 mg daily to 10 mg 3 times daily.

## Context and estimated impact for the NHS

### Cost effectiveness

No cost-effectiveness studies were identified that compared the use of off-label doses of cetirizine for chronic urticaria with other treatments or placebo.

**Table 1 Costs of non-sedating antihistamines licensed for urticaria**

	Usual licensed dose (adults and young people aged over 12 years) <sup>a</sup>	Estimated cost per 30 days excluding VAT <sup>b</sup>
Acrivastine	8 mg 3 times a day	£20.62
Bilastine	20 mg daily	£15.09
Cetirizine	10 mg daily	£1.06 <sup>c</sup>
Desloratadine	5 mg daily	£1.35
Fexofenadine	180 mg daily	£3.70
Levocetirizine	5 mg daily	£3.94

Loratadine	10 mg daily	£1.00
Mizolastine	10 mg daily	£6.92
Rupatadine	10 mg daily	£5.00

<sup>a</sup> Doses taken from the [summaries of product characteristics](#). The doses shown do not represent the full range that can be used and they do not imply therapeutic equivalence.

<sup>b</sup> Costs of solid dosage forms taken from the [Drug Tariff](#), May 2014

<sup>c</sup> Cost of tablets. Capsules are more expensive.

## Current drug usage

No estimate of the current use of off-label doses of cetirizine for chronic urticaria in UK clinical practice was identified.

The [NHS prescription cost analysis for England 2012](#) reported that 4,964,700 prescriptions for cetirizine were dispensed in primary care in England in 2011 at a net cost of £6,266,700 (net cost per item £1.26). It is not known how many of these prescription items were for chronic urticaria, or how many were for off-label doses.

## Information for the public

A [plain English summary](#) is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people with chronic urticaria who are thinking about trying off-label doses of cetirizine.

## Relevance to NICE guidance programmes

This use of off-label doses of cetirizine is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

NICE guidance related to chronic urticaria includes:

- [Food allergy in children and young people](#) (NICE clinical guidance CG116).
- [Atopic eczema in children](#) (NICE clinical guidance CG57).

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## Development of this evidence summary

The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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### Declarations of interest

No relevant interests declared.

### Changes after publication

**July 2014:** Minor maintenance

#### About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

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