Gouty arthritis: canakinumab

Evidence summary
Published: 23 July 2013
nice.org.uk/guidance/esnm23

Key points from the evidence

The content of this evidence summary was up-to-date in July 2013. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

Subcutaneous canakinumab 150 mg reduced pain intensity and the risk of new attacks of gout compared with intramuscular triamcinolone 40 mg. However, patients who used canakinumab experienced more adverse effects than those who used triamcinolone, including infections, neutropenia and thrombocytopenia. Canakinumab is considerably more expensive than other treatments.
Effectiveness

- Compared with triamcinolone, the mean pain score on a 100 mm visual analogue scale was 10.7 mm lower in the canakinumab group (95% confidence interval [CI] 6.0 mm to 15.4 mm, p<0.0001). Specialists have advised that this is of borderline clinical importance.

- Over 12 weeks, canakinumab reduced the risk of a new attack of gout by 62% (hazard ratio 0.38, 95% CI 0.26 to 0.57, p<0.0001).

- 16% of patients using canakinumab experienced at least 1 new attack of gout in 12 weeks, compared with 36% using triamcinolone (p value not reported).

Safety

- Over 24 weeks, serious adverse events were reported in 7.6% of patients using canakinumab and 3.1% of patients using triamcinolone (p value not reported).

- Infections were seen more commonly in the canakinumab group (20% compared with 12% in the triamcinolone group; p value not reported).

- Neutropenia and thrombocytopenia have been reported with canakinumab.

Patient factors

- Patients may prefer their gout to be managed optimally using standard oral treatments (non-steroidal anti-inflammatory drugs, colchicine and urate-lowering therapy) and oral corticosteroids before trying injectable treatments.

- Canakinumab is injected subcutaneously, whereas triamcinolone and other corticosteroids are generally injected intramuscularly or intra-articularly.

Resource implications

- The cost of 1 dose of canakinumab 150 mg is £9927.80.

- The cost of 1 dose of triamcinolone 40 mg is £1.49.

Key points

Gout is a disorder of purine metabolism characterised by a raised uric acid level in the blood and the deposition of urate crystals in joints and other tissues. These crystals trigger macrophages to produce interleukin-1 beta, producing an acute, painful inflammatory response. Canakinumab is a human monoclonal antibody that binds to human interleukin-1 beta, blocking its effects and preventing the production of inflammatory mediators.
In February 2013, the marketing authorisation for canakinumab was extended to include the symptomatic treatment of frequent gouty arthritis attacks (at least 3 attacks in the previous 12 months) in adults in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate.

This evidence summary is based on 2 randomised controlled trials (β-RELIEVED and β-RELIEVED-II) and their extension studies, the results of which were all published in 1 paper (Schlesinger et al. 2012).

In the studies, subcutaneous canakinumab 150 mg was statistically significantly more effective than intramuscular triamcinolone 40 mg at reducing pain intensity in the most affected joint at 72 hours post dose and delayed the time to first new attack of gout over 12 weeks (the co-primary outcomes). In the pooled analysis of β-RELIEVED and β-RELIEVED-II, at 72 hours mean pain scores were lower for canakinumab than for triamcinolone (25.0 mm compared with 35.7 mm; mean difference on 100 mm visual analogue scale 10.7 mm, 95% confidence interval [CI] 6.0 mm to 15.4 mm, p<0.0001). Although statistically significant, specialists have advised that this is of borderline clinical significance. Also, this dose of triamcinolone is considered to be low by specialists (including those informing the European public assessment report for canakinumab) and may be a suboptimal dose to use as a comparator.

Compared with triamcinolone, canakinumab statistically significantly reduced the risk of a new attack of gout by 62% (hazard ratio 0.38, 95% CI 0.26 to 0.57, p<0.0001) over the 12-week period. Of patients treated with canakinumab, 16.0% experienced at least 1 new attack of gout, compared with 35.8% of those treated with triamcinolone (statistical significance of difference not reported).

In the pooled analysis of the initial and extension studies, over 24 weeks, adverse events were reported in 149 (66.2%) patients treated with canakinumab 150 mg and 121 (52.8%) patients treated with triamcinolone 40 mg. They were reported to be serious but not fatal in 17 (7.6%) patients using canakinumab and 7 (3.1%) using triamcinolone. There was 1 death in each group; neither was considered by the investigators to be related to the study. Infections were reported in 46 (20.4%) patients using canakinumab and 28 (12.2%) patients using triamcinolone. The statistical significance of these differences was not reported.

The European public assessment report for canakinumab states that neutropenia and thrombocytopenia have been observed with canakinumab, with a possible dose-response relationship.
Around 20–30% of people affected by gout are women; however, only 9% of patients in the studies were female. Similarly, the peak prevalence of gout occurs in those aged 75 years or more; however in the study, the mean age of the participants was 53 years and only limited data were available for patients aged 75 years or more (Mickuls et al. 2005). Both colchicine and NSAIDs had been judged as unsuitable for 35% of patients in the studies. This means that 65% of patients still had at least 1 usual first-line treatment option open to them. Only 42% of patients had contraindications to, intolerance of, or were unresponsive to colchicine. Similarly, only 42% of patients were on urate-lowering therapy, suggesting suboptimal management of gout.

The cost of 1 vial of canakinumab 150 mg is £9927.80.

Specialists have advised that it is important to ensure that standard treatments for gout, including NSAIDs, colchicine and corticosteroids have been optimised before canakinumab is considered. Also, longer term, adequate urate-lowering therapy should be used to reduce the risk of ongoing attacks occurring. If this is done, the number of people with severe gout who may be eligible for treatment is likely to be very small.

### Key evidence


### 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

NICE terminated a planned single technology appraisal of canakinumab for treating gouty arthritis attacks and reducing the frequency of subsequent attacks because the manufacturer (Novartis) informed NICE that it would not be making an evidence submission for the appraisal.
The manufacturer stated that it will not be promoting canakinumab for treating gouty arthritis attacks and reducing the frequency of subsequent attacks in the UK (Novartis Pharmaceuticals UK Ltd: personal communication May 2013). However, specialists advised that it may be considered for this indication in a very small number of selected people with severe gout for whom other treatments are unsuitable or ineffective. This evidence summary has therefore been produced to help commissioners, budget holders and groups such as area prescribing committees to make informed decisions and aid local planning on the introduction of this drug.

**NICE guidance on pegloticase for treating severe, debilitating chronic tophaceous gout** (NICE technology appraisal guidance 291) was published in June 2013. NICE does not recommend pegloticase for people who have severe, chronic gout with tophi who have either tried oral gout drugs (specifically xanthine oxidase inhibitors such as allopurinol) and still have high uric acid levels, or cannot take oral gout drugs.

**NICE guidance on Febuxostat for the management of hyperuricaemia in people with gout** (NICE technology appraisal guidance 164) advises that febuxostat is an option for managing chronic hyperuricaemia in gout only for people who are intolerant of allopurinol or for whom allopurinol is contraindicated.

**Introduction**

Gout is a disorder of purine metabolism characterised by a raised uric acid level in the blood (hyperuricaemia) and the deposition of urate crystals in joints and other tissues. The presence of crystals causes acute, intermittent and painful attacks of gouty arthritis in the joints, usually the foot (especially the big toe), knee, hand or wrist. In chronic gout, the joints are affected by subcutaneous concentrations of urate crystals (nodular tophi). Renal damage and kidney stones may also occur. (See the NICE Clinical Knowledge Summary on gout and the final scope for the canakinumab technology appraisal.)

The estimated prevalence of gout in the UK is 1.4%: it affects more men than women. Prevalence significantly increases with age, and reaches more than 7% in men over the age of 75 (Mickuls et al. 2005). Around 72% of people with gout in the UK experience at least 1 gout flare annually. The frequency of flares is associated with serum uric acid levels. (See the final scope for the canakinumab technology appraisal.)

Recommendations on managing gout are available in the NICE Clinical Knowledge Summary on gout and the British Society for Rheumatology and British Health Professionals in Rheumatology Guideline for the management of gout. Non-steroidal anti-inflammatory drugs (NSAIDs) are the
first-choice treatment for acute attacks of gout (with gastroprotection if indicated). Colchicine is the second-line option but, based on clinical experience, may have a slower onset of action than NSAIDs. To reduce the risk of adverse effects (especially diarrhoea), the NICE Clinical Knowledge Summary on gout and the British Society for Rheumatology and British Health Professionals in Rheumatology Guideline for the management of gout recommend that dose of colchicine should be 500 micrograms 2 to 4 times a day (lower than that recommended in the summary of product characteristics). (See the British national formulary for details.) Corticosteroids (administered orally or by intra-articular, intramuscular or intravenous injection) are an alternative when NSAIDs or colchicine are unsuitable or not tolerated.

The NICE Clinical Knowledge Summary on gout advises that lifestyle advice should be offered to all patients (for example, reducing excessive alcohol consumption and intake of high purine foods and red meat) and comorbidities and risk factors (such as diabetes mellitus, hypertension, cardiovascular risk factors and obesity) should be assessed and managed. Resting and local application of ice packs to the affected joints is recommended for acute attacks of gout. If hyperuricaemia persists despite lifestyle modification and further attacks of gout occur, urate-lowering therapy, such as allopurinol, should be considered. NICE guidance on Febuxostat for the management of hyperuricaemia in people with gout (NICE technology appraisal guidance 164) advises that febuxostat is an option for managing chronic hyperuricaemia in gout only for people who are intolerant of allopurinol or for whom allopurinol is contraindicated. The British Society for Rheumatology and British Health Professionals in Rheumatology Guideline for the management of gout advises that uricosuric agents (such as sulfinpyrazone) are other second-line options.

**Product overview**

**Drug action**

The crystals in the joints and surrounding tissue, which form during a gouty arthritis attack, trigger macrophages to produce interleukin-1 beta, producing an acute painful inflammatory response. Canakinumab is a human monoclonal antibody that binds with high affinity to human interleukin-1 beta, blocking its effects and preventing the production of inflammatory mediators. (See the Ilaris summary of product characteristics.)

**New licensed therapeutic indication**

In October 2009, canakinumab (Ilaris) was licensed for treating cryopyrin-associated periodic syndromes. In February 2013, the marketing authorisation was extended to include the
symptomatic treatment of frequent gouty arthritis attacks (at least 3 attacks in the previous 12 months) in adults in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate.

Course and cost

According to the summary of product characteristics, canakinumab is indicated for treating acute gouty arthritis attacks when standard treatment has failed or is not appropriate. Urate-lowering therapy should be started or optimised to manage hyperuricaemia. Canakinumab should be initiated and supervised by physicians experienced in diagnosing and treating gouty arthritis, and in using biologics.

The recommended dose of canakinumab for adults with gouty arthritis is 150 mg administered subcutaneously as a single dose during an attack. For maximum effect, canakinumab should be administered as soon as possible after the onset of a gouty arthritis attack.

Gout that does not respond to initial treatment should not be retreated with canakinumab. In those people whose gout responds and who require retreatment, there should be an interval of at least 12 weeks before a new dose is administered.

The cost of 1 vial of canakinumab 150 mg powder for solution for injection is £9927.80 excluding VAT (MIMS, June 2013).

Evidence review

This evidence summary is based on 2 randomised controlled trials (RCTs; β-RELIEVED and β-RELIEVED-II) with the same design, and their extension studies, the results of which were published together (Schlesinger et al. 2012). The 2 initial studies assessed the efficacy and safety of a single dose of canakinumab compared with a single dose of corticosteroid in people with acute attacks of gouty arthritis for whom colchicine or non-steroidal anti-inflammatory drugs (NSAIDs) were unsuitable. The extension studies further evaluated the efficacy and safety of canakinumab. (See tables 1 and 2.)

- Design: two 12-week, multicentre, double-blind RCTs followed by 12-week, double-blind extension studies. β-RELIEVED (n=230) was undertaken in 56 centres in 16 European and other non-US countries. From this study, 175 patients entered the extension study. β-RELIEVED-II (n=226) was undertaken in 74 centres in 5 countries (primarily the USA);
160 patients entered the extension study. The inclusion criteria for the extension studies are unclear.

- Total population: 454 adults (91% male) aged 18–85 years (mean age 53 years) with:
  - a history of 3 or more self-reported gouty arthritis attacks in the previous 12 months (mean 5.2)
  - an acute attack for 5 days or less characterised by baseline pain intensity of 50 mm or more on a 0–100 mm visual analogue scale (VAS; mean 74 mm)
  - contraindications to, intolerance of, or unresponsiveness to NSAIDs (91%), colchicine (42%) or both (35%), and
  - a body mass index (BMI) of 45 kg/m² or less (mean 32 kg/m²).

53% of patients in the 2 studies had mono-articular gout, 60% had experienced gout for 6 years or more, and 29% had tophi. Most patients had comorbidities (83%) including hypertension (59%) and chronic kidney disease (84%). 53% had a BMI of more than 30 kg/m². Patients taking urate-lowering therapy (42%; usually allopurinol) had to be on a stable dose and regimen for at least 2 weeks before randomisation and were expected to remain on a stable regimen during the study. Patients were excluded if they were taking pain relief medication or biologics for specified periods before study entry, or had other acute inflammatory arthritis or infections. Baseline characteristics were generally well balanced across the treatment groups and between the initial studies. However, a greater proportion of patients in β-RELIEVED-II had mono-articular gout (61% compared with 45%); whereas, a greater proportion of patients in β-RELIEVED had tophi (39% compared with 19%) and comorbidities (87% compared with 78%), particularly hypertension, obesity and chronic kidney disease. Urate-lowering therapy was used more frequently in β-RELIEVED (53% compared with 32%).

- Intervention and comparison: in the RCTs, patients were randomised to receive canakinumab 150 mg by subcutaneous injection or triamcinolone acetate 40 mg by intramuscular injection, both with matching placebo. Overall, 56% of patients received treatment within 2 days of onset of the flare. The minimum period between 2 consecutive study drug administrations was 14 days. Patients having difficulty tolerating their pain or experiencing an attack within 14 days of receiving the study medication could take rescue medication (paracetamol or codeine or, if these were insufficient, a short course of oral prednisolone). In the extension studies, patients were treated on-demand within 5 days of onset of further gouty attacks with the same drug that they had received in the initial study.
Outcomes: the initial studies had 2 co-primary efficacy end points: pain intensity (VAS score) in the most affected joint at 72 hours post dose and time to first new gout attack over 12 weeks. Secondary outcomes included time to first new flare over 24 weeks; the proportion of patients taking rescue medication during the 7 days post dose; global assessments by patients and physicians; assessment of joint tenderness, swelling and erythema by physicians; and safety and tolerability. The primary objectives of the extension studies were to further evaluate the time to the next attack and to determine the longer-term safety profile of repeated on-demand use of canakinumab. Patient demographics and efficacy data were analysed using the modified intention-to-treat data set (all patients randomised who received at least 1 dose of study drug). Safety data were analysed using the safety set (all patients who received a study drug and had at least 1 post-baseline safety assessment).

The paper primarily reports the results and analyses using pooled data from β-RELIEVED and β-RELIEVED-II, although many results for the 2 studies are also reported individually. It is unclear if the pooled analysis was pre-specified. In this evidence summary, the results of the individual studies are presented in tables 1 and 2 and the pooled data are discussed in the text. Data that were not available in the paper were obtained from the European public assessment report for canakinumab (EMEA/H/C/001109/II/0010).

### Table 1 Summary of β-RELIEVED (Schlesinger et al. 2012)

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Canakinumab 150 mg</th>
<th>Triamcinolone 40 mg</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=113</td>
<td>28.1 mm</td>
<td>39.5 mm</td>
<td>Mean difference 11.4 mm 95% CI 4.6 mm to 18.2 mm p=0.001</td>
</tr>
<tr>
<td>Primary outcome 1: pain intensity (VAS score) in the most affected joint 72 hours post dose: least squares mean (standard error)</td>
<td>18.9%&lt;sup&gt;a&lt;/sup&gt; 95% CI 12.7% to 27.5%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>36.5%&lt;sup&gt;a&lt;/sup&gt; 95% CI 28.3% to 46.3%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>HR 0.45 95% CI 0.26 to 0.76 p=0.0014&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*Table 1 Summary of β-RELIEVED (Schlesinger et al. 2012)*
### Selected secondary outcomes:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Canakinumab 150 mg</th>
<th>Triamcinolone 40 mg</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of a new gout attack over 24 weeks</td>
<td>35.5%a</td>
<td>57.5%a</td>
<td>HR 0.48</td>
</tr>
<tr>
<td></td>
<td>95% CI 26.9% to 45.8%</td>
<td>95% CI 47.9% to 67.4%</td>
<td>95% CI 0.32 to 0.73</td>
</tr>
<tr>
<td>Proportion of patients taking rescue medication</td>
<td>31.0% (35/113)</td>
<td>52.5% (60/115)</td>
<td>OR 0.42</td>
</tr>
<tr>
<td></td>
<td>95% CI 0.24 to 0.73</td>
<td></td>
<td>p=0.0022</td>
</tr>
<tr>
<td>Safety over 24 weeks</td>
<td>n=113</td>
<td>n=115</td>
<td></td>
</tr>
<tr>
<td>Patients reporting serious (non-fatal) adverse events</td>
<td>9.7% (11/113)</td>
<td>4.3% (5/115)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI 0.24 to 0.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients reporting any adverse event</td>
<td>62.8% (71/113)</td>
<td>48.7% (56/115)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI 0.24 to 0.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients reporting infections</td>
<td>22.1% (25/113)</td>
<td>15.7% (18/115)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI 0.24 to 0.73</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio; p, p value; VAS, visual analogue scale.

a These are the Kaplan–Meier estimates of the incidence of new gout attacks at 12 weeks. The original primary outcome measure; median time to the first new gout attack, could not be estimated because fewer than 50% of people in both treatment groups experienced their first attack within 12 weeks.

b Data not reported in the paper; obtained from the European public assessment report for canakinumab (EMEA/H/C/001109/II/0010).

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**Table 2 Summary of β-RELIEVED-II (Schlesinger et al. 2012)**

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Canakinumab 150 mg</th>
<th>Triamcinolone 40 mg</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=112</td>
<td>n=114</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Mean difference</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Primary outcome 1: pain intensity (VAS score) in the most affected joint 72 hours post dose: least squares mean (standard error)</td>
<td>22.1 mm</td>
<td>31.9 mm</td>
<td>9.8 mm</td>
</tr>
<tr>
<td>Primary outcome 2: Probability of a new gout attack over 12 weeks</td>
<td>14.2%&lt;sup&gt;a&lt;/sup&gt; (95% CI 8.8% to 22.5%&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>38.2%&lt;sup&gt;a&lt;/sup&gt; (95% CI 29.8% to 48.0%&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>HR 0.32</td>
</tr>
<tr>
<td>Selected secondary outcomes:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of a new gout attack over 24 weeks</td>
<td>29.1%&lt;sup&gt;a&lt;/sup&gt; (95% CI 21.0% to 39.4%)</td>
<td>54.3%&lt;sup&gt;a&lt;/sup&gt; (95% CI 44.1% to 65.2%)</td>
<td>HR 0.40</td>
</tr>
<tr>
<td>Proportion of patients taking rescue medication</td>
<td>43.8% (49/112)</td>
<td>57.0% (65/114)</td>
<td>OR 0.52</td>
</tr>
<tr>
<td>Safety over 24 weeks</td>
<td>n=112</td>
<td>n=114</td>
<td></td>
</tr>
<tr>
<td>Patients reporting serious (non-fatal) adverse events</td>
<td>5.4% (6/112)</td>
<td>1.8% (2/114)</td>
<td></td>
</tr>
<tr>
<td>Patients reporting any adverse event</td>
<td>69.6% (78/112)</td>
<td>57.0% (65/114)</td>
<td></td>
</tr>
<tr>
<td>Patients reporting infections</td>
<td>18.8% (21/112)</td>
<td>8.8% (10/114)</td>
<td></td>
</tr>
</tbody>
</table>
Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio; p, p value; VAS, visual analogue scale.

These are the Kaplan–Meier estimates of the incidence of new gout attacks at 12 weeks. The original primary outcome measure; median time to the first new gout attack, could not be estimated because fewer than 50% of people in both treatment groups experienced their first attack within 12 weeks.

Data not reported in the paper; obtained from the European public assessment report for canakinumab (EMEA/H/C/001109/II/0010).

Clinical effectiveness

Subcutaneous canakinumab 150 mg was statistically significantly more effective than intramuscular triamcinolone 40 mg at reducing pain intensity in the most affected joint at 72 hours post dose and the time to first new attack of gout over 12 weeks (the co-primary outcomes).

In the pooled analysis of β-RELIEVED and β-RELIEVED-II (n=454), at 72 hours the improvement from baseline in mean pain score on the VAS pain scale was greater in the canakinumab group (from 74.1 mm at baseline to 25.0 mm, a reduction of 49.1 mm) than in the triamcinolone group (from 74.2 mm at baseline to 35.7 mmm, a reduction of 38.5 mm; statistical significance of improvements not reported). The mean difference in pain scores between the treatments was 10.7 mm (95% confidence interval [CI] 6.0 mm to 15.4 mm, p<0.0001). Compared with triamcinolone, canakinumab statistically significantly delayed the time to the first new flare and reduced the risk of a new flare by 62% (hazard ratio [HR] 0.38, 95% CI 0.26 to 0.57, p<0.0001) over the 12-week period. This was sustained at 24 weeks (HR 0.44, 95% CI 0.32 to 0.60, p<0.0001). Within 12 weeks, 16.0% of patients treated with canakinumab experienced at least 1 new attack of gout, compared with 35.8% of those treated with triamcinolone (odds ratio [OR] 0.34, 95% CI and statistical significance not reported).

Statistically significantly fewer patients treated with canakinumab took rescue medication (pooled analysis: 37.3% compared with 54.6%; OR 0.47, 95% CI not reported, p=0.0001). Oral corticosteroids were taken by 11.1% of patients in the pooled canakinumab group, compared with 23.6% of patients in the pooled triamcinolone group (statistical significance of difference not reported).

At 72 hours, canakinumab was statistically significantly more effective than triamcinolone in terms of global assessment by patients and physicians, and in physician assessments of joint tenderness, swelling and erythema.
Similar results were seen in the individual studies (see tables 1 and 2 for the key outcomes).

Safety

In the pooled analysis, over 24 weeks, adverse events were reported in 149 (66.2%) patients treated with canakinumab 150 mg and 121 (52.8%) patients treated with triamcinolone 40 mg. They were reported to be serious but not fatal in 17 (7.6%) patients using canakinumab and 7 (3.1%) using triamcinolone. There was 1 death in each group; neither was considered by the investigators to be related to the study. Infections were reported in 46 (20.4%) patients using canakinumab and 28 (12.2%) patients using triamcinolone. The statistical significance of these differences was not reported.

The Ilaris summary of product characteristics (SPC) states that more than 2300 people have been treated with canakinumab at a range of doses, including children, healthy volunteers and people in blinded and open-label clinical trials with cryopyrin-associated periodic syndromes, gouty arthritis or other interleukin-1 beta mediated diseases. The SPC states that canakinumab is associated with an increased incidence of serious infections, and that patients should be monitored carefully for signs and symptoms of infections during and after treatment. Caution should be exercised when treating patients with infections, a history of recurring infections, or underlying conditions that may predispose them to infections.

The most common adverse reactions seen with canakinumab in trials for gouty arthritis (more than 700 patients) are infections (for example, nasopharyngitis, sinusitis, upper respiratory tract infection, bronchitis, urinary tract infection, ear infection, cellulitis, gastroenteritis, influenza, pharyngitis and pneumonia); these have been reported to occur in more than 1 in 10 patients. Dizziness and vertigo, back pain, and fatigue and weakness are also reported to be common, with an incidence of between 1 in 100 and 1 in 10.

The European public assessment report for canakinumab states that neutropenia and thrombocytopenia have been observed with canakinumab, with a possible dose-response relationship. Canakinumab may increase serum uric acid levels, potentially worsening gout and increasing the need for prophylactic urate-lowering therapy.

Evidence strengths and limitations

The β-RELIEVED and β-RELIEVED-II studies were well designed and well reported. However, they have limitations that affect their application to clinical practice. Although both studies were double
blind, it is unclear whether allocation was concealed; unconcealed allocation is a potential source of bias.

The patients in the studies had long-standing, severe gout. Most (60%) had experienced gout for 6 years or more, around half (47%) had gout in more than 1 joint, and almost a third had tophi (29%). Most patients had comorbidities (83%) (including hypertension [59%], chronic kidney disease [84%] and obesity [53%]) that increased their risk of gout. The results of the studies may not be generalisable to people with fewer risk factors and less severe gout.

Around 20–30% of people affected by gout are women; however, only 9% of patients in the studies were female. Similarly, the peak prevalence of gout occurs in those aged 75 years or more; however, in the study, the mean age of the participants was 53 years and only limited data were available for patients aged 75 years or more (Mickuls et al. 2005).

Most patients (91%) in the β-RELIEVED and β-RELIEVED-II studies had contraindications to, intolerance of, or were unresponsive to NSAIDs. Only 42% of patients in the studies had contraindications to, intolerance of, or were unresponsive to colchicines; both colchicine and NSAIDs were unsuitable for 35% of patients. However, this means that 65% of patients had a remaining treatment option. Similarly, only 42% of patients were on urate-lowering therapy, suggesting suboptimal management of gout.

Specialists have advised that, characteristically, pain severity in acute gout is normally maximal within the first 24 hours, so pain relief at 72 hours may be considered a late assessment for a primary outcome.

The European public assessment report for canakinumab notes that the dose of triamcinolone used in the study is debatable and that it is a slow-release product with delayed efficacy. However, it also acknowledges that there is insufficient evidence that another comparator would have been more appropriate. The British national formulary advises that the initial dose of intramuscular triamcinolone should be 40 mg, repeated at intervals according to response, up to a maximum dose of 100 mg. It is not known how canakinumab compares with other corticosteroid treatment regimens.

The mean difference in pain score between canakinumab and triamcinolone was 10.7 mm on the VAS pain scale (95% CI 6.0 mm to 15.4 mm, p<0.0001). Although statistically significant, specialists have advised that this is of borderline clinical significance. No data are available on the proportion of patients who had a reduction in pain score judged to be clinically significant.
Potential rare and long-term adverse effects of canakinumab are unclear because of the lack of experience of this drug. Only 174 patients using canakinumab entered the extension studies, and only 60 were retreated within 24 weeks.

β-RELIEVED was undertaken in 56 centres in 16 countries and β-RELIEVED-II was undertaken in 74 centres in 5 countries. Therefore, some centres are likely to have enrolled fewer than 3 people. It is possible that this may have affected how consistently trial outcomes were assessed.

Data were gathered and analysed by the manufacturer of canakinumab, Novartis.

**Context**

_Treatment alternatives_

Canakinumab is licensed for the symptomatic treatment of frequent gouty arthritis attacks (at least 3 attacks in the previous 12 months) in adults in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate. At this stage in the treatment pathway there are currently no other options.

Specialists have advised that, particularly in secondary care, usual best practice for severe gout that has not been relieved by NSAIDs or colchicine and urate-lowering therapy is intra-articular aspiration and corticosteroid injection. Intramuscular, intravenous or oral corticosteroids may also be used, particularly when several joints are affected. In primary care, a short course of oral corticosteroids is generally considered.

The NICE Clinical Knowledge Summary on gout advises that hydrocortisone, methylprednisolone and triamcinolone may be used for intra-articular treatment of gout. Methylprednisolone and triamcinolone may also be given intramuscularly. The dose depends upon the steroid chosen, the route of administration, the size of the joint, and the severity of the condition. Corticosteroids are not specifically licensed for treating gout. If oral corticosteroid treatment is considered, a short course of a moderately high dose of oral prednisolone is recommended (for example prednisolone 20–40 mg once a day for 5 days).

**Costs of treatment alternatives**

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<th>Usual dose</th>
<th>Estimated cost excluding VAT</th>
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The studies showed that canakinumab 150 mg reduced pain intensity and the risk of new attacks of gout, compared with triamcinolone 40 mg. However, patients who used canakinumab experienced more adverse effects (including infections, neutropenia and thrombocytopenia) than those who used triamcinolone. The European public assessment report for canakinumab notes that the risks of canakinumab seem unacceptable in a population that can be treated with usual standard of care (non-steroidal anti-inflammatory drugs [NSAIDs], colchicine or corticosteroids and urate-lowering therapy), which have more acceptable and better established safety profiles. However, the European Medicines Agency concluded that canakinumab is an option for people with frequent gouty arthritis attacks (at least 3 attacks in the previous 12 months) in whom NSAIDs and colchicine are contraindicated, not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate.

Specialists have advised that it is important to ensure that standard treatments for gout (including NSAIDs, colchicine and corticosteroids) have been optimised before canakinumab is considered. Canakinumab may be an option for acute gout in people who have ongoing flare despite best practice acute treatment, or for whom standard treatments are unsuitable, so that urate-lowering
therapy (which can precipitate acute flares) can be started. The number of people with severe gout who may be eligible for treatment with canakinumab is likely to be very small.

Canakinumab is much more expensive than other treatment options, which is likely to limit its cost effectiveness.

**Estimated usage**

It is not possible to provide estimated usage based on the available data but the number of people with severe gout who may be eligible for canakinumab treatment is likely to be very small.

**References**

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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.

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