NICE advice

Remsima (infliximab biosimilar) for subcutaneous injection for managing Crohn's disease and ulcerative colitis

Evidence summary
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Product overview

The content of this evidence summary was up to date in February 2021. See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites for up-to-date information.

Remsima for subcutaneous injection (Celltrion Healthcare Hungary) is a biosimilar monoclonal antibody of infliximab that inhibits the activity of tumour necrosis factor (TNF)-alpha. It received a marketing authorisation for managing rheumatoid arthritis in December 2019 and received a license extension for Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and psoriasis in July 2020. This evidence

summary focuses on the license extension for Crohn's disease and ulcerative colitis only.

Likely place in therapy

As with all biologic disease-modifying antirheumatic drugs (DMARDs) for ulcerative colitis and Crohn's disease, Remsima (subcutaneous) would be prescribed and started in secondary care gastroenterology clinics. Unlike intravenous infliximab, which is usually given in secondary care, Remsima (subcutaneous) can be self-administered at home if the person, family member or carer has been given the appropriate training.

In practice Remsima (subcutaneous) is most likely to be used in people:

- who are already established on intravenous infliximab
- with stable disease but who have difficulty attending hospital appointments
- for whom the risk of attending hospital for intravenous infusions outweighs the benefits.

It may also be beneficial for people who are starting on infliximab who have not used a biologic before, or who are switching from a biologic with a different mechanism of action from the TNF-alpha inhibitors.

There are no data on people switching to Remsima (subcutaneous) from Remsima (intravenous) at administration frequencies higher than every 8 weeks, and there are no data on people switching from other infliximab products to Remsima (subcutaneous).

Factors for decision making

Effectiveness and safety

The efficacy and safety of Remsima (subcutaneous) compared with Remsima (intravenous) in people with Crohn's disease and ulcerative colitis was assessed in an unpublished open-label randomised, phase 1 trial (n=131). Results have been taken from a license extension variation to the European Public Assessment Report (EPAR) for Remsima. All participants received 2 doses of Remsima intravenously at weeks 0 and 2 before randomisation. Participants were then randomised to either intravenous or subcutaneous

Remsima.

Remsima (subcutaneous) was given at week 6 and then every 2 weeks up to week 54 (people who weighed under 80 kg received 120 mg and people who were 80 kg or more received 240 mg). The licensed dose of Remsima (subcutaneous) is 120 mg every 2 weeks.

Remsima (intravenous) was given at weeks 6, 14 and 22 and then switched to subcutaneous Remsima at week 30, where it was given once every 2 weeks up to week 54.

If possible, week 30 data are reported because this was when subcutaneous and intravenous Remsima were directly compared.

In people with active Crohn's disease, the efficacy of Remsima (subcutaneous) at week 30 appeared to be comparable to Remsima (intravenous) in terms of clinical response (Crohn's disease activity index [CDAI]-70 response and CDAI-100 response) and clinical remission (CDAI score of under 150 points).

- clinical remission (60.7% [17/28] and 56.0% [14/25] respectively)
- clinical response, CDAI-70 (67.9% [19/28] and 68.0% [17/25] respectively)
- clinical response, CDAI-100 (67.9% [19/28] and 64.0% [16/25] respectively).

No statistical analyses were reported.

Endoscopic remission (Simplified Endoscopic Activity Score for Crohn's Disease [SES-CD] score less than or equal to 2) was determined in a subgroup of participants at week 22 who had colonoscopy. The proportion of people in endoscopic remission at week 22 was higher in the Remsima (subcutaneous) group than in the Remsima (intravenous) group (35.7% [5/14] and 14.3% [1/7] respectively). No statistical analysis reported.

In people with active ulcerative colitis, the efficacy of Remsima (subcutaneous) was generally comparable to Remsima (intravenous) in terms of clinical remission (total Mayo score), clinical response (total and partial Mayo score) and mucosal healing.

- clinical remission, total Mayo score, week 22 (44.7% [17/38] and 25.6% [10/39] respectively)

- clinical response, total Mayo score at week 22 (63.2% [24/38] and 43.6% [17/39] respectively)
- clinical response, partial Mayo score at week 30 (86.8% [33/38] and 74.4% [29/39] respectively)
- clinical remission, partial Mayo score at week 30 (68.4% [26/38] and 53.8% [21/39] respectively)
- mucosal healing at week 22 (47.4% [18/38] and 30.8% [12/39] respectively).

No statistical analyses were reported.

Between week 6 and week 30, treatment related localised injection site reactions were more frequent in the subcutaneous group (10/66, 15.2%) than in the intravenous group (1/65, 1.5%). This is possibly why there were more treatment-related adverse events overall in the subcutaneous group (22/66, 33.3%) than in the intravenous group (15/65, 23.1%). During the entire maintenance phase, between week 6 and 54, the most frequently reported signs and symptoms of localised injection site reactions in all participants were injection site erythema. The majority of the participants recovered without any treatments. No serious localised injection site reactions were reported.

Between week 6 and week 30, the number of people who discontinued treatment because of a treatment related adverse event was 0/66 (0.0%) in the subcutaneous group compared with 3/65 (4.6%) in the intravenous group.

The EPAR concluded that the safety data for Remsima (subcutaneous) was considered adequate and supported the proposed extension of the license.

Limitations of the evidence

The data in the license extension variation to the European public assessment report (EPAR) for Remsima have some limitations. Firstly, they come from a study that has not yet been published in a peer-reviewed journal. Secondly, the study was small, and the primary outcome was pharmacokinetic. Therefore, the study was not powered to detect differences in the secondary efficacy and safety outcomes. No comparative statistical analyses were conducted for the clinical effectiveness outcomes.

Another limitation of this study is that people weighing 80 kg or more received 240 mg of

Remsima (subcutaneous) and people under 80 kg on 120 mg could have their dose increased to 240 mg. This differs from the licensed dose for the subcutaneous formulation, which is 120 mg for all weights without dose escalation. Therefore these findings may not be generalisable to all people receiving the licensed dose of 120 mg.

The study was open label and as such subject to potential bias. Some components of the outcome scores used are subjective, therefore are subject to bias in an open-label trial in which clinician and patient outcome reporting could be influenced by the treatment received.

Another limitation was that Remsima (subcutaneous) was only compared with Remsima (intravenous) and not with other biosimilars or Remicade, the infliximab intravenous reference product. However, the EPAR states that there is no regulatory requirement to repeat the demonstration of biosimilarity against the reference product once the marketing authorisation has been granted.

Colonoscopy was not performed on all participants. SES-CD was only assessed in people who had confirmed mucosal abnormalities at their previous assessment. Therefore only improvements are likely to be seen and any disease progression in people without abnormalities at previous assessment could be missed. The EPAR stated that, on request, the company provided convincing evidence that this approach did not produce skewed results but this evidence was not included in the EPAR.

Another limitation is that there are currently no data on the efficacy or safety of switching from intravenous to subcutaneous infliximab in people who are already established on intravenous infliximab, because all participants in the study were biologic-naive. There are also no long-term outcomes comparing Remsima (subcutaneous) with Remsima (intravenous) after 30 weeks. Although, participants in the study were followed-up for 54 weeks, participants in the Remsima (intravenous) group were switched to Remsima (subcutaneous) at week 30.

Person-centred factors

Infliximab is usually given by intravenous infusion in a hospital setting, which poses potential logistical problems such as travel, time, expense, time off work and childcare. All of these could be a barrier to the uptake of intravenous infliximab or its ongoing use. Some homecare providers offer intravenous infliximab, but expert advisers have suggested that the uptake of this option is low.

The NICE COVID-19 rapid guideline on gastrointestinal and liver conditions treated with drugs affecting the immune response recommends that people should continue with existing courses of treatment to minimise the risk of a flare-up. But it also recommends thinking about whether any changes are needed to minimise face-to-face contact during the COVID-19 pandemic, including route of administration.

Remsima (subcutaneous) allows patients, or their family members or carers, to administer the treatment themselves at home if they have received training. However, injection site reactions and dexterity problems may reduce uptake and adherence may be a problem once treatment is initiated. The frequency of dosing is higher with Remsima (subcutaneous), which is administered every 2 weeks compared with Remsima (intravenous), which is every 8 weeks.

Resource implications

The cost of prescribing Remsima (subcutaneous) for managing ulcerative colitis and Crohn's disease will vary by locality. Therefore, it is not possible to show the overall resource impact.

A resource impact tool allows localities to use their own figures. See the full evidence review for more information.

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