NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Remsima (infliximab biosimilar) for subcutaneous injection for managing rheumatoid arthritis

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This evidence review sets out the best available evidence on Remsima (infliximab biosimilar) for subcutaneous injection for managing rheumatoid arthritis. It should be read in conjunction with the evidence summary, which gives the key messages.

Commissioned by NHS England.

Disclaimer

The content of this evidence review was up to date in July 2020. 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.

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Contents

Background

Rheumatoid arthritis is a systemic chronic inflammatory autoimmune disease that typically affects synovial joints (such as those in the hands and feet), causing swelling, stiffness, pain and progressive irreversible joint destruction. Disease can also occur outside the joints, affecting other organs, including the lungs, heart and eyes. Rheumatoid arthritis is associated with increased mortality and increasing disability, which affects quality of life.

There are estimated to be around 400,000 people with rheumatoid arthritis in the UK. Of these, approximately 15% have severe disease. It is about 2 to 4 times more prevalent in women than in men. It can develop at any age, but the peak age of onset in the UK is about 40 to 70 years.

There is no cure for rheumatoid arthritis. In early disease, management aims to suppress disease activity and induce remission, prevent loss of function, slow or prevent joint damage, control pain and enhance self-management. In established disease, management should address complications and associated comorbidity, as well as the effect of the condition on the person's quality of life.

NICE's guideline on managing rheumatoid arthritis recommends that all adults with newly diagnosed active rheumatoid arthritis are offered first-line treatment with a conventional disease-modifying anti-rheumatic drug (cDMARD) as monotherapy using oral methotrexate, leflunomide or sulfasalazine as soon as possible. Hydroxychloroquine, also a cDMARD, can be considered for first-line treatment as an alternative to oral methotrexate, leflunomide or sulfasalazine for mild or palindromic disease. The dose should be escalated as tolerated. An additional cDMARD should be offered in combination in a step-up strategy when the treatment target (remission or low disease activity) has not been achieved despite dose escalation.

When disease remains severe (a disease activity score [DAS] 28 greater than 5.1), despite intensive therapy with a combination of cDMARDs, then infliximab (in combination with methotrexate) is one of the biologic DMARDs (bDMARDs) recommended in NICE's technology appraisal guidance on biologic DMARDs to treat

rheumatoid arthritis. The recommendations in this technology appraisal apply to the administration of infliximab by intravenous infusion only.

This evidence review considers Remsima, a biosimilar of infliximab, for subcutaneous injection (Celltrion Healthcare Hungary Kft), which received a marketing authorisation for managing rheumatoid arthritis in December 2019.

No other infliximab products are licensed in the UK for subcutaneous administration for managing rheumatoid arthritis.

Product overview

Mode of action

Infliximab is a monoclonal antibody that inhibits the activity of tumour necrosis factor (TNF)-alpha, a pro-inflammatory mediator that is partly responsible for damage to the joints in rheumatoid arthritis. It is referred to as a TNF-alpha inhibitor.

Remsima for subcutaneous injection is a biosimilar of infliximab. As a biosimilar medicine, Remsima is highly similar to another biological medicine (the 'reference medicine') that is licensed for use in rheumatoid arthritis. The reference medicine for Remsima is Remicade (infliximab).

The active substance of a biosimilar and its reference medicine is the same biological substance but, just like the reference medicine, the biosimilar has a degree of natural variability. Approved biosimilar medicines have proven that this variability and any differences between the biosimilar and its reference medicine do not affect safety or effectiveness. Further information is available in the European Medicines Agency's (EMA's) overview of biosimilar medicines and NHS England's information on biosimilar medicines.

Regulatory status

Remsima (subcutaneous), in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in:

- adult patients with active disease when the response to disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate, has been inadequate

- adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.

Dosing information

Remsima (subcutaneous) should be initiated as maintenance therapy 4 weeks after the last administration of 2 intravenous infusions of infliximab 3 mg/kg given 2 weeks apart. The recommended dose for Remsima (subcutaneous) is 120 mg once every 2 weeks and it must be given concomitantly with methotrexate.

When switching from maintenance infliximab (intravenous infusion) to Remsima (subcutaneous), the subcutaneous formulation may be administered 8 weeks after the last administration of the intravenous infusions of infliximab 3 mg/kg given every 8 weeks.

There is insufficient information on the switching of patients who received intravenous infusions of infliximab at doses higher than 3 mg/kg every 8 weeks to Remsima (subcutaneous).

Effectiveness

This evidence review discusses the best available evidence for Remsima (subcutaneous) for managing rheumatoid arthritis. The evidence is a phase 3 non-inferiority study (n=343) in people with rheumatoid arthritis, which compared administration of Remsima (subcutaneous) with Remsima (intravenous). This study (CT-P13 3.5, part 2) was included in the European public assessment report (EPAR) for Remsima and has not yet been published in a peer-reviewed journal.

This evidence review considers the evidence for Remsima (subcutaneous) within its licensed indication and does not include studies that considered other routes of administration or other indications.

Appendix A summarises details of the included study. Appendix B gives an overview of the results for clinical effectiveness.

Disease activity

The efficacy of Remsima (subcutaneous) compared with Remsima (intravenous) in people with rheumatoid arthritis was assessed in a randomised, phase 3 non-inferiority trial. All 343 patients received 2 doses of Remsima 3 mg/kg intravenously at weeks 0 and 2. The subcutaneous group (n=167) were randomised to receive Remsima 120 mg subcutaneously at week 6 and every 2 weeks up to week 54 with intravenous placebo. The intravenous group (n=176) were randomised to receive Remsima 3 mg/kg intravenously at weeks 6, 14 and 22 with subcutaneous placebo and then switched to Remsima 120 mg subcutaneous at week 30 once every 2 weeks up to week 54. Methotrexate and folic acid were given concomitantly in both groups.

The primary endpoint of the study was the treatment difference of the mean change in DAS28-CRP (disease activity score 28-C-reactive protein) from baseline to week 22. The estimate of treatment difference was 0.27 (95% confidence interval [CI] 0.02 to 0.52), which was greater than the pre-specified non-inferiority margin of –0.6, indicating non-inferiority.

The analysis of other efficacy endpoints showed that Remsima (subcutaneous) was comparable in terms of disease activity measured by DAS28-CRP, DAS28-ESR (DAS28-erythrocyte sedimentation rate) and American College of Rheumatology (ACR) response up to week 54.

The mean scores for DAS28-CRP and DAS28-ESR gradually decreased from baseline at each time point until week 54 in each treatment arm.

Prevention of progressive damage

No data were reported on prevention of progressive damage.

Safety

The safety profile of Remsima (intravenous) is well understood and described in the summaries of product characteristics.

The safety profile of Remsima (subcutaneous) compared with Remsima (intravenous) in people with rheumatoid arthritis was assessed in a randomised,

phase 3 non-inferiority trial. The safety profile of subcutaneous Remsima (n=168) was similar to the safety profile of the intravenous formulation (n=175); however, the study was powered for non-inferiority and not for safety outcomes.

The incidence of anti-infliximab antibodies following Remsima (subcutaneous) was comparable to Remsima (intravenous) and had no significant impact on efficacy and the safety profile.

Localised injection site reactions associated with Remsima (subcutaneous), were predominantly mild to moderate and included: erythema, pain, pruritus, swelling, induration, haematoma, oedema, bruising, coldness, irritation, paraesthesia, ulcer, urticaria, haemorrhage, rash and scab. Most of these reactions occurred immediately or within 24 hours of subcutaneous injection and resolved spontaneously without any treatment.

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 pose 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.

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

Limitations of the evidence

The data in 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.

The study duration was short. Although the whole trial was 54 weeks in duration, only the first 30 weeks of the study directly compared Remsima (subcutaneous) with Remsima (intravenous). However, the treatment arms were identical until week 6, by which time the main part of the response was already achieved. Although the study was powered to measure non-inferiority, after 22 weeks of treatment, the Remsima (subcutaneous) arm showed an improvement of 0.27 points in DAS28-CRP compared with the intravenous arm, although this difference is not considered clinically significant.

Unlike the dosing of Remsima (intravenous), which is adjusted according to body weight, Remsima (subcutaneous) is given at a fixed dose of 120 mg for all adults. People with a body mass index (BMI) of 35 or over were not included in the study, and there were only 7 people weighing over 100 kg in the Remsima (subcutaneous) group. Therefore, efficacy of Remsima (subcutaneous) is not known in people with a BMI of 35 or over and evidence is limited in people who weigh over 100 kg. A subgroup analysis conducted by the authors showed no significant difference in outcomes in people of different BMIs; however, the study was not powered for such subgroup analyses.

No patient-centred outcomes were reported. Subcutaneous administration is known to be preferable for some people, but it is possible that subcutaneous administration could affect treatment adherence. It is not possible to determine the effects of non-adherence from this study design.

Resource implications

The cost of prescribing Remsima (subcutaneous) for managing rheumatoid arthritis 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 resource impact assessment for a more detailed assessment of the budget impact of this medicine.

Likely place in therapy

As with all biologic disease-modifying antirheumatic drugs (DMARDs) for rheumatoid arthritis, Remsima (subcutaneous) would be prescribed and initiated in secondary care. Unlike intravenous infliximab, which is usually administered in secondary care rheumatology clinics, 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 to the TNF-alpha inhibitors.

There are no data on people switching to Remsima (subcutaneous) from Remsima (intravenous) at doses higher than 3 mg/kg or frequencies of administration higher than every 8 weeks, and there are no data on people switching from other infliximab products to Remsima (subcutaneous).

Development of the evidence review

Process

The evidence summary: process guide sets out the process NICE uses for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

Expert advisers and declarations of interest

Dr Louise Mercer, consultant rheumatologist, Stockport NHS Foundation Trust, no relevant interests to declare

Dr William Tillett, consultant rheumatologist, Royal United Hospitals NHS Foundation Trust, no relevant interests to declare

Alan Clatworthy, rheumatology pharmacist, Swansea Bay University Health Board, no relevant interests to declare

Terms used in this evidence review

American College of Rheumatology (ACR 20, 50 and 70)

The American College of Rheumatology (ACR) are response criteria used to determine the efficacy of treatments for rheumatoid arthritis. The ACR20 gives the proportion of people who have achieved a 20% improvement in tender and swollen joints as well as 20% improvement in 3 of 5 pre-defined criteria. The ACR50 represents the proportion achieving a 50% improvement and ACR70 represents a 70% improvement.

Biosimilar

A biosimilar medicine is a biological medicine that has been shown not to have any clinically meaningful differences from the originator medicine in terms of quality, safety and efficacy. Where NICE has already recommended the originator biological medicine, the same guidance will normally apply to a biosimilar of that originator.

Disease activity score 28 (DAS28-CRP or DAS28-ESR)

The disease activity score (DAS) is a combined score that is used to measure the disease activity in people with rheumatoid arthritis. The score includes the number of swollen and tender joints (in 28 joints), either the C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), and the patient's global assessment measured on a visual analogue scale. The DAS28 is a number between 0 and 10, indicating how active the person's rheumatoid arthritis is.

DAS28 scores calculated with the ESR instead of the CRP tend to give higher readings, particularly in women and older people.

Appendices

Appendix A: Summary of the included study

Study	Number of participants	Population	Intervention	Comparison	Primary outcome	Major limitations
CT-P13 3.5, part 2 (EPAR)	n=343	People years with rheumatoid arthritis. Mean age 51.4 (SD 12.29), 78.4% female.	Remsima (intravenous) 3 mg/kg at weeks 0 and 2, 120 mg Remsima (subcutaneous) at week 6 and every 2 weeks up to week 54. Methotrexate was given concomitantly. Remsima (intravenous) placebo (n=167).	Remsima (intravenous) 3 mg/kg at weeks 0, 2, 6, 14 and 22 and then switched to Remsima (subcutaneous) 120 mg at week 30 once every 2 weeks up to week 54. Methotrexate was given concomitantly. Remsima (subcutaneous) placebo (n=176).	Treatment difference of the change from baseline of DAS28-CRP at week 22.	The data from the RCT were not published at the time of this evidence review. No baseline population data available or data on methotrexate dose or route of administration in each arm. Short duration of comparative study.

References:

European public assessment report for Remsima

Summary of product characteristics for Remsima

Abbreviations: EPAR, European public assessment report; DAS28-CRP, disease activity score 28-C-reactive protein; RCT, randomised control trial; SD, standard deviation.

Appendix B: Results tables

CT-P13 3.5, part 2 (EPAR)

	Remsima SC (Remsima IV week 0 to 2 and Remsima SC week 6 to 54)	Remsima IV (Remsima IV week 0 to 30 and Remsima SC week 30 to 54)	Analysis
n	**165**	**174**	
Primary outcomes: Mean difference in DAS28-CRP (±SD) at week 22	-2.7 3.3 (±1.1) from baseline of 6.0 (±0.8)	-2.4 3.5 (±1.2) from baseline of 5.9 (±0.8)	Mean difference 0.27 (95% CI 0.02 to 0.52) EPAR analysis greater than the pre-specified non-inferiority margin of -0.6
Selected secondary outcomes	-	-	-
Mean difference in DAS28-ESR at week 22	-2.7 4.0 (±1.1) from baseline of 6.7 (±0.8)	-2.5 4.1 (±1.3) from baseline of 6.6 (±0.8)	Mean difference 0.2 No statistical analysis reported
Proportion of people achieving ACR20 clinical response at week 22	139/165 (84.2%)	137/174 (78.7%)	No statistical analysis reported
Proportion of people achieving ACR50 clinical response at week 22	85/165 (51.5%)	90/174 (51.7%)	No statistical analysis reported
Proportion of people achieving ACR70 clinical response at week 22	46/165 (27.9%)	49/174 (28.2%)	No statistical analysis reported
Safety and tolerability outcomes	-	-	-
Systemic injection reactions (rash, pruritus, flushing, and oedema)	1.2 per 100 patient-years	2.1 per 100 patient-years	No statistical analysis reported

	Remsima SC (Remsima IV week 0 to 2 and Remsima SC week 6 to 54)	Remsima IV (Remsima IV week 0 to 30 and Remsima SC week 30 to 54)	Analysis
Localised injection site reactions	17.6 per 100 patient-years	21.4 per 100 patient-years	No statistical analysis reported
Immunogenicity	The incidence of anti-infliximab antibodies following the SC Remsima was not higher than that of IV Remsima	The incidence of anti-infliximab antibodies following the SC Remsima was not higher than that of IV Remsima	No data or statistical analysis reported

References:

Summary of product characteristics for Remsima

Abbreviations: ACR, American College of Rheumatology; CI, confidence interval; CRP, c-reactive protein; DAS, disease activity score; DAS28-CRP, disease activity score 28-C-reactive protein; EPAR, European public assessment report; ESR, erythrocyte sedimentation rate; IV, intravenous; SC, subcutaneous; SD, standard deviation.

Appendix C: Quality assessment of included studies

Not applicable.

Appendix D: Literature search strategy

Database search strategies (Ovid Username: nicempc / Password: mpclit)
Database: Medline
Platform: Ovid
Version: Ovid MEDLINE(R) <1946 to February 28, 2020>
Search date: 2nd March 2020
Number of results retrieved: 152
Search strategy:

Database: Ovid MEDLINE(R) <1946 to February 28, 2020>
Search Strategy:

1	exp Arthritis, Rheumatoid/ (111451)
2	rheumatoid*.tw. (104224)
3	(caplan* adj2 syndrome).tw. (117)
4	(felty* adj2 syndrome).tw. (691)
5	((inflammatory or idiopathic) adj2 arthritis).tw. (9344)
6	"inflammatory polyarthritis".tw. (340)
7	or/1-6 (146894)
8	Infliximab/ (9995)
9	(infliximab* or CT-P13 or CTP13).tw. (10054)
10	8 or 9 (12616)
11	Biosimilar Pharmaceuticals/ (1848)
12	(biosimilar* or subcutaneous or sc).tw. (175398)
13	11 or 12 (175584)
14	10 and 13 (545)
15	Remsima*.tw. (57)
16	14 or 15 (547)
17	7 and 16 (164)
18	limit 17 to english language (154)
19	animals/ not humans/ (4640447)
20	18 not 19 (152)

Database: Medline in-process
Platform: Ovid
Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to February 28, 2020>
Search date: 2nd March 2020
Number of results retrieved: 39
Search strategy:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to February 28, 2020>
Search Strategy:

---
1 exp Arthritis, Rheumatoid/ (0)
2 rheumatoid*.tw. (8852)
3 (caplan* adj2 syndrome).tw. (4)
4 (felty* adj2 syndrome).tw. (25)
5 ((inflammatory or idiopathic) adj2 arthritis).tw. (1309)
6 "inflammatory polyarthritis".tw. (17)
7 or/1-6 (9816)
8 Infliximab/ (0)
9 (infliximab* or CT-P13 or CTP13).tw. (1432)
10 8 or 9 (1432)
11 Biosimilar Pharmaceuticals/ (0)
12 (biosimilar* or subcutaneous or sc).tw. (19771)
13 11 or 12 (19771)
14 10 and 13 (148)
15 Remsima*.tw. (7)
16 14 or 15 (150)
17 7 and 16 (39)
18 limit 17 to english language (39)
19 animals/ not humans/ (0)
20 18 not 19 (39)

Database: Medline epubs ahead of print
Platform: Ovid
Version: Ovid MEDLINE(R) Epub Ahead of Print <February 28, 2020>
Search date: 2nd March 2020
Number of results retrieved: 13
Search strategy:

Database: Ovid MEDLINE(R) Epub Ahead of Print <February 28, 2020>
Search Strategy:
---
1 exp Arthritis, Rheumatoid/ (0)
2 rheumatoid*.tw. (1458)
3 (caplan* adj2 syndrome).tw. (1)
4 (felty* adj2 syndrome).tw. (3)
5 ((inflammatory or idiopathic) adj2 arthritis).tw. (262)
6 "inflammatory polyarthritis".tw. (5)
7 or/1-6 (1639)
8 Infliximab/ (0)
9 (infliximab* or CT-P13 or CTP13).tw. (225)
10 8 or 9 (225)
11 Biosimilar Pharmaceuticals/ (0)
12 (biosimilar* or subcutaneous or sc).tw. (2369)
13 11 or 12 (2369)
14 10 and 13 (38)
15 Remsima*.tw. (1)
16 14 or 15 (38)
17 7 and 16 (13)
18 limit 17 to english language (13)

19 animals/ not humans/ (0)
20 18 not 19 (13)

Database: Medline daily update
Platform: Ovid
Version: Ovid MEDLINE(R) Daily Update <February 28, 2020>
Search date: 2nd March 2020
Number of results retrieved: 0
Search strategy

Database: Ovid MEDLINE(R) Daily Update <February 28, 2020>
Search Strategy:
---
1 exp Arthritis, Rheumatoid/ (73)
2 rheumatoid*.tw. (68)
3 (caplan* adj2 syndrome).tw. (0)
4 (felty* adj2 syndrome).tw. (0)
5 ((inflammatory or idiopathic) adj2 arthritis).tw. (14)
6 "inflammatory polyarthritis".tw. (0)
7 or/1-6 (101)
8 Infliximab/ (6)
9 (infliximab* or CT-P13 or CTP13).tw. (13)
10 8 or 9 (13)
11 Biosimilar Pharmaceuticals/ (7)
12 (biosimilar* or subcutaneous or sc).tw. (140)
13 11 or 12 (141)
14 10 and 13 (2)
15 Remsima*.tw. (0)
16 14 or 15 (2)
17 7 and 16 (0)
18 limit 17 to english language (0)
19 animals/ not humans/ (2478)
20 18 not 19 (0)

Database: Embase
Platform: Ovid
Version: Embase <1974 to 2020 Week 09>
Search date: 2nd March 2020
Number of results retrieved: 485
Search strategy:

Database: Embase <1974 to 2020 Week 09>
Search Strategy:
---
1 exp rheumatoid arthritis/ (195852)
2 rheumatoid*.tw. (164394)
3 (caplan* adj2 syndrome).tw. (92)
4 (felty* adj2 syndrome).tw. (717)
5 ((inflammatory or idiopathic) adj2 arthritis).tw. (21341)

6 "inflammatory polyarthritis".tw. (621)
7 or/1-6 (229022)
8 infliximab/ (49400)
9 (infliximab* or CT-P13 or CTP13).tw. (25466)
10 8 or 9 (50262)
11 biosimilar agent/ (4337)
12 (biosimilar* or subcutaneous or sc).tw. (279176)
13 11 or 12 (280064)
14 10 and 13 (2731)
15 Remsima*.af. (398)
16 14 or 15 (2776)
17 7 and 16 (1018)
18 limit 17 to english language (991)
19 nonhuman/ not human/ (4580057)
20 18 not 19 (976)
21 limit 20 to (books or chapter or conference abstract or conference paper or "conference review") (455)
22 20 not 21 (521)
23 limit 22 to (letter or note) (36)
24 22 not 23 (485)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL
Platform: Wiley
Version:
CDSR –Issue 3 of 12, Month year
CENTRAL – Issue 3 of 12, March 2020
Search date: 2nd March 2020
Number of results retrieved: CDSR - 1 ; CENTRAL - 55

#1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees 5957
#2 (rheumatoid*):ti,ab,kw 15331
#3 (caplan* near/2 syndrome):ti,ab,kw 0
#4 (felty* near/2 syndrome):ti,ab,kw 4
#5 ((inflammatory or idiopathic) near/2 arthritis):ti,ab,kw 982
#6 ("inflammatory polyarthritis"):ti,ab,kw 14
#7 #1 or #2 or #3 or #4 or #5 or #6 16035
#8 MeSH descriptor: [Infliximab] this term only 706
#9 (infliximab* or CT-P13 or CTP13):ti,ab,kw 2253
#10 #8 or #9 2253
#11 MeSH descriptor: [Biosimilar Pharmaceuticals] this term only 138
#12 (biosimilar* or subcutaneous or sc):ti,ab,kw 32874
#13 #11 or #12 32874
#14 #10 and #13 313
#15 (Remsima*):ti,ab,kw25
#16 #14 or #15 317
#17 #7 and #16 156
#18 "conference":pt or (clinicaltrials or trialsearch):so 481429
#19 #17 not #18 56

Database: HTA
Platform: CRD
Version: Up to 2018
Search date: 2nd March 2020
Number of results retrieved: 3
Search strategy:

1	MeSH DESCRIPTOR Infliximab	164	Delete
2	(infliximab* or CT-P13 or CTP13)	351	Delete
3	#1 OR #2	351	Delete
4	MeSH DESCRIPTOR Biosimilar Pharmaceuticals	6	Delete
5	(biosimilar* or subcutaneous or sc)	1039	Delete
6	(#4 or #5)	1039	Delete
7	#3 AND #6	17	Delete
8	(#3 AND #6) IN HTA	3	Delete

Trials registry search strategies
Clinicaltrials.gov
Search date: 28th Feb 2020
Number of results retrieved: 9
Search strategy: (Remsima AND rheumatoid)
NB: searching the following retrieved no additional relevant results: (subcutaneous AND infliximab AND rheumatoid)

Clinicaltrialsregister.eu
Search date: 28th Feb 2020
Number of results retrieved: 6
Search strategy: (Remsima AND rheumatoid)
NB: searching the following retrieved no additional relevant results: (subcutaneous AND infliximab AND rheumatoid)

Excluded registry results
All excluded results were irrelevant

Additional search notes

Rheumatoid arthritis population terms in the search strategy are from the MEDLINE & Embase literature searches for the rheumatoid arthritis NICE guideline NG100: https://www.nice.org.uk/guidance/ng100/evidence/f-dmards-pdf-4903172323 (pg99)

Appendix E: Excluded studies

A literature search for subcutaneous infliximab was conducted, which identified 526 references after duplicates were removed (see search strategy for full details). These references were screened using their titles and abstracts and no references were obtained. The schedule for the evidence review was affected by COVID-19 and the searches were re-run on 7 July 2020 to identify any additional papers which may have been published since the original search date. No additional references were identified.

Because no references were identified, data from study CT-P13 3.5, part 2, which were included in the European public assessment report (EPAR) for Remsima (subcutaneous), were used to inform this evidence review. A summary of CT-P13 3.5, part 2, is given in appendix A.