East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, Crawley CCG, Horsham & Mid-Sussex CCG

Evidence review for Surrey Prescribing Clinical Network

Medicine and proposed indication	Vedolizumab for treating moderately to severely active ulcerative colitis
Requested by	NICE technology appraisal guidance 342

SUMMARY

Clinical Effectiveness –
Reproduced from summary of NICE appraisal committee's key conclusions with reference to section in full guidance. For full detail see http://www.nice.org.uk/guidance/ta342

		Section
Availability, nature and quality of evidence	The evidence provided by the company to compare vedolizumab with conventional therapy was from a randomised controlled trial, which was considered robust. However, the Committee was aware that GEMINI I was not powered to test for a statistically significant difference in the treatment effect of vedolizumab between subgroups, that is people who had not had TNF-alpha inhibitor treatment before, and people in whom TNF-alpha inhibitors had failed.	4.6, 4.7
	To compare vedolizumab with the TNF-alpha inhibitors, the company used a network meta-analysis. The data available for the network meta-analysis, relating to the effectiveness of TNF-alpha inhibitors after TNF-alpha inhibitor failure was limited to only 1 comparison (with adalimumab).	4.9
Relevance to general clinical practice in the NHS	The Committee concluded that the clinical efficacy results from GEMINI I were generalisable to clinical practice, but that there was uncertainty about whether the proportion of people who had previous TNF-alpha inhibitor treatment in GEMINI I would be the same as in the population considered for vedolizumab treatment in England.	4.5
	The Committee noted that the summary of product characteristics suggests response to treatment should be assessed after 10 weeks, to determine whether treatment should be continued. However in GEMINI I, people were assessed for response at 6 weeks. The Committee concluded GEMINI I may have underestimated the proportion of people who would have a response to induction treatment in clinical practice, and that data on the outcome for those who responded after 6 weeks were not available from the trial.	4.6

Uncertainties generated by the evidence	The Committee considered the network meta-analyses presented by the company to estimate the relative effectiveness of vedolizumab compared with adalimumab, infliximab and golimumab. It noted that clinical data for infliximab and golimumab were not available for people who had previously had a TNF-alpha inhibitor. Therefore, for this subgroup a comparison could only be made between vedolizumab and adalimumab.	Section 4.9
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee heard from the company and the clinical experts that people in whom TNF-alpha treatment had failed could be considered to have ulcerative colitis that is more difficult to treat. The Committee was aware that GEMINI I was not powered to test for a statistically significant difference in the treatment effect of vedolizumab between subgroups.	4.7
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that, based on the data from GEMINI I, vedolizumab was clinically effective in the whole population, and in both subgroups, compared with conventional therapy. However, the Committee agreed that GEMINI I may have underestimated the proportion of people who would have a response to induction treatment in clinical practice	4.6, 4.7

Safety - Reproduced from summary of NICE appraisal committee's key conclusions with reference to section in full guidance.

The adverse events reported in GEMINI I were similar in the placebo and vedolizumab arms. The Committee was aware that cases of progressive multifocal leukoencephalopathy (PML) have been seen with natalizumab, an antibody that inhibits α4-integrin. It was aware that, because vedolizumab also inhibits an α4-integrin, the incidence of PML in people treated with vedolizumab is being closely monitored, although there have been no reports of PML. The Committee heard from clinical experts that natalizumab inhibits α4-integrin in all tissues of the bodies including the brain. Vedolizumab targets the gut, so the Committee believed the risk of PML in people treated with vedolizumab to be low. The Committee concluded that vedolizumab appeared to be safe and well tolerated by patients.

4.10

The long-term efficacy and safety of vedolizumab and the optimum duration of therapy remains unclear, in GEMINI I, people only had vedolizumab for up to 52 weeks. The clinical experts stated that the benefits of targeted immunosuppression with vedolizumab may not have been fully seen in GEMINI I because some people had vedolizumab plus a systemic immunosuppressant.

Patient factors

Like Infliximab, Vedolizumab is given by intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter. (Adalimumab and Golimumab are given by subcutaneous injection.) Continued therapy for people with ulcerative colitis should be carefully reconsidered if no evidence of therapeutic benefit is observed by week 10

Cost implications

Annual treatment cost per patient per drug (based on PAS for Vedolizumab and NHS list for others) from NICE template

Treatment	1st year		Subsequent years
Cost (£)	Induction (£)	Maintenance (£)	Maintenance (£)
Vedolizumab	6,150	10,763	13,325
Infliximab - proprietary	5,035	8,392	10,910
Infliximab - Biosimilar *	4,532	7,553	9,819

Adalimumab	2,817	7,794	10,611
Golimumab	3,052	8,393	9,919

When there is more than one NICE-approved treatment available, a discussion between the responsible clinician and the patient should take place about the advantages and disadvantages of the treatments available, taking into consideration therapeutic need and whether or not the patient is likely to adhere to treatment.
The least expensive will be chosen (taking into account administration costs, dosage and price per dose) unless an order of preference is stated in the TAs.

*In Surrey with local pricing agreements and patient access schemes taken into account:
Biosimilar infliximab (Inflectra) is the least expensive (over the first 2 years, including administration cost) followed closely by Adalimumab and Golimumab.
Vedolizumab and Remicade are considerably more expensive.

Relevant guidance / reviews

http://www.nice.org.uk/guidance/ta342
http://www.nice.org.uk/guidance/ta329

Likely place in therapy relative to current treatments

In line with NICE Vedolizumab will be offered as an option for treating moderately to severely active ulcerative colitis in adults.
It should be used within the marketing authorisation which states that vedolizumab is indicated 'for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, or lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha antagonist'. The recommended dosage of vedolizumab is 300 mg given by intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter. Continued therapy for people with ulcerative colitis should be carefully reconsidered if no evidence of therapeutic benefit is observed by week 10.

NICE states that when there is more than one NICE-approved treatment available, a discussion between the responsible clinician and the patient should take place about the advantages and disadvantages of the treatments available, taking into consideration therapeutic need and whether or not the patient is likely to adhere to treatment. Following this the least expensive will be chosen (taking into account administration costs, dosage and price per dose) unless an order of preference is stated in the TAs.

As the most expensive treatment option in this disease state we need to be clear on what therapeutic need it may be appropriate for.
Opinion has been sought of local gastroenterologists regarding the patients in whom vedolizumab might be used in preference to anti-TNF therapy.
The Network proposed vedolizumab would be suitable for a small cohort of patients where there were clinical indications to prefer it over lower cost therapies, for example in patients with high infection risk. They agreed the clinical indications for its use over the anti-TNFs should be collated and reviewed after 6 months by the Gastroenterology Network.

Recommendation to PCN

Vedolizumab will be offered as an option for treating moderately to severely active ulcerative colitis in adults when this expensive alternative is considered the most suitable therapy for the individual.
Applications to the CCGs for funding (Blueteq tick box forms) will collect information on reasons for choosing vedolizumab. This information will be reviewed by the Surrey Gastroenterology Network after 6 months.

Medicine details	
Name and brand name	Vedolizumab (Entyvio®) 300 mg powder for concentrate for solution for infusion
Licensed indication, formulation and usual dosage	Ulcerative Colitis Entyvio is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist. Crohn's Disease Entyvio is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.
Summary of mechanism of action, and relevant pharmacokinetics	Vedolizumab (Entyvio, Takeda) is a humanised monoclonal antibody. It targets α4β7 integrin, which is expressed in certain white blood cells that are found in the gut. α4β7 integrin is responsible for recruiting these cells to inflamed bowel tissue. Vedolizumab suppresses immune activity only in the gut, a step-change in the management of ulcerative colitis because other immunosuppressants affect immune activity in the whole body.
Important drug interactions	No interaction studies have been performed. Vedolizumab has been studied in adult ulcerative colitis and Crohn's disease patients with concomitant administration of corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate), and aminosalicylates. Population pharmacokinetic analyses suggest that co-administration of such agents did not have a clinically meaningful effect on vedolizumab pharmacokinetics. The effect of vedolizumab on the pharmacokinetics of commonly co-administered medicinal compounds has not been studied. Vaccinations Live vaccines, in particular live oral vaccines, should be used with caution concurrently with Entyvio
Monitoring requirements	All patients should be observed continuously during each infusion. For the first two infusions, they should also be observed for approximately two hours following completion of the infusion for signs and symptoms of acute hypersensitivity reactions. For all subsequent infusions, patients should be observed for approximately one hour following completion of the infusion.
Prescribing considerations	Ulcerative Colitis The recommended dose regimen of Entyvio is 300 mg administered by intravenous infusion at zero, two and six weeks and then every eight weeks thereafter. Continued therapy for patients with ulcerative colitis should be carefully reconsidered if no evidence of therapeutic benefit is observed by Week 10.
Other considerations	The company have not presented safety or efficacy data past 54 weeks of treatment. Cost effectiveness calculations are based on treatment stopping after 12 months.

Potential patient group (if appropriate to include)	
Discussion at Gastroenterology Network Meeting 15-07-15	The network had a keen interest in Vedolizumab as it presents an innovative treatment with a different mechanism of action to other drug treatment options for ulcerative colitis. Vedolizumab suppresses immune activity only in the gut, a step-change in the management of ulcerative colitis because other immunosuppressants affect immune activity in the whole body. The network highlighted however that vedolizumab appears from trial data to be relatively slow acting which may be a disadvantage as IBD patients often need rapid efficacy. The paucity of evidence over long-term efficacy and safety of vedolizumab and the optimum duration of therapy was discussed. The Network proposed vedolizumab would be suitable for a small cohort of patients where there was clinical indications to prefer it over lower cost therapies, for example in patients with high infection risk. There was agreement to have on the Blueteq form a free text box for reason why using rather than less expensive alternatives. The Pharmaceutical commissioning team would then be able to report these back to a network meeting in 6 months. The Network highlighted that vedolizumab may be used if anti-TNF has been tried and not been effective and this will need to be added to the pathway. There may be a case in future to also add second line anti-TNF use. The network agreed to consider sequential use of anti-TNF in IBD at their next meeting. This may link with antibody and drug level testing, escalation and de-escalation of therapy in line with levels.
Potential patient numbers per 100,000	
Outcomes required	Assess at 8-12 weeks using clinical scoring (a decrease in Mayo score of ≥3 points and ≥30% from Baseline, plus decrease in rectal bleeding) and/or steroid sparing effect

Summary of current treatment pathway
See pathway attached

Equity / Stakeholder views (if relevant)	
Decisions of local Trusts DTCs and neighbouring APCs	Ashford and St Peters Epsom and St Helier Frimley Park Kingston Royal Surrey County Surrey and Sussex South West London – in line with recommendations in this paper, tick box form available.
Recommendations from national / regional decision making groups	NICE - Vedolizumab is recommended, within its marketing authorisation, as an option for treating moderately to severely active ulcerative colitis in adults if the company provides it with the discount agreed in the PAS.
Stakeholder views	

CCG priorities	

Health economic considerations	
Cost per year per patient	£16,900 for 12 months, £13,325 following years however NICE economic analysis for cost effectiveness was 12 months only then stop. Plus tariff costs for OPD or day-case depending on Trust.
Alternative treatments cost per patient per year	Infliximab biosimilar list price £12,085 for 1st 12 months and £9,819 following years but NHS has discount available considerably reducing this price. This also has costs for OPD or day-case administration. Adalimumab £10,611 first and following years – delivered by homecare
Other financial considerations (if relevant)	
Health economic data (if available)	

References

Date:21/07/15

Prepared by: Liz Clark
Declaration of interest: None

Reviewed by:

East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, Crawley CCG, Horsham & Mid-Sussex CCG

Comments on Evidence review for Surrey Prescribing Clinical Network

Please include any comments you have answers to any questions asked as well as any additional references you feel may need to be included in the review. If there are any other of your colleagues that you feel we need to engage with please also let us know their names and where/how they can be contacted.

Medicine and proposed indication	
Prepared by	Name, designation and organisation
Comments on evidence review	
Additional evidence and references for consideration	Include any additional evidence and references you would like to submit for inclusion in the evidence review
Specific clinical questions	Specific questions arising from review
Other colleagues who should be contacted	Include name, designation and contact details of any other colleagues who should be consulted about this evidence
Declaration of interests	For example – any teaching, training, grants, consultancy, research funding, stock holding, nurse funding, equipment

Signature …….. Date ……