Surrey Heartlands Integrated Care System
Area Prescribing Committee (APC)

Integrated Care Partnership - Surrey Downs, Guildford & Waverley, North-West Surrey, and East Surrey Places & associated partner organisations.

NICE Technology Appraisals (TA) briefing paper for local implementation

NICE TA Guidance name and number	Upadacitinib for previously treated moderately to severely active Crohn's disease TA905		
Available at	https://www.nice.org.uk/guidance/ta905		
Date of issue	21st June 2023	**Implementation deadline**	21st July 2023

Medicine details[1]	
Name and brand name	Upadacitinib (Rinvoq)
Manufacturer	AbbVie
Mode of action	JAK 1 inhibitor
Licensed indication	RINVOQ is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent.
Formulation	Prolonged-release tablet
Dosage	Induction The recommended induction dose of upadacitinib is 45 mg once daily for 12 weeks. Maintenance The recommended maintenance dose of upadacitinib is 15 mg or 30 mg once daily based on individual patient presentation: • A dose of 15 mg is recommended for patients at higher risk of VTE, MACE and malignancy. • A dose of 30 mg once daily may be appropriate for patients with high disease burden who are not at higher risk of VTE, MACE and malignancy or who do not show adequate therapeutic benefit to 15 mg once daily. • A dose of 30 mg once daily may be appropriate for patients who have not achieved adequate therapeutic benefit after the initial 12-week induction. For these patients, upadacitinib should be discontinued if there is no evidence of therapeutic benefit after 24 weeks of treatment. • The lowest effective dose to maintain response should be used.

	For patients 65 years of age and older, the recommended maintenance dose is 15 mg once daily (see section 4.4). In patients who have responded to treatment with upadacitinib, corticosteroids may be reduced and/or discontinued in accordance with standard of care.
Comparison of NICE TA with Summary of Product Characteristics (SmPC)[2]	No differences noted. Please note: the summary of product characteristics for upadacitinib does not allow the following: a) Continuation of the 45mg induction dose after the initial 12-week induction period. This is the current dose considered by NICE as part of this NICE evaluation. Subsequent changes in the license following NICE publication will need to be considered by the Area Prescribing Committee and will not be routinely funded by local commissioners, as the incremental cost per QALY would not have been considered.

NICE TA recommendations[2]

Recommendations

1.1 Upadacitinib is recommended as an option for treating moderately to severely active Crohn's disease in adults, only if:

- the disease has not responded well enough or lost response to a previous biological treatment or
- a previous biological treatment was not tolerated or
- tumour necrosis factor (TNF)-alpha inhibitors are contraindicated. Upadacitinib is only recommended if the company provides it according to the commercial arrangement.

1.2 If people with the condition and their clinicians consider upadacitinib to be 1 of a range of suitable treatments, after discussing the advantages and disadvantages of all the options, use the least expensive. Take into account the administration costs, dosage, price per dose and commercial arrangements.

1.2 These recommendations are not intended to affect treatment with upadacitinib that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Please note: The NICE recommendations are for use of upadacitinib *after* a biological treatment due to treatment failure or intolerance, or if TNF-alpha inhibitors are contraindicated and generally *not* for first line use after conventional therapy (including immunosuppressive and/or corticosteroid treatments), unless TNF-alpha inhibitors are contraindicated.

Decision making framework (DMF)

National guidance and priorities

The ICS has a legal obligation to commission this medicine in line with the NICE TA.

- This NICE TA has been fast tracked and assigned an implementation deadline of 30 days.
- The implementation deadline is 21st July 2023.

Clinical effectiveness

Standard treatments for moderately to severely active Crohn's disease when conventional treatments stop working are biological treatments (such as TNF-alpha inhibitors, ustekinumab or vedolizumab).

Clinical trial evidence shows that upadacitinib increases the likelihood of disease remission compared with placebo. Indirect comparisons of upadacitinib with ustekinumab and vedolizumab suggest that it is as effective.

A cost comparison suggests that upadacitinib has a similar or lower cost than vedolizumab and ustekinumab. So upadacitinib is recommended.

Patient safety

- The product should be used within its product license.
- Upadacitinib is a Black Triangle drug – all suspected adverse reactions should be reported in order to identify rare adverse effects.
- An MHRA issued a Drug Safety Update on 26th April 2023 to inform healthcare professionals of new risk minimisation measures for JAK inhibitors used to treat chronic inflammatory disorders This is available at: Janus kinase (JAK) inhibitors: new measures to reduce risks of major cardiovascular events, malignancy, venous thromboembolism, serious infections and increased mortality - GOV.UK (www.gov.uk).

  Therefore, this must be considered and clinical judgement is needed to determine the suitability of upadacitinib for each person based on the risks and benefits of treatment.

- The committee concluded that the network meta-analyses indicated that upadacitinib was likely to have a similar adverse event profile to ustekinumab and vedolizumab.

Patient factors

- An additional treatment option would be valued by patients.
  - The clinical experts explained that there is an unmet need for new treatments for Crohn's disease, particularly for people whose disease is refractory or has lost response to treatment.
  - Upadacitinib has a different mechanism of action to other treatments. Therefore, it may be effective for a proportion of people whose disease does not respond to these existing treatments.
  - Upadacitinib is an oral drug, which is a benefit over other treatment options.
- This medicine is available under a homecare service so will be delivered directly to the patient.

Environmental impact

- Available as an oral tablet so less waste than other options which are either infusions and/or sub-cutaneous injections.

Equality & diversity

None listed in the NICE TA however upadacitinib is licensed only for adults – younger patients will not be able to access this treatment under this TA.

Note: Drugs approved by NICE for adult conditions will be commissioned in children at specialised paediatric centres if the patient meets the NICE criteria and there is evidence to suggest that the drug is safe and clinically appropriate to use in children as per the NHS England Medicines for Children Policy (see https://www.england.nhs.uk/publication/commissioning-medicines-for-children-specialised-services/ and a Blueteq form is available.

Place in therapy relative to available treatments

Upadacitinib is the first JAK available for use in Crohn's disease. If other JAK inhibitors are made available, a preferred cost-effective option will be chosen.

This means that there are now four different modes of action in Crohn's disease.

Taking into account the confidential prices for upadacitinib, ustekinumab and vedolizumab, the committee concluded that the total costs associated with upadacitinib were similar to or lower than the costs for ustekinumab and vedolizumab.

Stakeholder views

The paper was sent out for consultation and comments are listed on the front sheet.

Cost-effectiveness

The drug cost per Place according to NICE resources does not exceed £100,000.

a. Given the costs of the comparators vedolizumab and ustekinumab, there are predicted savings within the Surrey Heartlands ICS of £1,198,835. This is based on PAS/CAP prices and includes savings on drug costs and administration costs. See section 'NICE resource impact template' below for details.

Please note: The caveat is that the patent for ustekinumab is due to expire in the next year and the availability of biosimilar ustekinumab at a reduced cost will reduce the savings estimated.

Section 1: cost of the technology

a. Annual cost per patient (or complete course if shorter)
The list price per 28-tablet pack of upadacitinib is £805.56 for 15-mg tablets, £1,281.54 for 30-mg tablets and £2,087.10 for 45-mg tablets (excluding VAT; BNF online, accessed May 2023).

Table 1: annual costs for year 1 and year 2 (excluding VAT; BNF online, accessed May 2023) and not including price within commercial agreement.

	Drug regimen	Cost
Year 1 – induction and maintenance	3 months at 45mg od	£6,261.30
	9 months at 15mg od or	£7,250.04
	9 months at 30mg od	£11,533.86
	Total	**£13,511 - £17,795**
Year 2 - maintenance	12 months at 15mg od or	£9,667
	12 months at 30mg od	£15,378
		£9,667 - £15,378

b. Availability of CAP/PAS price:
Yes - the company has a commercial arrangement. This makes upadacitinib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

c. Price relative to comparable medicines:
This is the first JAK inhibitor available to treat Crohn's disease. Therefor no comparators are available.

Other options for use in Crohn's disease are:

Table 2: Cost of other options in Crohn's disease. Costs are NHS list price (excluding VAT) and do not take into account any commercial discounts, patient access scheme or service delivery costs. All costs assume no packs are split and therefore include the cost of wastage.

Drug	NICE	Date	Estimated annual drug acquisition costs	
			Year 1	Year 2
Adalimumab*	TA187	May-10	£12,064 - £13,428	£10,556 - £11,749
Infliximab*			£8,870 - £9,860	£8,237 - £9,156
Vedolizumab	TA352	Aug-15	£16,400 - £17,938	£13,325 - £14,350
Ustekinumab	TA456	Jul-17	£15,029	£10,735

*available as biosimilar

Section 2: NICE resource impact statement and template
Number of patients Year 1 and Year 5:

Potential patient numbers per 100,000:

b. NICE resource impact statement
None

c. NICE resource impact template
As per the NICE recommendations for upadacitinib, the eligible population is people who have treatment failure on biologic treatment and the comparators used are vedolizumab and ustekinumab.

The impact of future activity on cost (based on PAS/CAP prices) is predicted to have a saving for Surrey Heartlands ICS as follows:

Impact of future activity on drug costs	-£1,141,719
Impact of future activity on admin costs	-£57,116
Total	**-£1,198,835**

Please note: The caveat is that the patent for ustekinumab is due to expire and the availability of biosimilar ustekinumab at a reduced cost will reduce the savings estimated.

Drug costs for Surrey Heartlands:
As a potential saving is shown, the threshold of £100,000 per Place threshold is not exceeded.

Traffic light recommendation to APC

NHS Payment Scheme (NHSPS) excluded high-cost drug:
Yes

Recommended traffic light status and rationale:
e.g., RED – Specialist ONLY drugs - treatment initiated and continued by specialist clinicians.

PAD definitions, available at: Traffic Light Status (res-systems.net)

Implementation

NICE TA implementation must be within 30 days of publication.

Actions to implement:

a. Primary care
- This is a National Tariff excluded high-cost drug and is commissioned by ICSs for use in secondary care. There should be no prescribing in primary care.
- Primary care prescribers should be aware that their patient is receiving this medicine and ensure that this is recorded in the patient's notes in order to be alert to potential side-

effects and interactions with other medicines prescribed in primary care. This will also ensure that GP records, which are accessed by other healthcare providers, are a true and accurate reflection of the patient's medication.

b. Secondary care

- Providers are NHS hospital trusts.
- Trusts to follow internal governance procedures to add to their formulary and initiate homecare.
- The initiation, administration and on-going treatment is managed by secondary care.
- Specialists will be required to notify the high-cost drugs teams of initiation and response to treatment using the Blueteq® system.
- Homecare arrangements will be managed by the trust.

c. ICS

- This technology is commissioned by integrated care systems.
- Pathway to be discussed at the next Gastroenterology Network.
    - GN should discuss the sequencing of the drugs available in Crohn's disease given the NICE recommendations for use after a biological treatment.
- PAD and Joint Formulary entry to be made.

Proposed tick box forms

Blueteq® forms have been developed.

References:

1 RINVOQ 30 mg prolonged-release tablets Summary of Product Characteristics. emc. Available at: RINVOQ 30 mg prolonged-release tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) Accessed <21.6.23>

2 NICE Technology Appraisal Guidance: Upadacitinib for previously treated moderately to severely active Crohn's disease. Available at: https://www.nice.org.uk/guidance/ta905/resources Accessed <21.6.23>

3 NICE Resource Impact Report: Upadacitinib for previously treated moderately to severely active Crohn's disease. Available at: https://www.nice.org.uk/guidance/ta905/resources Accessed <21.6.23>

4 NICE Resource Impact Template: Upadacitinib for previously treated moderately to severely active Crohn's disease. Available at: https://www.nice.org.uk/guidance/ta905/resources Accessed <21.6.23>

Declaration of interest:

	Name	Role	Date	Declaration of interests (please give details below)
Prepared by	Tejinder Bahra	Lead MRU Pharmacist	21.6.23	None
Supported by				
Reviewed by	Georgina Randall	Senior MRU Technician		

Explanation of declaration of interest:

None.

Version control sheet:

Version	Date	Author	Status	Comment
1	25.7.23	T.Bahra	Final	

Blueteq® form:

1st line form

Please indicate whether patient meets the following NICE criteria:	Please tick
1. Please indicate which applies: A previous biological treatment was not tolerated (please give details below): : OR 1st line treatment with TNF-alpha inhibitors is contraindicated for this patient (contraindications to treatment may include heart failure and demyelinating disorders). Please provide details below::	
2. Patient has severe active Crohn's Disease. Please provide one or more disease activity scores below: **Crohn's Disease Activity Index of more than or equal to 300 OR** State score: Date taken: **Harvey Bradshaw Index (HBI) of more than or equal to 8/9** State score: Date taken: **OR Alternative scoring if applicable:** If these markers do not apply, please give alternative QOL score here:	
3. This patient's crohn's disease has responded inadequately to conventional therapy including corticosteroids, mercaptopurine, methotrexate or azathioprine, or they cannot tolerate, or have medical contraindication for such therapies **Please indicate which conventional therapies have been trialled below** ○ Corticosteroids ○ Mercaptopurine ○ Azathioprine (with or without allopurinol) ○ Methotrexate Please provide details of any medical contraindications here::	
4. FOR INFORMATION Funding will be approved for induction. Objective evidence of a response should be provided following induction (24 weeks after initiation) using the appropriate continuation form on blueteq. If the patient has responded to the initial (INDUCTION) course the commissioners will confirm funding up to 12 months (from initiation). This continuation form is to be used every 12 months thereafter if treatment withdrawal is not appropriate.	

2nd line

Please indicate whether patient meets the following NICE criteria:	Please tick
1. Patient has lost response to a previous biological treatment.	○ Yes ○ No
2. Please provide one or more disease activity scores below? **Crohn's Disease Activity Index (CDAI) OR** Current score: [ ] Date current score taken: [ ] **Harvey Bradshaw Index (HBI)** Current score: [ ] Date current score taken: [ ] **OR Alternative scoring if applicable:** If these markers do not apply, please give alternative QOL score here: [ ] Date current score taken: [ ]	
4. FOR INFORMATION Funding will be approved for induction. Objective evidence of a response should be provided following induction (24 weeks after initiation) using the appropriate continuation form on blueteq. If the patient has responded to the initial (INDUCTION) course the commissioners will confirm funding up to 12 months (from initiation). This continuation form is to be used every 12 months thereafter if treatment withdrawal is not appropriate.	

3rd line

Please indicate whether patient meets the following NICE criteria:	Please tick
1. Patient has lost response to TWO previous biological treatments.	○ Yes ○ No
2. Please provide one or more disease activity scores below: **Crohn's Disease Activity Index (CDAI) OR** Current score: [ ] Date current score taken: [ ] **Harvey Bradshaw Index (HBI)** Current score: [ ] Date current score taken: [ ] **OR Alternative scoring if applicable:** If these markers do not apply, please give alternative QOL score here: [ ] Date current score taken: [ ]	
4. FOR INFORMATION Funding will be approved for induction. Objective evidence of a response should be provided following induction (24 weeks after initiation) using the appropriate continuation form on blueteq. If the patient has responded to the initial (INDUCTION) course the commissioners will confirm funding up to 12 months (from initiation). This continuation form is to be used every 12 months thereafter if treatment withdrawal is not appropriate.	

4th line (& beyond)

Please indicate whether patient meets the following NICE criteria:	Please tick
1. Patient has lost response to AT LEAST THREE previous biological treatments.	○ Yes ○ No
2. Please provide one or more disease activity scores below: **Crohn's Disease Activity Index (CDAI) OR** Current score: _____ Date current score taken: _____ **Harvey Bradshaw Index (HBI)** Current score: _____ Date current score taken: _____ **OR Alternative scoring if applicable:** If these markers do not apply, please give alternative QOL score here: _____ Date current score taken: _____	
3. This application has been supported by the Surrey Gastroenterology Clinical Network MDT as per the agreed process?	○ Yes ○ No
4. FOR INFORMATION Funding will be approved for induction. Objective evidence of a response should be provided following induction (24 weeks after initiation) using the appropriate continuation form on blueteq. If the patient has responded to the initial (INDUCTION) course the commissioners will confirm funding up to 12 months (from initiation). This continuation form is to be used every 12 months thereafter if treatment withdrawal is not appropriate.	

Continuation form

Please indicate whether patient meets the following NICE criteria:	Please tick
1. Patient has demonstrated an objective response to treatment? Please provide date induction was initiated here (if within the last 12 months): :	○ Yes ○ No
2. Please provide one or more disease activity scores below: **Crohn's Disease Activity Index (CDAI) OR** Current score: Date current score taken: **HBI (Harvey Bradshaw Index)** Current score : Date current score taken : **OR Alternative scoring if applicable:** If these markers do not apply, please give alternative QOL score here: Date current score taken:	
3. Only complete question 4 if this patient has been on this treatment for 12 months or more.	
4. Patient is either NOT in clinical remission? (e.g. HB > 4 and or CDAI >150) OR is in clinical remission and trial withdrawal is not appropriate at this time. (Please check YES if you agree with this statement)	○ Yes ○ No
7. INFORMATION ONLY: **If the patient has responded to the initial (INDUCTION) doses the high cost drugs team will confirm funding up to 9 months (from induction)** **This continuation form is to be used every 12 months if treatment withdrawal is not appropriate.**	