NICE National Institute for Health and Care Excellence

Redacted

Upadacitinib for treating moderate rheumatoid arthritis [ID3878]

ACM 1 PART 2 – strictly confidential

SLIDES FOR COMMITTEE MEMBERS ONLY

ERG: PenTAG

Company: Abbvie

12 August 2021

Upadacitinib (Rinvoq, Abbvie)

Description of technology	A Janus-kinase (JAK) 1 inhibitor that blocks the JAK-signal transducer and activator of transcription (STAT) pathway and inflammatory responses.
Marketing authorisation	Upadacitinib is indicated for the treatment of moderate to severe active RA in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). It can be used as a monotherapy or in combination with methotrexate.
Dosage and administration	15 mg orally administered once daily.
Proposed place in treatment pathway for moderate RA	Upadacitinib can be used in the moderate RA population after: • 1 csDMARD • 2 or more csDMARDs Treatment options for RA also differ by methotrexate and rituximab tolerance

History of this appraisal and disease area

ACM 1 ID1400:J anuary 2020

- Positive recommendation for severe RA
- Negative recommendation for moderate RA
- ACD issued

ACM2: September 2020

- Positive recommendation for severe RA
- Negative recommendation for moderate RA
- FAD issued for severe RA (now TA665)
- ACD issued for moderate RA (now ID3878)

ACM1: ID3878 Today

- Moderate RA only

TA676 Filgotinib approved for moderate & severe RA

- February 2021

TA715 Adalimumab, etanercept and infliximab approved for moderate RA

- July 2021

Other technologies now recommended for moderate RA

- **Filgotinib**, **adalimumab**, **etanercept** and **infliximab** with methotrexate, recommended as an option
  - after inadequate response to intensive therapy with 2 or more conventional disease-modifying antirheumatic drugs (csDMARDs)
  - disease is moderate or severe (a disease activity score [DAS28] of 3.2 or more)
- Filgotinib, adalimumab and etanercept monotherapy recommended if methotrexate not tolerated or contraindicated
- If more than one treatment is suitable, treatment with the least expensive drug recommended
- Biosimilars for adalimumab, etanercept and infliximab available
- Response assessed at 6 months, and stopped if not sustained

3 issues outstanding

1. Treatment sequence
   a) For moderate disease: how best to account for best supportive care (BSC), and what source/value to use for efficacy of BSC & account for placebo effect in trial
   b) What options are available in both arms after progression to severe disease (i.e. should Upa be comparator arm sequence)
2. Uncertainties relating to the rate of progression from moderate to severe RA
3. What might an acceptable ICER look like given precedent from recent appraisals and comments from stakeholders on the uncertainties

Treatment sequencing

Current cmte preferred approach in UPA (and filgotinib)

	Moderate	After progression to severe
Tx	bDMARD 1 → cDMARDs	ADA > RTX > SAR > MTX** > cDMARDs
Source/ %	Tx arm SELECT trials ([redacted]) → 0%	-
Cx	PBO → cDMARDs	ADA > RTX > SAR > MTX** > cDMARDs
Source/ %	Placebo arm SELECT trials ([redacted]) → 0%	-

TA715 cmte preferred approach

	Moderate	After progression to severe
Tx	bDMARD 1 > MTX > cDMARDs	ADA > RTX > TCZ* > MTX** > cDMARDs
Source/ %	Tx arm SELECT trials ([redacted]) > 45.2% from NMA > 0%	-
Cx	MTX > cDMARDs	ADA > RTX > TCZ* > MTX** > cDMARDs
Source/ %	45.2% from NMA > 0%	-

*was SAR in UPA appraisal

**MTX at this point not included in most analyses but removing/adding only has a minor impact on results

Treatment sequencing comments

- **ACD**: SELECT as a source of placebo response appropriate
- **Company**: TA715 consistent with treatment pathways & sources for with TA466, TA480, TA485 – this appraisal should be consistent with them
- Not appropriate to apply treatment response to BSC in comparator due to placebo observed in trials. Contradicts precedent where csDMARD efficacy from NMA is used
  - Treatment response to BSC contradicts committee's considerations that csDMARDS as BSC is not associated with EULAR response
  - Applying treatment response to BSC only to account for placebo effect suggests patients would be given a placebo pill – but this does not happen in practice
- Company disagree with Upa being included this severe sequence – IL-6 in 3rd line is a precedent (including in TA715) – *issue of fairness?*
- **NRAS**: These are international trials, with geographical heterogeneity
- **BSR**: BSC appropriate comparator, but not the placebo response from SELECT. SELECT-NEXT only required 1 csDMARD failure. When entering a study, high expectation of a response by participants

Other uncertainties

- **ACD:** 19% of people have disease progression after 2 years but longer-term predictions may not reflect clinical practice
- **Company**: rate of progression from moderate to severe disease does not contribute to uncertainty in the cost effectiveness of upadacitinib
- **BSR**: disease activity in people with RA without treatment tends to persist with similar disease activity over time
  - DAS: composite score to reflect disease activity. Not a measure of disability. Patients with moderate DAS have progression in disability and joint damage measured by HAQ but remain with moderate DAS
  - Minority develop an increase in active synovitis over time reflected by an increase in DAS > 5.1 (i.e. severe)
  - Cttee agreed with ERAN database that 19% of patients increase DAS score from a moderate to a severe range. No evidence that a significantly larger number of patients will do so over a longer period of time. "Our analysis of the ERAS database does not also suggest that this is a common outcome"

Acceptable ICER

- **ACD**: Committee preferred to see an ICER around £20,000/QALY due to uncertainties in:
  - the response rates in the placebo arms of the trials did not reflect clinical practice. Unlikely that a EULAR response would be seen after an inadequate response with 2 conventional DMARDs
  - long-term rate of progression from moderate to severe disease
  - the most appropriate treatment sequence for people whose disease progresses from moderate to severe

Company: 4 treatments have now been recommended in moderate RA, thereby considerably reducing the uncertainty in this indication for items above. Inconsistent with TA715

BSR: NICE acting unfairly. Upadacitinib is innovative. Disagree with uncertainties

BSR/ NRAS: Inconsistent with previous appraisals in RA including TA715

ICERs – analyses conducted

Scenario

Moderate Sequences

		1st line	2nd line	3rd line
1	Sequence 1	UPA+MTX	MTX	cDMARDs
	Sequence 2	MTX	cDMARDs	..
2	Sequence 1	UPA+MTX	cDMARDs	..
	Sequence 2	MTX	cDMARDs	..
3	Sequence 1	UPA+MTX	MTX	cDMARDs
	Sequence 2	MTX	cDMARDs	..
4	Sequence 1	UPA+MTX	cDMARDs	..
	Sequence 2	MTX	cDMARDs	..
5 b-DMARD-IR NMA for UPA+MTX in severe RA	Sequence 1	UPA+MTX	MTX	cDMARDs
	Sequence 2	MTX	cDMARDs	..
6 b-DMARD-IR NMA for UPA+MTX in severe RA	Sequence 1	UPA+MTX	cDMARDs	..
	Sequence 2	MTX	cDMARDs	..

Severe Sequences

	1st line	2nd line	3rd line	4th line	5th line
Sequence 1	ADA+MTX	RTX+MTX	TCZ+MTX	MTX	cDMARDs
Sequence 2	ADA+MTX	RTX+MTX	TCZ+MTX	MTX	cDMARDs

- *Scenario 1: Company preferred (?), similar to TA715*
- *Scenario 4: Cmte preferred in ACD (?)*

	1st line	2nd line	3rd line	4th line	5th line
Sequence 1	ADA+MTX	RTX+MTX	TCZ+MTX	MTX	cDMARDs
Sequence 2	ADA+MTX	RTX+MTX	UPA+MTX	MTX	cDMARDs

- Company disagree with this severe *sequence – IL6 in 3rd line is a precedent (including TA715)*
- *ERG disagrees and considers this might better reflect NHS* practice

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ERGs ICERs - results

Sequences 1 vs 2	Inc. cPAS
Scenario 1	[redacted]
Scenario 2	[redacted]
Scenario 3	[redacted]
Scenario 4	[redacted]
Scenario 5	[redacted]
Scenario 6	[redacted]

Considerations for committee

- Adalimumab, etanercept, infliximab and filgotinib (& biosimilars) now recommended by NICE
- Company argues that the approach used by MTA (TA715) should be used
- Impact on NHS from recommending upadacitinib as an option now limited because of availability of other technologies
  - Can be limited further by including recommendation to select least-expensive. Eg
  - *TA676: "Choose the most appropriate treatment after discussing the advantages and disadvantages of the treatments available with the person having treatment. If more than 1 treatment is suitable, start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose). This may vary from person to person because of differences in how the drugs are taken and treatment schedules*."
  - This might address potential equality issues around needle-phobia, as upadacitinib (and filgotinib) can be taken orally

Abbreviations

Abbreviation	
ABT	abatacept
ADA	adalimumab
bDMARD	biologic disease-modifying antirheumatic drug
BRC	baricitinib
BSC	best supportive care
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CTZ	certolizumab pegol
DAS-28	disease activity score 28-joint count
ETN	etanercept
GOL	golimumab
HAQ-DI	health assessment questionnaire disability index
IFX	infliximab
IR	Inadequate response
IV	Intravenous
JAK	Janus kinase
MTX	methotrexate
RA	Rheumatoid arthritis
PBO	placebo
RTX	rituximab
SC	subcutaneous
SRL	sarilumab
TCZ	tocilizumab
TFC	tofacitinib
TNF-alpha	tumour necrosis factor alpha
UPA	upadacitinib

Consultation response

- Consultation comments received from:
  - British Society for Rheumatology (endorsed by the Royal College of Physicians)
  - National Rheumatoid Arthritis Society (NRAS)
  - AbbVie (company)
  - UCB (comparator company)
  - 1 web comment

  See papers for full comments – not all issues covered in this presentation