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HEALTH TECHNOLOGY BRIEFING
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Upadacitinib for Ankylosing Spondylitis

NIHRIO ID	24077	**NICE ID**	10370
Developer/Company	AbbVie Ltd.	**UKPS ID**	655010

Licensing and market availability plans	Currently in phase II clinical trials.

SUMMARY

Upadacitinib is in clinical development for the treatment of active ankylosing spondylitis (AS) in adults. AS is a long-term condition in which the spine and other areas of the body become inflamed. The inflammation can lead to back pain, fatigue and in serious cases to severe disability as the bones of the spine fuse into a fixed position or joints become progressively damaged. Some patients with AS do not respond well to current treatment options, resulting in a clear unmet medical need.

Upadacitinib acts by selectively blocking a protein called Janus-Associated Kinase 1 (JAK1 and JAK1/3). JAKs contribute to the processes within the cell to produce an immune or inflammatory response. There is an emerging body of evidence establishing that JAK dependent enzymes are major contributors to the progression of immune-mediated diseases such as AS and that blocking such enzymes can be beneficial. Upadacitinib is taken orally and if licensed, it will offer an additional treatment option for patients with active AS.

PROPOSED INDICATION

The treatment of active ankylosing spondylitis in adult patients previously untreated with biological disease-modifying antirheumatic drugs, inadequate response to at least two or intolerance or contraindication to non-steroidal anti-inflammatory drugs.[1]

TECHNOLOGY

DESCRIPTION

Upadacitinib (Rinvoq, ABT-494) is a selective and reversible Janus kinase (JAK) inhibitor, which is administered orally. In human cellular assays, upadacitinib preferentially inhibits signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2.[2]

JAKs are intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, haematopoiesis and immune surveillance. The JAK family of enzymes contains four members, JAK1, JAK2, JAK3 and TYK2 which work in pairs to phosphorylate and activate signal transducers and activators of transcription (STATs). This phosphorylation, in turn, modulates gene expression and cellular function. JAK1 is important in inflammatory cytokine signals while JAK2 is important for red blood cell maturation and JAK3 signals play a role in immune surveillance and lymphocyte function.[2]

In the phase II/III (NCT03178487) clinical trial, patients received an oral dose of upadacitinib 15mg (or placebo) once daily for a 14-week period.[1,3] The long-term efficacy and safety of upadacitinib will be collected in the ongoing SELECT-AXIS 1 extension period for up to 2 years.[3]

INNOVATION AND/OR ADVANTAGES

Apart from biologic disease-modifying anti-rheumatic drugs (DMARDS), there are limited options available for AS patients who have an inadequate response or contraindication to nonsteroidal antiinflammatory drugs (NSAIDs). Upadacitinib could provide an option for this unmet need.[4] Additionally, since patients with AS are typically young and might have active lifestyles, a treatment option administered orally might be particularly important in this patient population.[3] Currently approved therapies for AS patients, when NSAIDs are insufficient in controlling the disease, are administered either by injections or intravenous infusions.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Upadacitinib as monotherapy or in combination with methotrexate is licensed in the UK for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs.[2]

Very common ($\geqslant$ 1/10) adverse effects of upadacitinib include: upper respiratory tract infections.[2]

Upadacitinib is in phase III clinical trials for rheumatoid arthritis, atopic dermatitis, spondyloarthritis, ulcerative colitis, Crohn's disease, giant cell arteritis and psoriatic arthritis and phase II trials for systemic lupus erythematosus and hidradenitis suppurativa.[5]

PATIENT GROUP

DISEASE BACKGROUND

AS is an autoimmune disease that mainly involves inflammation of the spine joints, sacroiliac joints and their adjacent soft tissues, such as tendons and ligaments. In more advanced cases, this inflammation can lead to fibrosis and calcification, resulting in the loss of flexibility and the fusion of the spine, resembling "bamboo" with an immobile position. The main clinical manifestations include back pain and progressive spinal rigidity as well as inflammation of the hips, shoulders, peripheral joints and fingers/toes and fatigue.[6,7]

While the cause of AS remains unclear, it is thought to be an interplay of genetic and environmental factors. The prevalence of AS has a clear correlation with the human leukocyte antigen (HLA)-B27 positive rate in specific populations. Studies have revealed that in HLA-B27-positive populations, the prevalence rate of AS is ~5%–6%.[6] Microbial infection can act as a triggering factor of the host innate immune system and AS development.[6] AS tends to first develop in teenagers and young adults. It's also around 2 times more common in men than in women.[8]

CLINICAL NEED AND BURDEN OF DISEASE

The prevalence of AS in the UK is believed to be 0.05%-0.23%.[9] Applying these figures to population estimates in 2020, it can be estimated there are between 28,141 and 129,450 adults with AS in England.[10]

Hospital Episode Statistics show that in 2018-19 there were 3,578 Finished Consultant Episodes (FCE), 2,640 admissions and 1,693 FCE bed days with the primary diagnosis AS (ICD10 code M45) in England.[11] In 2018 there were 7 deaths with AS as the underlying cause of death (ICD10 code M45) in England and Wales.[12]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There's no cure for AS, but treatment is available to help relieve the symptoms. Treatment involves physiotherapy and exercise, painkillers including NSAIDs, biological treatments, corticosteroids and DMARDs. Some patients with AS may need joint replacement surgery and regular follow up is recommend as symptoms tend to come and go.[13,14]

CURRENT TREATMENT OPTIONS

Biological disease-modifying antirheumatic drugs recommended for the treatment of severe ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs include adalimumab, certolizumab pegol, etanercept, golimumab and infliximab.[15]

Secukinumab is recommended as an option for treating active ankylosing spondylitis in adults whose disease has responded inadequately to conventional therapy.[15]

PLACE OF TECHNOLOGY

If licensed, upadacitinib will provide an additional treatment option for adults with active ankylosing spondylitis previously untreated with biological disease-modifying antirheumatic

drugs, inadequate response to at least two or intolerance or contraindication to non-steroidal anti-inflammatory drugs.

CLINICAL TRIAL INFORMATION

Trial	**SELECT Axis 1,** NCT03178487, 2017-000431-14; A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Upadacitinib in Subjects With Active Ankylosing Spondylitis **Phase II -** Active, not recruiting **Location:** EU (inc UK) United States, Canada and other countries. **Primary completion date:** January 2019
Trial design	Randomised, quadruple-blind, parallel assignment.
Population	n=187, aged 18 years and older, clinical diagnosis of Ankylosing Spondylitis, fulfilled modified New York criteria, previously untreated with biological disease-modifying antirheumatic drugs, inadequate response to at least two or intolerance or contraindication to non-steroidal anti-inflammatory drugs
Intervention(s)	Upadacitinib 15 mg once daily orally[3]
Comparator(s)	Placebo
Outcome(s)	Primary outcomes measure(s): • Proportion of participants with Assessment of SpondyloArthritis International Society (ASAS) 40 response [Time frame: At week 14] See trial for full list of other outcomes.
Results (efficacy)	Significantly more patients had an ASAS 40 response in the upadacitinib group versus in the placebo group at week 14 (48 [52%] of 93 patients vs 24 [26%] of 94 patients; p=0·0003; treatment difference 26% [95% CI 13-40]).[3]
Results (safety)	Adverse events were reported in 58 (62%) of 93 patients in the upadacitinib group versus 52 (55%) of 94 in the placebo group. The most common adverse event in the upadacitinib group was increased creatine phosphokinase (eight [9%] of 93 patients in the upadacitinib group vs two [2%] of 94 patients with placebo).[3]

ESTIMATED COST

Upadacitinib is already marketed in the UK. The NHS indicative price is:[16]

- a pack of 28 x 15 mg tablets costs £805.56.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors (TA407). September 2016.

- NICE technology appraisal. TNF-alpha inhibitors for ankylosing spondylitis and nonradiographic axial spondyloarthritis (TA383). February 2016.
- NICE guideline. Spondyloarthritis in over 16s: diagnosis and management (NG65). February 2017. Last updated June 2017.
- NICE quality standard. Spondyloarthritis (QS170). June 2018.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Rheumatology Services (Adult). A13/S/a.

OTHER GUIDANCE

- Assessment of SpondyloArthritis international Society and European League Against Rheumatism. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. 2017.[17]
- British Society of Rheumatology and British Health Professionals in Rheumatology. Guideline for the treatment of axial spondyloarthritis (including ankylosing spondylitis) with biologics. 2017.[18]

ADDITIONAL INFORMATION

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