RINVOQ®▼ (upadacitinib)

Healthcare Professional Educational Guide

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance; Website: www.hpra.ie. Adverse Events and Product Complaints can also be reported to AbbVie at +353 1 4287900.

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Information in this guide

This educational guide contains important safety information that you need to consider when prescribing upadacitinib to patients, including how to reduce the risk to patients, to:

1. Serious and opportunistic infections including tuberculosis (TB)
   - Testing and screening before prescribing
   - Herpes zoster – varicella zoster viral reactivation
2. Contraception, pregnancy and breast-feeding
3. Major adverse cardiovascular events
4. Venous thromboembolic events – deep venous thrombosis (DVT) or pulmonary embolus (PE)
5. Malignancy
6. Gastrointestinal (GI) perforation

In addition, the guide contains information on:

- Indications for use and posology for upadacitinib
- Use in patients aged ≥ 65 years
- Patient Card
- Indications which include doses higher than 15 mg once daily
  - ☐ Upadacitinib in atopic dermatitis
  - ☐ Upadacitinib in Inflammatory Bowel Disease (IBD) – Ulcerative Colitis (UC), Crohn's disease (CD)

If you prescribe upadacitinib, **please read this guide in full** along with **the RINVOQ® SmPC**.

About upadacitinib

Upadacitinib is an oral selective and reversible Janus kinase (JAK) inhibitor. In human cellular assays, upadacitinib preferentially inhibits signaling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2.

Indications for upadacitinib

Review the indication section of the RINVOQ® SmPC, remember:

Rheumatoid arthritis

RINVOQ® is indicated 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 disease-modifying anti-rheumatic drugs (DMARDs). RINVOQ® may be used as monotherapy or in combination with methotrexate.

Psoriatic arthritis

RINVOQ® is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. RINVOQ® may be used as monotherapy or in combination with methotrexate.

Non-radiographic axial spondyloarthritis (nr-axSpA)

RINVOQ® is indicated for the treatment of active non-radiographic axial spondyloarthritis in adult patients with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs).

Ankylosing spondylitis (AS, radiographic axial spondyloarthritis)

RINVOQ® is indicated for the treatment of active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.

Atopic dermatitis

RINVOQ® is indicated for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.

Ulcerative colitis

RINVOQ® is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent.

Crohn's disease

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.

Posology

Review the posology section of the RINVOQ® SmPC on how to use the 15 and 30 mg doses in AD, UC and CD.

- As a reminder, for the AD indication and maintenance dosing in UC and CD, the 15 mg dose is recommended for patients at higher risk of venous thromboembolism (VTE), major adverse cardiovascular events (MACE) and malignancy as described in the Posology and Warning and Precautions section of the RINVOQ® SmPC.

Use of upadacitinib in patients ≥ 65 years

Given the increased risk of certain clinical outcomes in patients ≥ 65 years of age, as observed with another JAK inhibitor, upadacitinib should only be used if no suitable treatment alternatives are available.

- In patients ≥ 65 years of age, there is an increased risk of adverse reactions with upadacitinib 30 mg once daily.
- Consequently, for indications in which the 30 mg dose may be used for long-term maintenance, the recommended dose for long-term use in patients ≥ 65 years of age is 15 mg.

Patient Card

Explain the importance of the Patient Card (PC) when discussing upadacitinib risks with your patients or patient caregivers.

It contains information that patients and caregivers need to know before, during, and after treatment with upadacitinib.

- The Patient Card tells patients and caregivers of signs and symptoms they should be aware of when they are using upadacitinib.
- Tell patients and caregivers to read the Patient Card along with the Patient Information Leaflet.
- Tell patients and caregivers that other physicians involved in their care should read the Patient Card.
- Use this HCP guide when discussing the risks of upadacitinib with your patients.
- Provide the patient with a PC.

1. Serious and opportunistic infections including TB

Upadacitinib is contraindicated in patients with active TB or active serious infections, including localised infections.

Upadacitinib increases the risk of serious, sometimes fatal infections, including opportunistic infections and tuberculosis (TB).

- The most frequent serious infections reported with upadacitinib included pneumonia and cellulitis. Cases of bacterial meningitis and sepsis have also been reported.
- Opportunistic infections reported include tuberculosis, multidermatomal herpes zoster, oral/ oesophageal candidiasis, and cryptococcosis.
- Refer to section 4.4 and 4.8 of the SmPC for further data on the risk of infections.
- Consider the risks and benefits of treatment prior to initiating upadacitinib in patients:
  - with chronic or recurrent infection
  - who have been exposed to tuberculosis
  - with a history of a serious or an opportunistic infection
  - who have resided or travelled in areas of endemic tuberculosis or endemic mycoses; or with underlying conditions that may predispose them to infection.
- Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with upadacitinib. It is important to tell patients and caregivers to get immediate medical attention if they have signs suggesting infection. This is to ensure rapid evaluation and appropriate treatment, including possible interruption of upadacitinib.
- There is a higher incidence of infections in the elderly and in diabetic populations in general, caution should be used when treating the elderly and patients with diabetes.

Testing and screening before prescribing

Herpes Zoster

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), was reported in clinical studies (see section 4.8 of the SmPC). If a patient develops herpes zoster, interruption of upadacitinib therapy should be considered until the episode resolves.

Tuberculosis (TB)

Screen patients to rule out active TB. Do not prescribe upadacitinib to patients with active TB. If latent TB is diagnosed, anti-TB therapy should be considered prior to starting upadacitinib. Anti-TB therapy should be considered prior to initiation of upadacitinib in patients with previously untreated latent TB or in patients with risk factors for TB infection. Refer to the RINVOQ® SmPC for important drug-drug interactions to consider if TB therapy is needed.

Infections

- Before and during upadacitinib treatment, check absolute lymphocyte and absolute neutrophil counts (refer to the RINVOQ® SmPC for guidance on *dose initiation* and *dose interruption* based on absolute lymphocyte and absolute neutrophil counts and how frequently to monitor). Treatment should not be initiated, or should be temporarily interrupted, in patients with ANC < 1 x 10^9 cells/L or ALC < 0.5 x 10^9 cells/L observed during routine patient management.
- Screen patients for viral hepatitis and monitor for reactivation in accordance with clinical guidelines.

If a new infection develops

- If a patient develops any new infection during treatment, carry out diagnostic testing appropriate for an immunocompromised patient immediately.
- If the infection is a serious or an opportunistic infection – temporarily stop upadacitinib.
- Use appropriate antimicrobial therapy, and closely monitor the patient.
- If the patient is not responding to antimicrobial therapy - temporarily stop upadacitinib.
- Do not re-start upadacitinib until the infection is controlled.

Vaccines

- Before starting upadacitinib, it is recommended that you bring all patients up to date with all immunisations (including prophylactic zoster vaccinations) – in agreement with current immunisation guidelines.
- Do not use live, attenuated vaccines during, or immediately prior to starting upadacitinib treatment.

Examples of live, attenuated vaccines include but are not limited to vaccines for measles/ mumps/ rubella, live attenuated influenza vaccine given as a nasal spray, oral polio vaccine, yellow fever vaccine, Zostavax™ used to prevent herpes zoster, BCG vaccine and varicella vaccine.

Counsel the patient on the signs and symptoms of infection, the risk of live vaccines and when to seek immediate medical attention.

2. Contraception, pregnancy, and breast-feeding

Upadacitinib was found to cause birth defects in animals – cardiovascular and bone effects. There are limited data in humans. However, based on animal data, there is a potential risk to a human foetus.

Pregnancy and contraception

- Upadacitinib is contraindicated during pregnancy.
- Women of child-bearing potential should use effective contraception both during treatment, and for 4 weeks after stopping upadacitinib treatment.
- Counsel your patient that upadacitinib is contraindicated during pregnancy, the requirement to use effective contraception and to inform you immediately if they think they could be pregnant, are planning to become pregnant, or if pregnancy is confirmed.
- If a patient becomes pregnant while taking upadacitinib the parents should be informed of the potential risk to the foetus.
- Do not prescribe upadacitinib for women who are breast-feeding or intend to breast feed. Data in animals shows excretion of upadacitinib in milk but it is not known if upadacitinib passes into human breast milk.

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3. Major adverse cardiovascular events (MACE)

Treatment with upadacitinib was associated with dose-dependent increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Elevations in LDL cholesterol decreased to pre-treatment levels in response to statin therapy, although evidence is limited.

MACE – considerations with upadacitinib use

- Upadacitinib should only be used if no suitable treatment alternatives are available in the following patients who are considered at risk for MACE:
  - ☐ age ≥ 65 years
  - ☐ current or past long-time smokers
  - ☐ history of atherosclerotic cardiovascular disease or other cardiovascular risk factors
- Assess lipid levels 12 weeks after starting upadacitinib. Monitor and manage lipid levels during treatment, according to clinical guidelines for hyperlipidaemia.
- Tell your patients and their caregivers that you will be monitoring their lipid levels.

4. Venous thromboembolic events – DVT or PE

DVT and PE – considerations with upadacitinib use

- In patients with risk factors for MACE or malignancy, upadacitinib should only be used if no suitable treatment alternatives are available.
- In patients with known risk factors for VTE other than MACE or malignancy risk factors, upadacitinib should be used with caution. Risk factors for VTE include:
  - ☐ previous VTE
  - ☐ patients undergoing major surgery
  - ☐ immobilisation
  - ☐ use of combined hormonal contraceptives or hormone replacement therapy
  - ☐ inherited coagulation disorder
- Counsel your patient on the signs and symptoms of DVT and PE and when to seek medical attention
- Patients should be re-evaluated periodically during upadacitinib treatment to assess for changes in VTE risk.
- Promptly evaluate patients with signs and symptoms of VTE and discontinue upadacitinib in patients with suspected VTE, regardless of dose.

5. Malignancy

Malignancy – considerations with upadacitinib use

- Upadacitinib should only be used if no suitable treatment alternatives are available in the following patients who are considered at risk for malignancy:
  - ☐ age ≥ 65 years
  - ☐ patients who are current or past long-time smokers
  - ☐ other malignancy risk factors (i.e. current malignancy, or history of malignancy prior to initiating therapy)
- Periodic skin examination is recommended for patients, particularly those with risk factors for skin cancer.

6. GI perforation

GI perforation – consideration with upadacitinib

- Upadacitinib should be used with caution in patients who may be at risk for gastrointestinal perforation (e.g., patients with diverticular disease, a history of diverticulitis, or who are taking nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or opioids).
- Patients with active Crohn's disease are at increased risk for developing intestinal perforation.
- Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of diverticulitis or gastrointestinal perforation.

Upadacitinib in atopic dermatitis (including adolescents)

If considering the 30 mg upadacitinib dose in an adult less than 65 years of age with atopic dermatitis, remember:

- There is an increased rate of serious infections and herpes zoster for the 30 mg compared to the 15 mg dose.
- A higher rate of malignancies, was observed with upadacitinib 30 mg compared to 15 mg.
- There is an increase in plasma lipids for the 30 mg compared to the 15 mg dose.
- See RINVOQ® SmPC for dosing.
- A dose of 15 mg is recommended for patients at higher risk of VTE, MACE and malignancy.
- Use the lowest effective dose to maintain response.

Remember

- Upadacitinib 30 mg once daily dose is not recommended with strong CYP3A4 inhibitors: such as clarithromycin, itraconazole, ketoconazole, grapefruit products, since upadacitinib is metabolised by CYP3A4. Consider alternatives to strong CYP3A4 inhibitor medicines in the long-term.
- Food or drink containing grapefruit should be avoided during treatment with upadacitinib.
- Upadacitinib 30 mg once daily is not recommended for patients with severe renal impairment.

Upadacitinib use in adolescents 12 years and older with atopic dermatitis

- See RINVOQ® SmPC for the recommended dose in adolescents.
- In considering whether to administer vaccines to adolescents, some vaccines recommended by local guidelines are live, attenuated vaccines (ie. measles/mumps/rubella, varicella and BCG). These vaccines should not be given during or immediately prior to starting upadacitinib.
- Remind adolescents of the potential pregnancy risks and the appropriate use of effective contraception.
- If your adolescent patient has not experienced menarche, let them or their caregivers know to contact you once they experience menarche while taking upadacitinib.

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Upadacitinib in UC or CD

Upadacitinib induction and maintenance dosing should be reviewed in the RINVOQ® SmPC.

When considering whether to use the 15 or 30 mg dose for maintenance, remember:

- There is an increased rate of serious infections and herpes zoster for the 30 mg compared to the 15 mg dose.
- A higher rate of malignancies, was observed with upadacitinib 30 mg compared to 15 mg.
- See RINVOQ® SmPC for dosing.
- A dose of 15 mg is recommended for patients at higher risk of VTE, MACE and malignancy.
- For maintenance dosing, use the lowest effective dose to maintain response.

Remember

- For patients receiving strong inhibitors of CYP3A4 (e.g., clarithromycin, itraconazole, ketoconazole, grapefruit products), upadacitinib 30 mg once daily is the recommended induction dose and upadacitinib 15 mg once daily is the recommended maintenance dose. Consider alternatives to strong CYP3A4 inhibitor medicines in the long-term.
- Food or drink containing grapefruit should be avoided during treatment with upadacitinib.
- In patients with severe renal impairment: Upadacitinib 30 mg once daily is the recommended induction dose and upadacitinib 15 mg once daily is the recommended maintenance dose.

Further information

- Please refer to the full Summary of Product Characteristics for RINVOQ® (upadacitinib) for further information regarding the safety of this product.
- Please contact AbbVie medical information at 01-4287900 if you have any questions or require additional copies of this HCP Guide or the Patient Card.
- Digital copies of the SmPC, PIL and education materials are available on the HPRA's website, www.hpra.ie

Additional Patient Cards can be obtained from www.rinvoq.eu

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