NEW DRUGS

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Upadacitinib

Approved indication: rheumatoid arthritis

Rinvoq (AbbVie)
15 mg modified-release tablets

Upadacitinib is the third Janus kinase (JAK) inhibitor to be approved for rheumatoid arthritis after baricitinib and tofacitinib. These drugs modify immune and inflammatory processes by blocking the cytokine pathway that leads to the activation of lymphocytes.[1,2]

Upadacitinib is indicated for patients with moderate–severe rheumatoid arthritis who have not adequately responded, or are intolerant, to at least one or more conventional disease-modifying antirheumatic drugs (DMARDs). The drug has been investigated in several phase III randomised clinical trials.[3-7] Response to treatment was defined as at least a 20% improvement on the American College of Rheumatology scale (ACR20). At the recommended daily dose of 15 mg, statistically more people responded to upadacitinib, as monotherapy or when added to conventional DMARDs, than to placebo or methotrexate (see Table).

The most common adverse effects with upadacitinib in the trials included urinary and upper respiratory tract infections, altered liver function and nausea. Rare but serious adverse events included malignancy, thrombosis and gastrointestinal perforation.

As with other JAK inhibitors, serious and sometimes fatal infections can occur with upadacitinib – pneumonia and cellulitis were the most commonly reported in the trials. Opportunistic infections such as tuberculosis, multi-dermatomal herpes zoster, oral candidiasis, cryptococcosis and pneumocystosis have also occurred. Upadacitinib should not be used in patients with active infections and caution is urged in those with chronic or recurrent infection or a history of tuberculosis. Care should also be taken in older patients and those with diabetes. Screening for tuberculosis and viral hepatitis is recommended and vaccinations, particularly against herpes zoster, should be up to date before treatment is started.

Upadacitinib can be prescribed as monotherapy or in addition to methotrexate and other conventional DMARDs. It should not be given with other JAK inhibitors, biological DMARDS or potent immunosuppressants like azathioprine or ciclosporin. Upadacitinib should not be started if lymphocytes are less than 0.5 x 10^9 cells/L or neutrophils are less than 1 x 10^9 cells/L. Haemoglobin must be at least

Table **Efficacy of upadacitinib in moderate–severe rheumatoid arthritis**

Trial	Treatment	Efficacy - ACR20*
SELECT EARLY[3] 947 methotrexate-naïve patients randomised to upadacitinib or methotrexate for 12 weeks	upadacitinib 15 mg/day	76%
	upadacitinib 30 mg/day	77%
	methotrexate	54%
SELECT MONOTHERAPY[4] 648 patients with inadequate response to methotrexate randomised to switch to upadacitinib monotherapy or continue methotrexate for 14 weeks	upadacitinib 15 mg/day	68%
	upadacitinib 30 mg/day	71%
	methotrexate	41%
SELECT NEXT[5] 661 patients with inadequate response to at least one conventional DMARD (methotrexate, sulfazine or leflunomide) randomised to add upadacitinib or placebo for 12 weeks	upadacitinib 15 mg/day	64%
	upadacitinib 30 mg/day	66%
	placebo	36%
SELECT COMPARE[6] 1629 patients with inadequate response to methotrexate randomised to add upadacitinib, adalimumab or placebo for 48 weeks (ACR20 measured at 12 weeks)	upadacitinib 15 mg/day	71%
	adalimumab 40 mg every 2 weeks	63%
	placebo	36%
SELECT BEYOND[7] 499 patients with inadequate response or intolerance to biological DMARDs and receiving conventional DMARDs randomised to add upadacitinib or placebo for 12 weeks	upadacitinib 15 mg/day	65%
	upadacitinib 30 mg/day	56%
	placebo	28%

DMARD disease-modifying antirheumatic drug
* defined as the proportion of patients who had at least a 20% improvement on the American College of Rheumatology scale

Some of the views expressed on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

80 g/L. Upadacitinib is not recommended in severe hepatic impairment (Child-Pugh C).

Upadacitinib is mainly metabolised by cytochrome P450 (CYP) 3A4, and to a lesser extent by CYP2D6. It has no active metabolites. Steady-state concentrations are reached within four days following once-daily dosing. It has a half-life of 9–14 hours. Two-thirds of the dose is excreted unchanged in the urine (24%) and faeces (38%) and a third is excreted as metabolites.

Giving upadacitinib with a strong CYP3A4 inducer (e.g. rifampicin) may decrease its efficacy, while strong CYP3A4 inhibitors (e.g. clarithromycin) could increase the risk of toxicity. Patients should therefore be closely monitored if they are taking these types of medicines.

Upadacitinib is a category D drug and is not recommended in pregnancy. In animal studies, it caused fetal malformations in early pregnancy. The drug is also not recommended during breastfeeding and was found to be excreted in the milk of lactating rats.

Upadacitinib seems to be effective in moderate–severe rheumatoid arthritis used alone or added to a patient's conventional DMARD therapy. However, close monitoring is recommended as there is a risk of serious and sometimes fatal adverse effects, particularly infections. To date, there have been no head-to-head trials with other JAK inhibitors.

T manufacturer provided the product information

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, and the European Medicines Agency and the Therapeutic Goods Administration.

A:

ANSWERS TO SELF-TEST QUESTIONS

1 False 2 False
3 False 4 False

EDITORIAL OFFICE

For general correspondence such as Letters to the Editor, contact the Editor.

Postal The Editor
Australian Prescriber
GPO Box 266
Canberra, ACT 2600

Telephone +61 2 8217 8700

Email info@australianprescriber.com

Website nps.org.au/australian-prescriber

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