Medicines Adverse Reactions Committee

Meeting date	8/09/2022	Agenda item	3.2.1
Title	**Recent safety signals related to use of Janus kinase inhibitors**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
Tofacitinib	Jaqinus	Pfizer
Upadacitinib	Rinvoq	AbbVie
Ruxolitinib	Jakafi	Novartis

PHARMAC funding	Tofacitinib – approved but not available/marketed Upadacitinib – approved and PHARMAC funded (under Special Authority) for rheumatoid arthritis Ruxolitinib – approved and PHARMAC funded (under Special Authority)
International action	**EMA** – Safety review of JAK inhibitors for inflammatory disorders. **MHRA** – *Drug Safety Updates* – Tofacitinib: new measures to minimise the risk of major adverse cardiovascular events and malignancies, and thromboembolism and serious and fatal infections. **FDA** – FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death from JAK inhibitors that treat certain chronic inflammatory conditions.
Classification	Prescription medicine

Advice sought	**The Committee is asked to advise:**
	• Whether the risk of MACE, malignancies and thromboembolic events applies to all JAK inhibitors used in inflammatory disease.
	• Whether regulatory action is required to improve the risk benefit balance of **tofacitinib** considering the outcome of the ORAL Surveillance Study. Such actions may include:
	  ○ Strengthening the warning and precautions section of the data sheet so that individuals 65 years and older, current/past smoker, with thromboembolic, cardiovascular and malignancy risk factors should only use tofacitinib if no suitable alternatives are available.
	  ○ Restricting the therapeutic indications of tofacitinib to individuals who have had an inadequate response or intolerance to one or more DMARD.
	• Whether similar regulatory action should be applied to **upadacitinib** to improve the risk benefit balance?
	• Should the **ruxolitinib** data sheet be updated to reflect the results of the ORAL Surveillance study?
	• Whether further communication is required other than in MARC's remarks?

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1 PURPOSE

In a recent large post-authorisation safety study (ORAL Surveillance), participants taking tofacitinib for rheumatoid arthritis, who were aged 50 years and older with at least one cardiovascular risk factor had a higher risk of major adverse cardiovascular events (MACE), malignancies (excluding non-melanoma skin cancer), serious infections, thromboembolic events and mortality compared to participants taking tumour necrosis factor inhibitors (TNFi).

This has triggered international regulatory action to minimise the risk of these events to at risk groups and to improve the overall risk-benefit balance of tofacitinib and other Janus kinase (JAK) inhibitors indicated for inflammatory diseases.

Review from the United States Food and Drug Administration (FDA) considered that although other JAK inhibitors approved for inflammatory diseases (upadacitinib and baricitinib) have not been studied to the same extent as tofacitinib, these medicines share the same mechanism of action and therefore may have similar risks. As a result, the FDA considered the risk of these events of interest as a JAK-class effect. The US product labelling for all JAK inhibitors used for inflammatory diseases has been updated with warnings on the risk of MACE, malignancies, thromboembolic events and mortality. In addition, the use of all JAK inhibitors for all inflammatory diseases have been restricted to patients who have not responded to or cannot tolerate one or more TNFi.

The purpose of this report is to seek advice from the Medicines Adverse Reactions Committee on whether regulatory action should be taken to improve the risk-benefit balance of tofacitinib, and whether similar action should also be taken for other approved JAK inhibitors.

2 BACKGROUND

2.1 Janus Kinase

2.1.1 Cytokine receptors

Cytokines are a large group of structurally diverse proteins that include interleukins (IL), chemokines, colony-stimulating factors (CSF), interferon (IFN), transforming growth factors and tumour necrosis factors [1].

A common way to categorise cytokines is by the cytokine receptors they bind to (Figure 1). Type I and Type II cytokine receptors are dependent on the catalytic activity of JAK enzymes bound to the cytoplasmic portion of the receptor to mediate downstream effects [1].

Figure 1: Schematic representation of cytokines, Type I and II cytokine receptors and associated JAKs [1]

Comments:

Over 50 cytokines and signalling proteins rely on JAK to mediate downstream effects. Potentially targeting multiple cytokines and signally proteins involved in inflammatory medicated immune diseases could be more efficacious compared to biological treatment where only one cytokine is affected. However, there may be unwanted blockade of other cytokine signalling necessary for other functions.

2.1.2 JAK-STAT pathway

When a cytokine binds to a Type I or Type II receptor (Figure 2), a confirmation change occurs in the receptor resulting in reciprocal activation of two juxtapositioned JAKs through auto and/or transphosphorylation [2]. The phosphorylated JAKs forms docking sites for STAT proteins. At this docking site, JAK phosphorylates STAT. STAT then dissociates from the receptor and forms homodimers or heterodimers. These dimers translocate to the cell nucleus to regulate transcription of target genes [3].

Figure 2: Schematic of the JAK-STAT pathway [4]

2.1.3 JAK isoforms

JAKs work in pairs, either forming heterodimers or homodimers to mediate downstream signalling. The pairing of JAKs within a given cytokine receptor is determined by their association with specific receptor chains.

There are four JAK isoforms: JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2) [5].

JAK1 – is important for signalling of receptors activated by interleukin (IL) 6, IL-10, IL-11, IL-19, IL-20, IL-22, and interferon (IFN) alpha, IFN-beta, and IFN-gamma. JAK1 pairs with JAK2 or TYK2 to regulate several pro-inflammatory cytokines [5].

JAK2 – can pair with another JAK2 (forming a homodimer) which is important for signalling for hormone-like cytokines erythropoietin, thrombopoietin, growth hormone, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-3, and IL-5. These cytokines are important for red blood cell, platelets, and myeloid cell development. JAK2 can also pair with JAK1 and TYK2 [5].

JAK3 – is predominately expressed in haematopoietic cells and is activated by IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21. These cytokines are important for lymphocyte activation, function, and proliferation (adaptive immunity). JAK3 pairs only with JAK1 to mediate downstream signalling relating to adaptive immunity [5].

TYK2 – pairs with either JAK1, JAK2 or another TYK2 molecule to facilitate signalling of IL-12, IL-23, and type 1 IFNs [5].

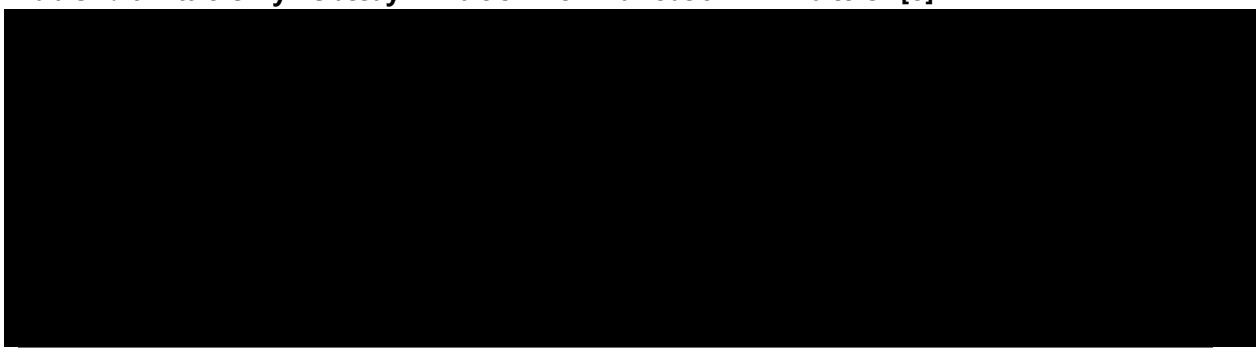
2.1.4 JAK inhibitor selectivity

There has been research aimed at developing molecules that preferentially target JAK1 to treat immune mediated inflammatory diseases. The rationale for targeting JAK1 is that the anti-inflammatory effect should

be maintained, due to the key role of JAK1 in signalling downstream of pro-inflammatory cytokines, with effects on JAK2-dependent processes such as production of red blood cells and platelets, and JAK3-dependent processes such as lymphopoiesis minimised. As such, a JAK1-selective inhibitor could have an improved benefit–risk profile compared with other less selective JAK inhibitors [6].

The specificity of approved JAK inhibitors to certain JAK isoforms have been demonstrated in enzyme assays (Table 1) and *in vitro* cellular assays. *In vivo* and therapeutic studies have not necessarily replicated this specificity [7].

Table 1: *in vitro* enzyme assay inhibition from various JAK inhibitors* [8]



*The IC_{50} value is the concentration (nM) needed to inhibit 50% of activation (IC_{50}) of different JAK inhibitors. A low IC_{50} value suggests higher potency to the JAK isoform. JAK isoform selectivity is determined by ratio and difference between IC_{50}'s for different JAK isoforms [8]. Enzymatic assays demonstrates that tofacitinib has 5.1-fold, and 3.6-fold greater selectivity for JAK1 over JAK2 and JAK3 respectively. For upadacitinib, there was a 75-fold and 17.4-fold greater selectivity for JAK1 over JAK2 and JAK3 respectively [9].

Table 2 outlines information on JAK selectivity of approved JAK inhibitors in New Zealand. In general, tofacitinib is known as a pan-JAK inhibitor (affecting all JAKs), upadacitinib is more selective against JAK1, and ruxolitinib is selective for JAK1 and JAK2.

Table 2: Approved JAK inhibitors and information on their selectivity of JAK isoforms

JAK inhibitor	Information on JAK selectivity from their respective data sheet
Tofacitinib	**In vitro kinase/enzyme assays:** Inhibits JAK1, JAK2, JA3, and to a lesser extent TYK2 **In cellular settings where JAK signal in pairs:** Preferentially inhibits signalling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2. Inhibition of JAK1 and JAK3 by tofacitinib blocks signalling through the common gamma chain-containing receptors for several cytokines, including IL-2, -4, -7, -9, -15, and -21. These cytokines are integral to lymphocyte activation, proliferation and function, and inhibition of their signalling may thus result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signalling by additional pro-inflammatory cytokines, such as IL-6 and type I and II interferons. At higher exposures, inhibition of erythropoietin signalling could occur via inhibition of JAK2 signalling.
Upadacitinib	A selective and reversible inhibitor of JAK1. Upadacitinib more potently inhibits JAK1 compared to JAK2 and JAK3. In cellular potency assays that correlated with the *in vivo* pharmacodynamic responses, upadacitinib demonstrated 50–70-fold greater selectivity for JAK1 over JAK2 and >100-fold for JAK1 over JAK3. Atopic dermatitis pathogenesis is driven by pro-inflammatory cytokines (including IL-4, IL-13, IL-22, TSLP, IL-31 and IFN-γ) that transduce signals via the JAK1 pathway. Inhibiting JAK1 with upadacitinib reduces the signalling of many mediators which drive the signs and symptoms of atopic dermatitis such as eczematous skin lesions and pruritus. Inhibition of IL-6 Induced STAT3 and IL-7 Induced STAT5 Phosphorylation In healthy volunteers, the administration of upadacitinib (immediate release formulation) resulted in a dose- and concentration-dependent inhibition of IL-6 (JAK1/JAK2)-induced STAT3 and IL-7 (JAK1/JAK3)-induced STAT5

	phosphorylation in whole blood. The maximal inhibition was observed 1 hour after dosing which returned to near baseline by the end of dosing interval.
Ruxolitinib	An inhibitor of JAK1 and JAK2 with nanomolar potency. Myelofibrosis (MF) and Polycythemia vera (PV) are myeloproliferative neoplasm (MPN) known to be associated with dysregulated JAK1 and JAK2 signalling.

Selectivity results using *in vitro* cellular models (through cytokine stimulation and measuring phosphorylated STAT) can vary. Many factors can affect the selectivity of JAK inhibitors such as dose (at higher doses, JAK inhibitors lose selectivity), cytokines used for stimulation, STAT substrate and cell type [9]. Multiple contemporary comparative *in vitro* and *ex vivo* studies of JAK inhibitors have been published and have generally reached similar conclusions that JAK inhibitors use in rheumatoid arthritis all potently inhibited JAK1, with some subtle differences around the effects on JAK2 or JAK3 [10].

In biological systems, JAK work in pairs. Upon cytokine stimulation to the cytokine receptor, the two neighbouring JAKs are brought closer together, cross-phosphorylate and activate each other [10].

JAK1 is the most 'promiscuous' JAK as it can pair with all JAK isomers. Therefore, all JAK inhibitors that target JAK1 will also interfere with the other JAK isoforms that share signalling with JAK1. In this case, inhibition of JAK1 will interfere with receptor signalling of JAK1/JAK2, JAK1/TYK2, and JAK1/JAK3 pairs. Because JAK1 is always paired with another JAK isoform in carrying out its function, even a JAK1-selective agent will affect the signalling of cytokine receptors that are also dependent on JAK2, JAK3 or TYK2 [10].

Figure 3: JAK-inhibitors use for immune mediate inflammatory diseases and their overall (including clinically derived) selectivity and presumed interference (+ or -) with certain cytokine pathways [11]

*Clinically derived selectivity: for example, upadacitinib *in vitro* studies suggests it is selective for JAK1, however decreases haemoglobin levels observed in Phase 3 trials suggest that at clinically relevant doses (particularly the 30 mg) upadacitinib may also have some effects on JAK2.

Comments:

JAK isoform selectively is relative and not absolute.

It is suggested that *in vitro* data on selectivity of different JAKs may potentially explain the different efficacy and safety event rates observed in clinical trials. However, in the absence of head-to-head clinical trials, it is difficult to conclude the relative efficacy and safety of more 'specific' JAK inhibitors (eg, upadacitinib) with less selective inhibitors (tofacitinib -also known as a 'pan-JAK' inhibitor).

It is currently uncertain whether the adverse events of interests are related to JAK inhibition, or from some other mechanism.

2.2 JAK inhibitors approved in New Zealand

JAK inhibitors are used in immune mediated inflammatory and myeloproliferative diseases. In New Zealand they have been approved for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondylarthritis, atopic dermatitis and myelofibrosis (primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis). Table 3 outlines JAK inhibitors approved in New Zealand, their approved indications and dose.

Table 3: JAK inhibitors approved in New Zealand, their approved indications and dose

JAK inhibitor **(availability and funding status)**	**Approved indications and dose**
Tofacitinib (approved but not available, not PHARMAC funded)	**Rheumatoid arthritis** For the treatment of the signs and symptoms of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to methotrexate. JAQINUS can be used alone or in combination with nonbiological disease-modifying antirheumatic drugs, including methotrexate. JAQINUS may be used as monotherapy or in combination with methotrexate (MTX) or other nonbiological disease-modifying antirheumatic drugs (DMARDs). The recommended dosage is **5 mg administered twice daily.**
Upadacitinib (available and PHARMAC funded)	**Rheumatoid arthritis:** The treatment of adults with moderately to severely active rheumatoid arthritis. Rinvoq may be used as monotherapy or in combination with methotrexate or other conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). The recommended dose of Rinvoq is **15 mg once daily**. **Atopic dermatitis:** Rinvoq is indicated for the treatment of adults and adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy. Adults: The recommended dose of Rinvoq is **15 mg or 30 mg once daily** for adults. Consider dose selection based on individual patient presentation. **For patients ≥ 65 years of age, the recommended dose of Rinvoq is 15 mg once daily**. Adolescents (from 12 to 17 years of age): The recommended dose of Rinvoq is **15 mg once daily for adolescents weighing at least 40 kg.** Rinvoq has not been studied in adolescents weighing less than 40 kg. Concomitant Topical Therapies: Rinvoq can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used for sensitive areas such as the face, neck, and intertriginous and genital areas. **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. The recommended dose of Rinvoq is **15 mg once daily**. Rinvoq may be used as monotherapy or in combination with a non-biological DMARD. **Ankylosis spondylitis:** Rinvoq is indicated for the treatment of active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy. The recommended dose of Rinvoq is **15 mg once daily.** **Non-radiographic Axial Spondyloarthritis:** The recommended dose of Rinvoq is **15 mg once daily.**
Ruxolitinib (available and PHARMAC funded)	The treatment of disease-related splenomegaly or symptoms in patients with primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis. Jakavi is indicated for the treatment of adult patients with polycythemia vera who are resistant to or intolerant of hydroxyurea.

2.3 Place in therapy

2.3.1 Rheumatoid arthritis (tofacitinib and upadacitinib)

The aim of treatment for RA is to achieve and maintain remission or low disease activity with the use of disease-modifying antirheumatic drug (DMARD) therapy. DMARDs are a group of medicines that have the potential to reduce or prevent joint damage and to preserve joint integrity and function [12].

Treatment decisions are based on disease activity, safety issues and other patient factors, such as existing comorbidities and stage of the disease.

1. Anti-inflammatory medicines such as non-steroidal anti-inflammatories (NSAIDs) or glucocorticoids are used in patients with active RA. These agents act rapidly to reduce disease activity while a DMARD is introduced.
2. Conventional synthetic DMARDs (csDMARDs) are first line. Methotrexate (MTX) should be part of the first treatment strategy. If MTX is contraindicated or intolerant, leflunomide or sulfasalazine should be considered as part of the first treatment strategy.
3. If treatment target is not achieved with the first csDMARD, other csDMARDs should be considered.
4. If treatment target is not achieved, a biological DMARD (bDMARD) or targeted synthetic DMARD (tsDMARD) should be added [12].

Comparative efficacy of JAK inhibitors and bDMARDs in RA:

The ORAL Strategy study aimed to assess the comparative efficacy of tofacitinib monotherapy, tofacitinib+methotrexate, and adalimumab+methotrexate in RA patients with a previous inadequate response to methotrexate. This study showed non-inferiority between tofacitinib+methotrexate versus adalimumab+methotrexate [13].

The Phase 3 trial, SELECT-COMARE assessed the comparative efficacy of upadacitinib versus adalimumab or placebo in patients on background methotrexate. This 48-week study showed upadacitinib with MTX demonstrated a significantly higher proportion of patients achieving clinical responses versus adalimumab with MTX [14].

In New Zealand, available DMARDs are:

- csDMARD: methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, gold salts.
- bDMARD: TNFi (adalimumab, etanercept, infliximab), anti-CD20 (rituximab), antiCD80 (abatacept) and anti-IL's (tocilizumab, secukinumab).

- tsDMARD: JAK inhibitors – tofacitinib and upadacitinib.

Other pharmacological treatments for RA include azathioprine, cyclosporin, cyclophosphamide.

Upadacitinib is only funded for the treatment of RA.

2.3.2 Psoriatic arthritis (upadacitinib)

There are many pharmacological overlaps with treatment in patients with RA and psoriatic arthritis (PsA). The aim of therapy is to control inflammation and prevent discomfort, joint damage, and disability [15].

1. In patients with peripheral arthritis with an inadequate response to at least one csDMARD, a bDMARD should be commenced. In patients without bad prognostic factors or those with mild disease activity may be indicated to rotate to a second csDMARD before starting a bDMARD.
2. In patients with peripheral arthritis with an inadequate response to at least one csDMARD and at least one bDMARD, or when a bDMARD is not appropriate, a JAK inhibitor may be considered. 'Not appropriate' means, for example, non-adherence to injections or a strong patient preference for an oral drug.
3. In patients who fail to respond adequately to, or are intolerant of a bDMARD, switching to another bDMARD or tsDMARD should be considered, including one switch within a class [15].

Comparative efficacy of JAK inhibitors and bDMARDs in PsA:

The Select-PsA 1 trial compared upadacitinib 15 mg or 30 mg once daily to adalimumab over 24 weeks in patients with psoriatic arthritis who had an inadequate response to non-biologic DMARDs. The 15-mg and 30-mg doses of upadacitinib were noninferior to adalimumab with respect to the ACR20 response at week 12; the 30 mg dose, but not the 15 mg dose, was superior to adalimumab with respect to the ACR20 response. The incidences of adverse events and serious adverse events, including serious infections, were similar with the 15 mg dose of upadacitinib and adalimumab but were more frequent with the 30 mg dose of upadacitinib [16].

Comments:

Although upadacitinib is approved for PsA, this indication is currently not funded under PHARMAC's Special Authority.

2.3.3 Axial spondyloarthritis (upadacitinib)

Axial spondyloarthritis (SpA) includes ankylosing spondylitis (AS) and non-radiographic axial SpA [17].

In most patients with symptomatic (SpA), a NSAID is used as initial therapy. In some patients, NSAIDs is all that is required [17].

In patients with an inadequate response to initial therapy with at least two different NSAIDs consecutively, consider adding a TNFi is added rather than an IL-17 inhibitor or a JAK inhibitor [17].

Comparative efficacy of JAK inhibitors and bDMARDs in SpA:

There are currently no head-to-head trial comparing the efficacy of upadacitinib with a bDMARD.

Comments:

Although upadacitinib is approved for SpA, this indication is currently not funded under PHARMAC's Special Authority criteria.

2.3.4 Atopic dermatitis (upadacitinib)

Pharmacological treatment for atopic dermatitis (AD) can be categorised as topical and systemic (oral) therapy. Systemic treatments are indicated in moderate-to-severe AD and refractory forms of disease [18]. Systemic therapy may involve oral H_1 antihistamines, steroids, immunosuppressive and anti-inflammatory agents (such as ciclosporin and methotrexate), and biological agents (currently there are no biological agents approved for AD in New Zealand) [19]. Upadacitinib is approved for the treatment of adults and adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy [20].

Comparative efficacy of JAK inhibitors and bDMARDs in AD:

A randomised Phase 3 trial (Heads Up) compared the safety and efficacy of upadacitinib with the bDMARD dupilumab (not approved in New Zealand). This study concluded that upadacitinib showed superior efficacy compared with dupilumab in terms of achieving higher level of skin clearance and itch relief with more rapid onset [21].

Comments: Although upadacitinib is approved for AD, this indication is currently not funded under PHARMAC's Special Authority criteria.

Atopic dermatitis is the only indication where 30 mg once daily is used. In Phase 3 AD trials, participants consistently demonstrated greater clinical improvements across skin clearance measures on 30 mg compared to 15 mg. All other indications such as RA, SpA, and PsA is restricted to 15 mg once daily.

2.3.5 Myeloproliferative neoplasms (ruxolitinib)

Ruxolitinib is indicated for the treatment of disease-related splenomegaly or symptoms in patients with primary myelofibrosis, post-polycythaemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis. Ruxolitinib is also indicated for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea [22].

2.4 Usage

The Pharmaceutical Data web tool contains dispensing information on funded medicines dispensed in pharmacies to named individuals between 2016 to 2020. It does not capture privately funded medicines.

There is no usage data for tofacitinib as this is not funded or marketed in New Zealand.

There is no usage data for upadacitinib as it was funded after 2020.

The number of people dispensed ruxolitinib for the period 2018 (when this medicine was first funded) to 2020 is outlined in Table 4.

Table 4: Number of people dispensed ruxolitinib by dose between 2016 to 2020

Year	Ruxolitinib 5 mg	Ruxolitinib 15 mg	Ruxolitinib 20 mg	Total by year
2018	29	21	16	**66**
2019	64	41	55	**160**
2020	85	46	78	**209**
Total by dose	**178**	**108**	**149**	

Source: Pharmaceutical Data web tool available: https://minhealthnz.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 8 August 2022)

2.5 Safety concerns from the tofacitinib clinical development programme

Tofacitinib was the first JAK inhibitor approved for the treatment for RA in 2012 by the United States Food and Drug Administration (FDA). During the clinical development programme, increases in serum lipid levels (and the concerns of an increased risk of cardiovascular events), and an increased incidence of cancers (including lymphoma) and serious infections were observed [23].

The FDA therefore mandated the sponsor to conduct a:

> *Controlled clinical trial to evaluate the long-term safety of tofacitinib in patients with rheumatoid arthritis. The trial should include two doses of tofacitinib and an active comparator. The trial should be of sufficient size and duration to evaluate safety events of interest, including cardiovascular adverse events, opportunistic infections, and malignancy.*

The sponsor conducted a prospective head-to-head safety trial comparing tofacitinib with TNF inhibitors – this was known as the ORAL Surveillance study (A3921133). The final results were published in January 2022 (refer to Annex 1 for full article) [24].

2.6 Results of the ORAL Surveillance study (A3921133) [24]

Background: A randomised phase 3b-4, open-label, non-inferiority study to evaluate the safety and efficacy of tofacitinib as compared with a TNF inhibitor in patients with rheumatoid arthritis.

Methods: Patients included were 50 years of age or older with at least one additional cardiovascular risk factor. Key exclusion criteria were current or previous cancer, except adequately treated non-melanoma skin cancer (NMSC). Patients were randomly assigned in a 1:1:1 ratio to receive open-label tofacitinib 5 mg or 10 mg twice daily, or a TNFi (adalimumab 40 mg fortnightly, or etanercept 50 mg weekly). Background methotrexate was continued unless modification was clinically indicated. The first patient was enrolled in March 2014. In the interim analysis in February 2019 a higher frequency of pulmonary embolism (PE) among patients on 10 mg tofacitinib compared to those on a TNFi was observed. In addition a higher mortality with tofacitinib 10 mg compared to 5 mg or with a TNFi was observed which led to all patients on 10 mg switching to 5 mg.

Hazard ratios were calculated for each dose of tofacitinib relative to TNFi, with two-sided 95% confidence intervals.

The co-primary endpoints were adjudicated MACE (death from CV causes, non-fatal myocardial infarction, or non-fatal stroke) and cancer (excluding NMSC). Non-inferiority would be shown if the upper limit of the two-sided 95% confidence interval for these hazard ratios were less than 1.8 for the combined tofacitinib doses as compared with a TNF inhibitor (primary comparison) or less than 2.0 for tofacitinib at a dose of 10 mg twice daily as compared with a dose of 5 mg twice daily (secondary comparison). The trial could only be concluded when at least 1,500 patients had been followed for 3 years, and 103 MACEs and 138 malignancies (excluding NMSC) had occurred.

The secondary safety endpoints included adverse events of special interest (AESI) such as serious and opportunistic infections, hepatic events, NMSC, death from any cause, VTE, all arterial thromboembolism, other CV events other than MACE.

Secondary efficacy endpoints looked at patient reported outcomes: SDAI score, HAQ-DI which were assessed at baseline and during scheduled follow-up visits.

Patients were analysed in their originally assigned group, including those required to switch the tofacitinib dose from 10 mg twice daily to 5 mg twice daily in February 2019.

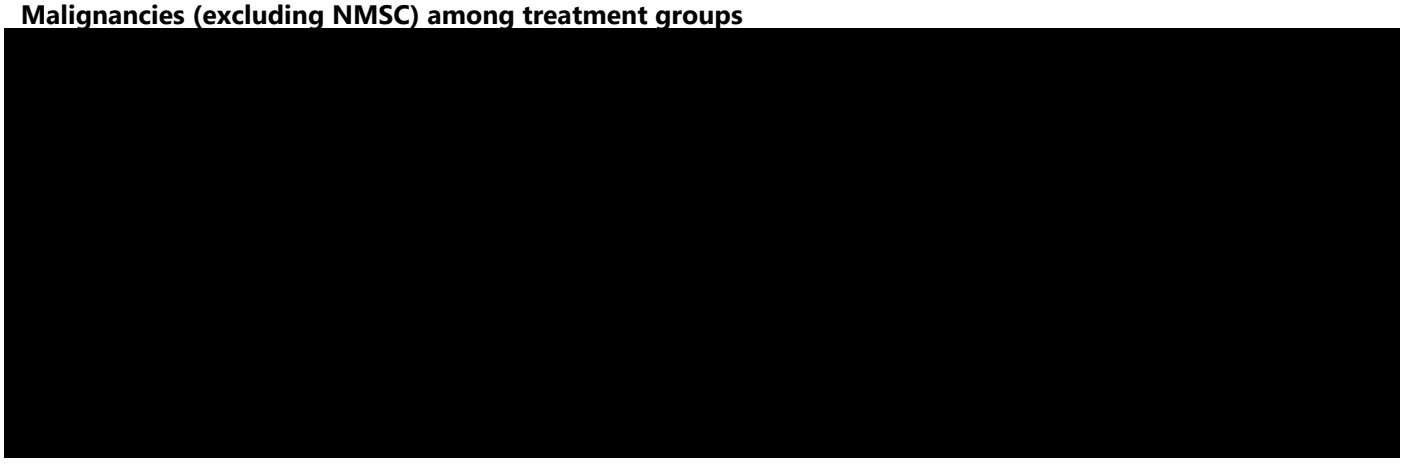
Results: 1,455 received tofacitinib at a dose of 5 mg twice daily, 1,456 received tofacitinib at a dose of 10 mg twice daily, and 1,451 received a TNFi. Patient exposure for tofacitinib 5 mg, 10 mg twice daily, and TNFi was 5,073.49, 4,773.41, and 4,940.72 patient-years respectively. At baseline, 31% of patients were 65 years of age or older and the mean duration of RA was more than 10 years.

Adjudicated MACE: with a median follow up of 4 years, the incidence of MACE was higher in the combined tofacitinib group (3.4%, 98 patients) than TNFi (2.5%, 37 patients). The HR was 1.33 (95% CI, 0.91 to 1.94) therefore non-inferiority was not shown (Figure 4). Non-inferiority was shown between 5 mg and 10 mg tofacitinib. The most common cause of MACE was non-fatal MI with tofacitinib and non-fatal stroke with TNFi.

Figure 4: (A) hazard ratio/HR (95% CI) and (B) – Incidence rates/IR (95% CI first events per 100 PY) for MACE among treatment groups

Adjudicated cancers: with a median follow up of 4 years, the incidence of cancer was higher in the combined tofacitinib dose (4.2%, 122 patients) than TNFi (2.9%, 42 patients) (Figure 5). The HR was 1.48 (95% CI, 1.04 to 2.09) therefore non-inferiority was not shown. Non-inferiority was shown between 5 mg and 10 mg tofacitinib. The most common cause of cancer was lung cancer (and for haematological cancer was lymphoma) with tofacitinib and breast cancer with TNFi.

Figure 5: (A) hazard ratio/HR (95% CI) and (B) – Incidence rates/IR (95% CI first events per 100 PY) for Malignancies (excluding NMSC) among treatment groups



Subgroup analysis for MACE and malignancies (excluding NMSC) by age: the risk of MACE and cancer between tofacitinib and TNFi were more pronounced in patients 65 years and older than in patients < 65 years of age (Figure 6)

Figure 6: Age-stratified analysis by ≥65 years and <65 years of age, displaying hazard ratio/HR (95% CI) and IRs (95% CI events per 100 PY) for MACE (A and B top panel) and malignancies excl. NMSC (A and B bottom panel)

Secondary safety endpoints:

The most frequent adverse events and serious adverse events that emerged according to system organ class were infections and infestations (Table 5). Upper respiratory tract infections, bronchitis, and urinary tract infections were the most common adverse events, and pneumonia the most common serious adverse event, across trial groups.

- Opportunistic and serious infections and NMSC were more frequent with both tofacitinib groups than with TNFi. The HR was statistically significant for both tofacitinib dose compared to TNFi.
- The incidence of death from any cause, pulmonary embolism (PE) and venous thromboembolism (VTE) were higher with 10 mg tofacitinib compared to 5 mg tofacitinib or TNFi.
- Hazard ratios for adjudicated PE were more than 1, but 95% confidence intervals were wide.

This trial showed increased lipid levels with tofacitinib which are caused by reduced cholesterol ester catabolism. This has not previously been associated with an increased risk of MACE.

Table 5: Adverse events (safety analysis population, 28-day on treatment time)

Efficacy endpoint on patient-reported outcomes: efficacy was similar across treatments with improvements from month 2 and sustained through trial completion.

Conclusions: Among patients with RA, 50 years or older with one cardiovascular risk factor, the risk of MACE and cancers with tofacitinib were higher compared with TNF inhibitors. The efficacies of tofacitinib and TNF inhibitors were similar across multiple scores which raises the question of the risk-benefit profile of tofacitinib.

Strengths and limitations: Strength included a large patient cohort followed up for 6 years with 16,448 patient-year exposure and that up to 50% of patients across treatment groups were followed up for at least 48 months. Limitations were the high rates of discontinuation which may have affected the outcome of the study, and the lack of other control groups. Both adalimumab or etanercept was used (depending on country availability) therefore it is unclear whether the relative risk will differ among the two TNFi.

Comment:
Differences in the risk of MACE, malignancies, thromboembolism, infection and mortality were observed between tofacitinib and TNFi. The risk benefit balance could be managed by the sequence of medicines tried ie, not to use tofacitinib until an individual has tried other available therapies.

The risk of some events of interest also occurs with TNFi use. For example, events of malignancies were higher in TNFi users compared to placebo in controlled trials. Therefore the risk of malignancies may be even higher for tofacitinib considering non-inferiority was not demonstrated in ORAL Surveillance.

2.7 Potential mechanisms underlying thromboembolism, MACE and malignancies observed with JAK inhibitors

Some adverse events associated with JAK inhibitors are predicted by mechanisms related to the blockade of cytokines that use JAK–STAT for signalling. For example, the increased risk of serious and opportunistic infections observed in clinical trials is likely due to inhibition of JAK3-dependent cytokines that are important for the development and function of Natural Killer (NK) cells [25].

In contrast, thromboembolism and MACE are unexpected events and the mechanisms involved are not completely understood. In addition, the downstream effects of JAK inhibition *in vivo* is still not fully characterised [26].

Thromboembolism: Several potential mechanisms were suggested including the potential relationship between tofacitinib and clotting-related factors, the potential role for pro-inflammatory cytokines such as TNF and IL-6 and the complex interaction between monocytes, neutrophils, platelets, and the coagulation cascade, and numerous pro- and anti-coagulant factors that regulate the clotting cascade But for which the role of JAK-STAT signalling in the regulation of these various pathways, either directly or indirectly, is not well characterised [27].

Malignancy: A concern with immunosuppression is the potential for increased risk of malignancy. The possible mechanisms through which JAK inhibitors might negatively impact immune responses to cancer include interference with T and NK cell function in immunosurveillance and the antineoplastic role of interferons [25].

MACE: May be potentially related to blocking of downstream signalling of IL-6 [25]. Elevation in total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) have been reported for JAK inhibitors such as tofacitinib and upadacitinib. These elevations are usually noted within 12 weeks of starting treatment but then stabilise. Despite these increases, LDL/HDL and total cholesterol/HDL ratio remained constant throughout [5]. Similar to tocilizumab (a IL-6 receptor inhibitor), an increase in these ratios did not appear to increase the risk of MACE [25].

3 SCIENTIFIC INFORMATION

The following sources of information are provided to review the risk of MACE, malignancies (excluding NMSC), thromboembolic events and mortality for tofacitinib, upadacitinib and ruxolitinib.

- Tofacitinib: a literature search for observational studies was conducted for events of interest. In general, clinical trial participants are not followed long enough to detect rarer events or events that have a long time to onset. In addition, the sponsor's Periodic Benefit Risk Evaluation Report (PBRER) is summarised [redacted]
- Upadacitinib: the same strategy for tofacitinib has been applied.
- Ruxolitinib: is used for patients with myeloproliferative neoplasm. Therefore, the risk benefit balance will be different for the events of interest. Only the sponsor's review of these events in their PBRER is summarised.

3.1 Tofacitinib

3.1.1 Observational studies reviewing adverse events of interest for tofacitinib versus TNFi

3.1.1.1 Khosrow-Khavar F et al (2022) – Tofacitinib and risk of cardiovascular outcomes: results from the Safety of TofAcitinib in Routine care patients with Rheumatoid Arthritis (STAR-RA) study [28]

Refer to Annex 2 for full article.

Aim**:** The aim of this large population-based observational study using claim and health insurance databases was to further examine the risk of CV outcomes with tofacitinib in patients with RA treated in routine clinical care settings.

Methods: RA patients treated with tofacitinib or TNFi were retrieved from three health or claims databases – Optum, MarketScan and Medicare.

Two cohorts were created using the databases:

- A 'real-world evidence (RWE) cohort' consisting of routine care patients which included patients at least 18 years of age at cohort entry date.
- A 'randomised controlled trial (RCT)-duplicate cohort' mimicking inclusion and exclusion criteria of the ORAL surveillance study. This would allow the authors to calibrate their results using this cohort to assess the validity of the study and ensure the results were comparable with those of the ORAL study.

The primary endpoint was defined as a composite CV outcome consisting of hospitalisations for MI or stroke. Individual CV outcomes were also examined independently as secondary outcomes including MI, stroke, heart failure hospitalisation, coronary revascularisation, and all-cause mortality.

Cox proportional hazards models with propensity score fine stratification weighting were used to estimate HR with 95% CIs for the primary and secondary endpoints. 76 potential confounders were accounted for.

In the RWE cohort, subgroup analysis on primary endpoints was done based on age (≤65 and >65 years), sex, and baseline CVD, and previous use of bDMARDs. Propensity score matching was also done where each patient initiating tofacitinib was matched with a patient initiating TNFi.

Sensitivity analyses were also conducted by restricting the TNFI comparator group in RWE and RCT-duplicate cohorts to only adalimumab and etanercept users.

Lastly, the risk of herpes zoster was used as a positive control outcome as previous studies have established an increased risk of herpes zoster with tofacitinib.

Results:

RWE cohort:

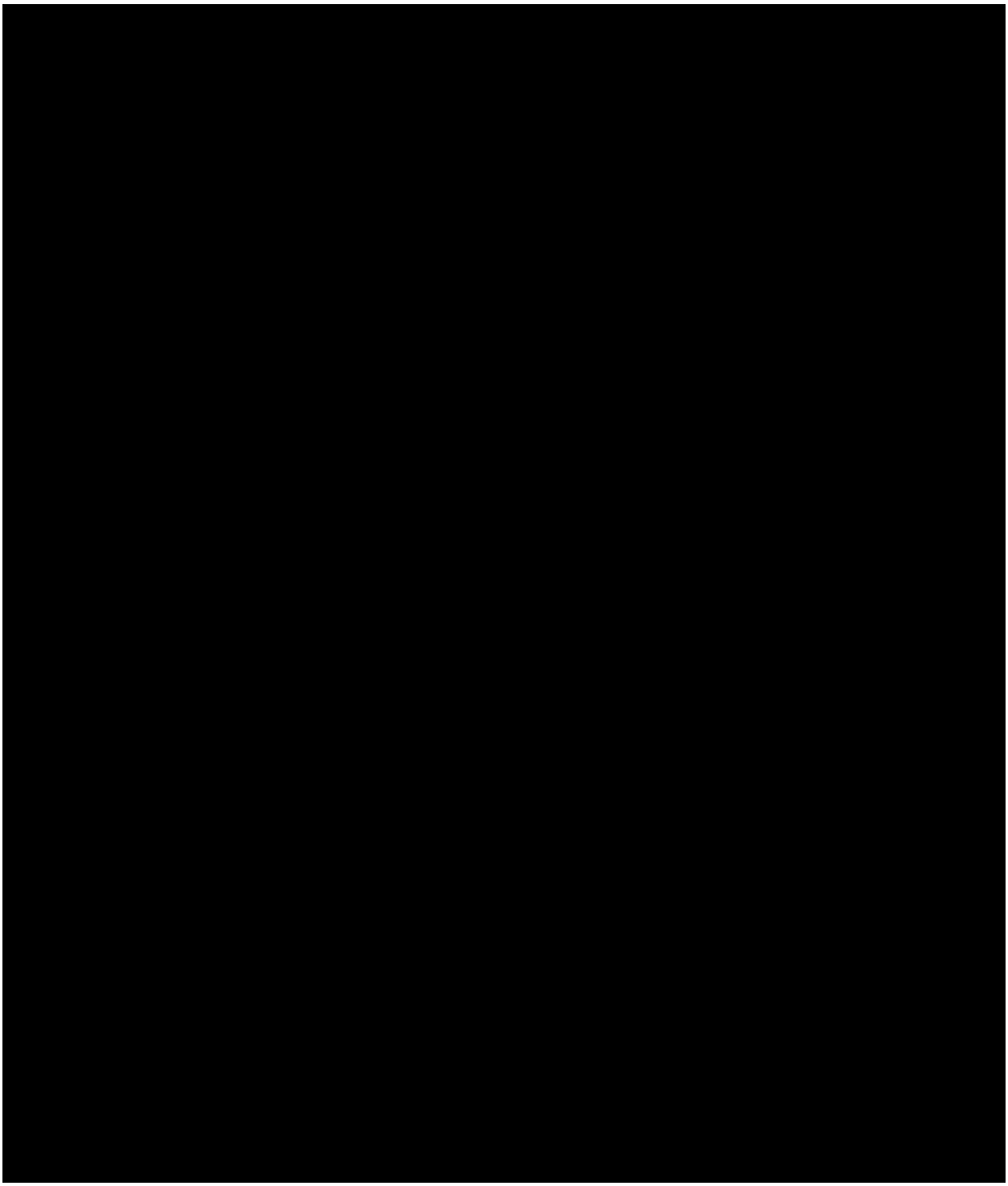
28,568, 34,083, and 39,612 patients met the inclusion criteria from Optum, MarketScan and Medicare respectively, of whom 13.2%, 15.6% and 9.5% initiated treatment on tofacitinib. Prevalence of CVD risk factors and previous use of co-medications were slightly higher in tofacitinib users compared to TNFi users. 13% of patients in Optum, 10% in MarketShare and 31% from Medicare had a history of CVD. Propensity-score fine stratification achieved excellent covariate balance with standardised differences close to zero across all covariates.

Primary endpoint: pooled weighted HR (95% CI) for composite CV outcomes when comparing tofacitinib vs TNFi was 1.01 (0.83 to 1.23) with weighted rate difference 0.02 (-0.19 to 0.23) CV events per 100 person-years (Figure 7). No differences in cumulative incidence of composite CV outcomes were observed when comparing tofacitinib vs TNFi in any of the databases.

Figure 7: Forest plot of propensity-score fine stratification weighted HRs and corresponding 95% CIs for composite cardiovascular outcomes when comparing tofacitinib with TNFi in patients with RA in RWE cohort (top panel) and RCT-duplicate cohort (bottom panel).

Primary endpoint subgroup analysis (Figure 8): showed the pooled weighted HR for composite CV outcomes were 1.27 (0.95 to 1.70) and 0.81 (0.61 to 1.07) among patients with and without CVD respectively. The pooled weighted HR for composite CV outcomes were similar in patients ≤65 (1.00, 0.66 to 1.50) and >65 years of age (1.05, 0.84 to 1.33). No association was observed across other subgroups including among males, females, previous use/no use of bDMARDs. Consistent results were observed across other sensitivity analyses, including propensity-score matching.

Figure 8: Forest plot of propensity-score fine stratification weighted HRs and corresponding 95% CIs for composite cardiovascular outcomes for subgroup analyses in RWE study cohort.



Secondary endpoint: the pooled weighted HR for individual CV outcomes were 1.04 (0.82 to 1.33) for MI, 0.93 (0.66 to 1.31) for stroke, 1.07 (0.79 to 1.46) for heart failure hospitalisation, and 1.04 (0.78 to 1.40) for coronary revascularisation when comparing tofacitinib to TNFi users. The pooled weighted HR for all-cause mortality was 1.20 (0.98 to 1.46). Positive control outcome for herpes zoster was successfully replicated.

RCT-duplicate cohort:

6878, 8071 and 20 121 patients were identified from Optum, MarketScan and Medicare, respectively, of whom 11.6%, 14.3% and 7.7% initiated treatment with tofacitinib. Overall, propensity-score fine stratification weighting achieved excellent covariate balance in this study population with standardised differences close to zero for all covariates.

Primary endpoint (Figure 7) pooled weighted HR (95% CI) for composite CV outcomes when comparing tofacitinib with TNFi was 1.24 (0.90 to 1.69) with weighted rate difference 0.28 (-0.24 to 0.80) CV events per 100 person-years. The cumulative incidence of composite CV outcomes was similar when comparing tofacitinib with TNFi users in Optum and MarketScan, but slightly higher among tofacitinib users in Medicare. In the sensitivity analysis, restricting TNFi to adalimumab and etanercept (like in the ORAL Surveillance study), the pooled weighted HR was 1.32 (0.94 to 1.86).

Conclusions**:** There was no statistically significant increase in the risk of CV outcomes with tofacitinib compared to TNFi, among patients with RA treated in the real-world setting. However, concordant with results from ORAL Surveillance study, there was an elevated risk of CV events, though not statistically significant, in RA patients with CV risk factors/history of CVD in those on tofacitinib compared to TNFi. Therefore, an elevated risk of composite CV outcomes with the use of tofacitinib cannot be ruled out in this population with certain risk factors.

Comments:
This study supports the observation seen in the ORAL Surveillance study that patients on tofacitinib with CV risk factors have an elevated risk (although not statistically significant) of developing CV outcomes compared to those without CV risk factors. Results from the RCT-duplicate cohort were also consistent with those reported from the ORAL Surveillance study (pooled weighted HR 1.24, 95% CI 0.90 to 1.69 vs ORAL Surveillance: 1.33, 95% CI 0.91 to 1.94).

3.1.1.2 Desai RJ et al (2021) – Risk of venous thromboembolism associated with tofacitinib in patients with rheumatoid arthritis: a population-based cohort study [29]

Background: Previous research comparing tofacitinib vs TNFi initiation using data from two large insurance programmes in the USA noted a numerical, but not statistically significant increase in risk of VTE among tofacitinib initiators with a HR of 1.33 (95% CI 0.78, 2.24). Therefore, the aim of this cohort study using claims databases was to reassess VTE with more recent data.

Methods:

This cohort study used three claims databases to identify tofacitinib and TNFi users. Enrolees in MarketScan and Optum are representative of a commercially insured population. US Medicare is a federal health insurance programme and provides healthcare coverage for nearly all legal residents of the USA aged 65 years and some disabled patients aged < 65 years.

Patients were excluded if they had cancer or history of VTE during the baseline period. Users of other biologics or JAK inhibitors at any time prior to the index date were also excluded.

The primary outcome of interest was a composite endpoint of incident VTE (including pulmonary embolism or deep vein thrombosis) based on inpatient diagnoses. The secondary outcome of interest evaluated pulmonary embolism and deep vein thrombosis separately.

60 baseline covariates were assessed related to RA treatment history and risk of VTE.

Two sensitivity analyses were conducted. The first followed an intention-to-treat principle up to 365 days after treatment initiation. The second analysis defined the composite VTE outcome based on inpatient or outpatient claims to capture VTE cases managed in both settings.

Results: A total of 42,201, 25,078 and 20,374 RA patients meeting all inclusion criteria were identified from MarketScan, Medicare and Optum, respectively, of whom 7.1%, 7.1% and 9.7% were tofacitinib initiators. The mean age was 50, 71 and 52 years in MarketScan, Medicare and Optum, respectively.

The crude incidence rates (IRs per 100 person-years with 95% CI) of VTE for tofacitinib vs TNFi 0.42 were (0.20–0.77) and 0.35 (0.29–0.42) in MarketScan, 1.18 (0.68–1.92) and 0.83 (0.71–0.97) in Medicare, and 0.19 (0.04–0.57) and 0.34 (0.26–0.44) in Optum.

Propensity-score weighted HRs showed no significant differences in the risk of VTE between tofacitinib and TNFi in any of three databases or in the pooled adjusted HR (95% CI) of 1.13 (0.77–1.65) (Figure 9). Similarly, for the secondary endpoints, propensity-score weighted HR (95% CI) was 1.00 (0.79–1.26) for DVT and 1.02 (0.60–1.73) for PE.

The results from the sensitivity analyses showed (1) following the intention-to-treat up to 365 days after treatment initiation the a pooled adjusted HR (95% CI) of 0.92 (0.65–1.32) and (2) where VTE events were identified from inpatient or outpatient claims, the pooled HR (95% CI) was 0.98 (0.80–1.21) (Figure 9).

Figure 9: Propensity score weighted Kaplan-Meier plots for the risk of VTE after initating tofacitinib vs a TNFi in RA patients

Authors' conclusions: In this cohort study using claims databases, patients with RA treated with tofacitinib 5 mg twice daily in routine care did not have an increased risk for VTE overall, or individual components of DVT or PE, compared with those treated with TNFi. The results showing no differences on absolute or relative scales were consistent across sensitivity analyses and across three databases

3.1.2 Sponsor's evaluation

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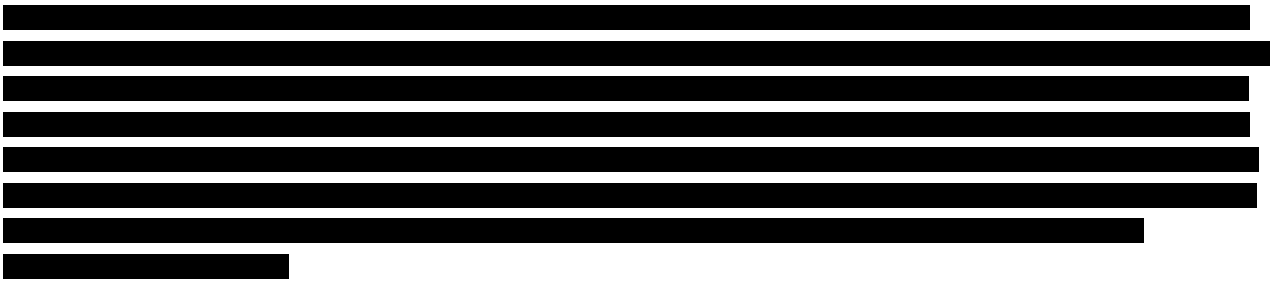

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4 CARM reports

As of 30 July 2022, there have been 13 reports of suspected adverse reactions where a Janus kinase inhibitor was the suspect medicine (see Table 31 and Annex 3 for the CARM line listing). Of these reports 3 were for tofacitinib, 3 for upadacitinib, and 7 for ruxolitinib. Overall, the limited number of reports is influenced by the low usage of these medicines (ie, possibly due to availability and funding)

Baricitinib is not approved however has been funded by PHARMAC since February 2022 as a COVID-19 treatment. No reports have been made to CARM for baricitinib.

[redacted]

CV events: across the three JAK inhibitors, there have been two reports of CV reactions – subarachnoid haemorrhage with tofacitinib (CARM ID 126345) and pulmonary hypertension and cardiac failure right with ruxolitinib (CARM ID 131317).

Infections and blood abnormalities: viral infections were reported (herpes zoster with tofacitinib and pneumonia with upadacitinib). Haematological events have also been reported across the JAK inhibitors.

Elevated lipids have reported for tofacitinib and upadacitinib.

Other events of interest: no cases of thromboembolic events, malignancies or secondary malignancies were reported.

Table 31: Any reactions reported to CARM where a JAK inhibitor (tofacitinib, upadacitinib and ruxolitinib) was the suspect medicine to 30 July 2022

JAK inhibitor/ dose / indication	CARM ID	Age in years	Sex	Reaction(s)
Tofacitinib [redacted]	119684	72	M	Pneumonitis
Tofacitinib [redacted]	126345	67	F	Subarachnoid haemorrhage Thrombocytopenia Encephalopathy Hypertriglyceridaemia Consciousness decreased
Tofacitinib [redacted]	141083	75	M	Herpes zoster virus infection
Upadacitinib [redacted]	142804	57	F	Pancreatitis Hyperlipaemia C-reactive protein positive
Upadacitinib [redacted]	143649	69	F	Constipation Anal pain
Upadacitinib [redacted]	144250	28	F	Pneumonia viral Asthma aggravated
Ruxolitinib [redacted]	123485	85	M	Disease progression
Ruxolitinib [redacted]	128671	72	M	Pancytopenia Metastases
Ruxolitinib [redacted]	131317	61	M	Pulmonary hypertension Dyspnoea Cardiac failure right
Ruxolitinib [redacted]	132834	74	M	Thrombocytopenia Haematoma Haemorrhage Anaemia Weight increase
Ruxolitinib [redacted]	134022	60	M	Hepatic cirrhosis Anaemia Oesophageal varices Serum ferritin increased
Ruxolitinib [redacted]	136173	62	F	Disease progression
Ruxolitinib 30 mg/day [redacted]	137281	64	M	Bladder discomfort Micturition frequency

[redacted]

5 REGULATORY ACTION AND REVIEW

5.1 European Medicines Agency [30]

The EMA's PRAC review is currently ongoing.

In the treatment of inflammatory disorders, other JAK inhibitors work in a similar way to tofacitinib. Therefore, the EMA's PRAC review will consider whether the risks are associated with all JAK inhibitors approved for inflammatory disorders. The sponsor of each JAK inhibitor has been asked to:

- Review their safety data on MACE, myocardial infarction, malignancy, VTE, serious infections, and all-cause mortality from completed and ongoing clinical trials, long term extension studies, and observational studies stratified by dose. Event rates observed and HRs for the JAK inhibitor vs active comparators should be calculated.
- Perform a literature review and provide in-house data to address potential class effect of JAK inhibitors.
- Discuss whether the safety outcomes of the ORAL surveillance study including MACE (particularly MI), VTE, serious infections, malignancies, and mortality as observed in patients with RA can be considered class effects of JAK inhibitors, across all indications in inflammatory diseases.

Following the review of the above information, the PRAC will make a decision on whether the risks observed in the ORAL Surveillance are associated with all JAK inhibitors used for inflammatory disorders and whether the marketing authorisations for these medicines should be amended.

The EMA has already implemented similar risk minimisation activities to data sheet for tofacitinib (see MHRA below).

5.2 UK's Medicines and Healthcare products Regulatory Agency [31, 32]

The MHRA issued two *Drug Safety Updates* following the interim results of ORAL Surveillance in 2019 and the final results in 2021. New measures to minimise risk of events of interest have been introduced for tofacitinib:

VTE:

- For any dose and in any indication, caution should be used in patients with known risk factors for venous thromboembolism in addition to the underlying disease.
- Inform patients of the signs and symptoms of venous thromboembolism before they start tofacitinib and advise them to seek prompt medical help if they develop signs such as a painful swollen leg, chest pain, or shortness of breath
- Discontinue tofacitinib treatment permanently if signs of venous thromboembolism occur

Serious infections:

- Patients older than 65 years of age are at an increased risk of serious infections and should be treated with tofacitinib only if there is no alternative treatment.

MACE:

- The following predictive risk factors were identified: age older than 65 years, current or past smoking, history of diabetes, and history of coronary artery disease (including past myocardial infarction, coronary heart disease, stable angina pectoris, or coronary artery procedures)
- Only consider use of tofacitinib in patients with these cardiovascular risk factors, irrespective of indication, if no suitable treatment alternative is available

Malignancies:

- The following predictive risk factors were identified: age older than 65 years and current or past smoking

- Only consider use of tofacitinib in patients with these and other malignancy risk factors (current or previous history of malignancy other than successfully treated NMSC), irrespective of indication, if no suitable alternative treatment is available

5.3 US Food and Drug Administration [33]

Following the final results of ORAL Surveillance, the FDA considered that although other JAK inhibitors approved for inflammatory diseases has not been studied to the same extent, these medicines share the same mechanism of action and therefore may have similar risks. Therefore, the FDA extrapolated the study findings to all JAK inhibitors used for inflammatory conditions.

As a result, in January 2022, the FDA introduced class labelling updates for all JAK inhibitors approved for inflammatory disease to contain the following:

- Boxed warnings about the increased risks of serious heart-related events, cancer, blood clots, and death with JAK inhibitors compared to TNFi
- Healthcare professionals should consider the benefits and risks for an individual patient prior to initiating or continuing treatment with JAK inhibitors, particularly for patients with a history of smoking, those with risk factors for cardiovascular disease and those with a malignancy
- Restricting the indication to limit all approved uses to patients who have not responded or cannot tolerate one or more TNFi.

The above labelling updates do not apply for JAK inhibitors used for blood disorders such as ruxolitinib. However a 'weaker' warning has been added to highlight the results from the ORAL Surveillance study and for prescribers to consider the risks and benefits.

6 Warning and precautions advice resulting from the ORAL Surveillance study – comparison across the NZ, US and EU data sheets (on 11 August 2022)

Note this data sheet review only includes warning and precaution advice. It does not include information the sponsor has put in the data sheet describing the results of the ORAL Surveillance study.

6.1 Jaqinus (tofacitinib)

	New Zealand	United States	EU
Therapeutic Indications (for RA)	JAQINUS is indicated for the treatment of the signs and symptoms of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to methotrexate. JAQINUS can be used alone or in combination with non-biological disease modifying antirheumatic drugs, including methotrexate. *Comment: The Committee could recommend restricting the indication to individuals who have had an inadequate response or intolerance to one or more DMARD.*	[Tofacitinib] is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis **who have had an inadequate response or intolerance to one or more TNF blockers.** *Comment: In US, tofacitinib is also used for other inflammatory conditions (PsA, AS, UC and JIA). The FDA has restricted all these indications to individuals who have had an inadequate response or intolerance to one or more TNF inhibitor.*	Tofacitinib in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients **who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs (DMARDs)**
Section 4.4 – VTE	Assess patients for VTE risk factors before starting treatment and periodically during treatment. Use JAQINUS **with caution** in elderly patients and in patients in whom other risk factors are identified. Urgently evaluate patients with signs and symptoms of VTE. Discontinue tofacitinib while evaluating suspected VTE, regardless of dose or indication. *Comment: To strengthen the warning on VTE, risk factors for VTE should be listed as seen in the EU SmPC.* *In addition:* *"In patients over 65 years of age and in patients whom other risk factors for VTE are identified, tofacitinib should only be used if no suitable treatment alternatives are available".*	Promptly evaluate patients with symptoms of thrombosis and discontinue [tofacitinib] in patients with symptoms of thrombosis. **Avoid** [tofacitinib] in patients that may be at increased risk of thrombosis.	Tofacitinib should be used with caution in patients with known risk factors for VTE, regardless of indication and dose **VTE risk factors include previous VTE, patients undergoing major surgery, immobilisation, myocardial infarction (within previous 3 months), heart failure, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder, malignancy. Additional VTE risk factors such as age, obesity (BMI ≥30), diabetes, hypertension, smoking status should also be considered.** Promptly evaluate patients with signs and symptoms of VTE and discontinue tofacitinib in patients with suspected VTE, regardless of dose or indication.

Section 4.4 – MACE (including myocardial infarction)	Caution should be used in treating elderly patients, patients who are current or past smokers, and patients with other cardiovascular risk factors. *Comment: To strengthen the warning for MACE, the Committee could recommend adopting the warning used in the EU SmPC: "In patients over 65 years of age, patients who are current or past smokers, and patients with other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available".*	Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with [tofacitinib], particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. Discontinue [tofacitinib] in patients that have experienced a myocardial infarction or stroke.	**In patients over 65 years of age, patients who are current or past smokers, and patients with other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available.**
Section 4.4 – Malignancies and lymphoproliferative disorders (excluding NMSC)	Consider the risks and benefits of JAQINUS treatment prior to initiating therapy in patients with current or a history of malignancy other than a successfully treated NMSC or when considering continuing JAQINUS in patients who develop a malignancy. The possibility exists for JAQINUS to affect host defenses against malignancies. The impact of treatment with JAQINUS on the development and course of malignancies is not known, but malignancies were observed in clinical studies with JAQINUS. Caution should be used in treating elderly patients, patients who are current or past smokers, and patients with other malignancy risk factors *Comment: To strengthen the warning for malignancies, the Committee could recommend adopting the warning used in the EU SmPC: "In patients over 65 years of age, patients who are current or past smokers, and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer) tofacitinib should only be used if no suitable treatment alternatives are available".*	Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with [tofacitinib], particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy while on treatment, and patients who are current or past smokers.	**In patients over 65 years of age, patients who are current or past smokers, and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer) tofacitinib should only be used if no suitable treatment alternatives are available.**
Section 4.4 – Mortality	Not in section 4.4, however Section 5.1 describes the mortality findings from ORAL Surveillance study.	The FDA labelling describes the results of the ORAL Surveillance study in warnings and precautions section followed by this advice: Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with [tofacitinib].	Morality findings from ORAL Surveillance are outlined in Section 5.1.

6.2 Rinvoq (upadacitinib)

	New Zealand	United States	EU
Therapeutic Indications	Rheumatoid Arthritis Rinvoq is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis. Rinvoq may be used as monotherapy or in combination with methotrexate or other conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). Atopic Dermatitis Rinvoq is indicated for the treatment of adults and adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy. 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 a non-biological DMARD. Ankylosing spondylitis Rinvoq is indicated for the treatment of active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy. Non-radiographic Axial Spondyloarthritis Rinvoq is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation. *Comments: The Committee could recommend restricting (any of the above indications) to individuals who have had an inadequate response or intolerance to one or more conventional therapy/treatment.* *Currently, the indications for atopic dermatitis, psoriatic arthritis, and ankylosing spondylitis are already worded in a way that it is used second line.*	Rheumatoid Arthritis RINVOQ® (upadacitinib) is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis **who have had an inadequate response or intolerance to one or more TNF blockers.** Psoriatic arthritis RINVOQ is indicated for the treatment of adults with active psoriatic arthritis **who have had an inadequate response or intolerance to one or more TNF blockers.** Atopic dermatitis RINVOQ is indicated for the treatment of adults and pediatric patients 12 years of age and older with refractory, moderate to severe atopic dermatitis whose disease is **not adequately controlled with other systemic drug products, including biologics, or when use of those therapies are inadvisable.**	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. Axial spondyloarthritis *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 antiinflammatory 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.**

	Only the indications for rheumatoid arthritis and non-radiographic axial spondyloarthritis would need to be revised.		
Section 4.4 –VTE	Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving JAK inhibitors, including Rinvoq. In a large randomised active-controlled study in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a dose-dependent increased incidence of VTE was observed with tofacitinib (a different JAK inhibitor) compared with TNF blockers. If clinical features of DVT/PE occur, patients should be evaluated promptly, followed by appropriate treatment. *Comment: To strengthen the warning on VTE, the risk factors for VTE should be listed as seen in the EU SmPC.* *In addition, if the Committee considers this to be a JAK inhibitor class effect, the following could be adopted:* *"In patients over 65 years of age and in patients whom other risk factors for VTE are identified, upadacitinib should only be used if no suitable treatment alternatives are available".*	If symptoms of thrombosis occur, patients should discontinue RINVOQ and be evaluated promptly and treated appropriately. **Avoid** RINVOQ in patients that may be at increased risk of thrombosis.	Risk factors that should be considered in determining the patient's risk for DVT/PE include older age, obesity, a medical history of DVT/PE, patients undergoing major surgery, and prolonged immobilisation. If clinical features of DVT/PE occur, upadacitinib treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment.
Section 4.4 – MACE	In a large randomised active-controlled study in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, an increased incidence of MACE, including myocardial infarction (MI), was observed with tofacitinib (a different JAK inhibitor) compared with TNF blockers. Consider the risks and benefits of Rinvoq treatment prior to initiating therapy in patients with cardiovascular risk factors or when considering continuing Rinvoq in patients who develop MACE. *Comment: If the Committee considers this to be a JAK inhibitor class effect, the following could be adopted (using the warning in the EU SmPC for tofacitinib): "In patients over 65 years of age, patients who are current or past smokers, and patients with other cardiovascular risk factors, upadacitinib should only be used if no suitable treatment alternatives are available".*	Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. Discontinue RINVOQ in patients that have experienced a myocardial infarction or stroke.	Nothing additional that is not currently in the NZ data sheet.

Section 4.4 – Malignancies	The risk of malignancies including lymphoma is increased in patients with rheumatoid arthritis. Immunomodulatory medications may increase the risk of malignancies including lymphoma. In a large randomised active-controlled study in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, an increased incidence of malignancy, particularly lung cancer, lymphoma and non-melanoma skin cancer (NMSC), was observed with tofacitinib (a different JAK inhibitor) compared to Tumor Necrosis Factor (TNF) blockers. Malignancies were observed in clinical studies of Rinvoq (see 4.8 ADVERSE EFFECTS). A higher rate of malignancies, driven by NMSC, was observed with Rinvoq 30 mg compared to Rinvoq 15 mg. Consider the risks and benefits of Rinvoq treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated NMSC or when considering continuing Rinvoq in patients who develop a malignancy. *Comment: If the Committee considers this to be a JAK inhibitor class effect, the following could be adopted (using the warning in the EU SmPC for tofacitinib): "In patients over 65 years of age, patients who are current or past smokers, and patients with other malignancy risk factors (eg, current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer) upadacitinib should only be used if no suitable treatment alternatives are available".*	Nothing additional that is not currently in the NZ data sheet.	Nothing additional that is not currently in the NZ data sheet.
Section 4.4 – Mortality	No information. *Comment: To strengthen Section 4.4, the Committee could recommend including a warning statement on mortality, as seen in the FDA labelling (ie, state the results of the ORAL Surveillance study, and to consider the risks and benefits).*	In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed in patients treated with the JAK inhibitor compared with TNF blockers. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ.	No information.

6.3 Jakavi (ruxolitinib)

	New Zealand	United States	EU
Therapeutic Indications	Jakavi is indicated for the treatment of disease-related splenomegaly or symptoms in patients with primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis. Jakavi is indicated for the treatment of adult patients with polycythemia vera who are resistant to or intolerant of hydroxyurea.	Myelofibrosis Jakafi is indicated for treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF in adults. Polycythemia Vera Jakafi is indicated for treatment of polycythemia vera (PV) in adults who have had an inadequate response to or are intolerant of hydroxyurea.	Myelofibrosis (MF) Jakavi is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis. Polycythaemia vera (PV) Jakavi is indicated for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.
Section 4.4 – VTE	No information. *Comment: The Committee could recommend adopting the US warning statement.*	Another JAK-inhibitor has increased the risk of thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. In patients with MF and PV treated with Jakafi in clinical trials, the rates of thromboembolic events were similar in Jakafi and control treated patients. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately	No information.
Section 4.4 – MACE	No information. *Comment: The Committee could recommend adopting the US warning statement.*	Another JAK-inhibitor has increased the risk of MACE, including cardiovascular death, myocardial infarction, and stroke (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur.	No information.
Section 4.4 – Secondary malignancies	No information. *Comment: The Committee could recommend adopting the US warning statement.*	Another JAK-inhibitor has increased the risk of lymphoma and other malignancies excluding NMSC (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated. Patients	No information.

		who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Jakafi, particularly in patients with a known secondary malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers.	
Section 4.4 – Mortality	No information. *Comment: The Committee could recommend adopting the US warning statement.*	*Comment: No dedicated warning statement on mortality. However, death is covered in warning and precautions section of MACE – "Another JAK-inhibitor has increased the risk of MACE, **including cardiovascular death**, myocardial infarction, and stroke (compared to those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which Jakafi is not indicated".*	No information.

7 DISCUSSION AND CONCLUSIONS

ORAL Surveillance study and uncertainties

The ORAL Surveillance study was a large, randomised, post-market, open-label, non-inferiority study comparing the safety and efficacy of tofacitinib versus TNFi. The study population consisted of patients with rheumatoid arthritis aged ≥50 years and with at least one cardiovascular risk factor. This study was powered to detect enough events of MACE and malignancies. The results of this study showed a higher risk of MACE, malignancies, thromboembolic events, infections and all-cause mortality in patients taking tofacitinib compared to a TNFi. The risk was also higher in patients ≥65 years of age compared to patients <65 years of age.

This study also demonstrated the two treatment arms had similar clinical efficacy which raises the important consideration on whether tofacitinib should only be used following TNFi/other treatment failure or intolerance.

The risk of some events of interest also occurs with TNFi use. For example, events of malignancies were higher in TNFi users compared to placebo in controlled trials. Therefore the risk of malignancies may be even higher for tofacitinib considering non-inferiority was not demonstrated in ORAL Surveillance.

Indeed, the results of ORAL Surveillance have triggered international regulatory action and review.

The FDA has determined that although other JAK inhibitors approved for inflammatory diseases have not been studied to the same extent as tofacitinib, the same mechanism of action is shared and therefore they may have similar risks. This resulted in a class-labelling update for all JAK inhibitors used for any inflammatory diseases with cautionary warnings and restricting the indication for use only in patients who have had an inadequate response to, or intolerance of, one or more TNFi.

The EMA's PRAC is currently reviewing whether the risks observed in the ORAL Surveillance are associated with all JAK inhibitors used for inflammatory disorders and if the marketing authorisations for these medicines should be amended. The EU product information for tofacitinib contains a warning that tofacitinib should be used only if no suitable alternatives exist in patients ≥65 years old, with a history of smoking, risk factors for cardiovascular disease or malignancy.

In vitro, different JAK inhibitors exhibit inhibitory selectivity for certain JAK isoforms. However, it is unclear how this specificity translates to differences in safety and efficacy in the real world with clinically relevant doses without head-to-head trials. *In vivo* and therapeutics studies have not necessarily replicated the specificity seen *in vitro*.

Another factor to consider is that JAKs work in pairs to mediate downstream signalling. JAK1 can pair with all other JAK isoforms so there is potential that other cytokines relying on other JAK-dependent pathways are affected.

To date, plausible mechanisms have not been clearly identified for the adverse events of interest to explain a JAK inhibitor class effect. However, given JAK inhibition can affect the signalling of many cytokines involved in normal homeostatic function, there may be unwanted effects. It is also important to consider that patients with inflammatory diseases have a higher risk for developing malignancies, MACE, and thromboembolic events than the general population. Some risks are also related to disease severity.

Overall, there is uncertainty whether the results from the ORAL Surveillance are applicable to other JAK inhibitors and to the other various inflammatory diseases they are indicated for.

Approved JAK inhibitors in New Zealand

In New Zealand there are three approved JAK inhibitors. Tofacitinib is indicated for the treatment of rheumatoid arthritis whereas upadacitinib is also indicated for the treatment of psoriatic arthritis, ankylosis spondylitis, non-radiographic axial spondyloarthritis, and atopic dermatitis. Ruxolitinib is indicated for the treatment of myeloproliferative neoplasms.

Tofacitinib:

In general, observational studies published in the literature and in the Corrona Registry did not suggest an increased risk of MACE, malignancies, thromboembolic events and all-cause mortality with tofacitinib versus TNFi. Although numerically higher IRs were observed in patients taking tofacitinib versus TNFi for these events, the confidence intervals overlapped.

The current data sheet in New Zealand has information that reflects the results observed in the ORAL Surveillance study. In addition, there are warnings that caution should be used in certain populations who are at risk of malignancies, MACE, and thromboembolic events.

Upadacitinib:

For upadacitinib, no large post-market study has been conducted to the same extent as the ORAL Surveillance study to determine whether the risk of MACE, malignancies (excluding NMSC), and thromboembolic events are elevated. [redacted]. Atopic dermatitis is the only indication approved for use at a 30 mg dose however the data sheet states for patients ≥65 years of age, the recommended dose is 15 mg once daily.

The current data sheet in New Zealand has information that reflects the results observed in the ORAL Surveillance study. In addition, there are warnings that healthcare professionals should consider the risks and benefits of treatment prior to initiating therapy in certain patients with risk factors for MACE and malignancies. For thromboembolism, patients should be evaluated for VTE and treated.

Ruxolitinib:

Ruxolitinib is indicated for myeloproliferative neoplasms. The patient population with myeloproliferative disorders differs from patient populations with inflammatory conditions for which other JAK inhibits are indicated for. Therefore, the risk-benefit balance differs. Considering the differences in the risk-benefit balance, the FDA has added a 'weaker' warning to the labelling advising caution and that risk factors should be considered with their use. No restrictions to the indication were imposed.

The current data sheet in New Zealand does not have information that reflects the results observed in the ORAL Surveillance study.

Overall risk-benefit considerations

JAK inhibitors are a new class of medicine demonstrating comparable clinical efficacy to TNFi for various inflammatory diseases. JAK inhibitors have the advantage over TNFi being administered orally and having a faster onset of action.

There are however current uncertainties regarding the safety of JAK inhibitors. Unlike tofacitinib, no similar studies have assessed the risk of MACE, malignancies (excluding NMSC), and thromboembolic for other JAK inhibitors and for other inflammatory conditions other than rheumatoid arthritis. However, since JAK inhibitors share the same specific targets and mechanisms of action, all JAK inhibitors may carry the same risk.

The Committee is asked to consider whether regulatory action is required to improve the risk-benefit balance of approved JAK inhibitors in New Zealand in light of the ORAL Surveillance study results. Actions may include updates to the medicine data sheet to strengthen the warnings and precautions for use and/or restricting the therapeutic indications (see comments in red in section 6 of this report).

8 ADVICE SOUGHT

The Committee is asked to advise:

- Whether the risk of MACE, malignancies and thromboembolic events applies to all JAK inhibitors used in inflammatory disease.

- Whether regulatory action is required to improve the risk benefit balance of **tofacitinib** considering the outcome of the ORAL Surveillance Study. Such actions may include:
    - Strengthening the warning and precautions section of the data sheet so that individuals 65 years and older, current/past smoker, with thromboembolic, cardiovascular and malignancy risk factors should only use tofacitinib if no suitable alternatives are available.
    - Restricting the therapeutic indications of tofacitinib to individuals who have had an inadequate response or intolerance to one or more DMARD.
- Whether similar regulatory action should be applied to **upadacitinib** to improve the risk benefit balance?
- Should the **ruxolitinib** data sheet be updated to reflect the results of the ORAL Surveillance study?
- Whether further communication is required other than in MARC's remarks?

9 ANNEXES

Annex 1 – Ytterberg et al 2022. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. *New England Journal of Medicine*

Annex 2 – Khosrow-Khavar et al 2022. Tofacitinib and risk of cardiovascular outcomes: results from the Safety of TofAcitinib in Routine care patients with Rheumatoid Arthritis (STAR-RA) study. *Ann Rheum Dis*

Annex 3 – CARM line listing

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