XELJANZ (tofacitinib citrate) for the treatment of patients with rheumatoid arthritis

MEDICINES EVIDENCE PACK TO SUPPORT FORMULARY AND GUIDELINES DECISION MAKING

Healthcare professionals are asked to report any suspected adverse reactions. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Any suspected adverse reactions may also be reported to Pfizer medical information on 01304 616161.

Prescribing information for XELJANZ is provided at the back of this document.

Patients treated with XELJANZ should be given the Patient Alert Card (PAC). The PAC, along with Prescriber Checklists and a Prescriber Brochure forms part of the Risk Minimisation Programme materials (RMP) which can be found at the eMC website https://www.medicines.org.uk/emc/
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# XELJANZ overview in rheumatoid arthritis

## Table 1: Overview of XELJANZ for the treatment of rheumatoid arthritis

<table>
<thead>
<tr>
<th>Brand name</th>
<th>XELJANZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic name</td>
<td>Tofacitinib citrate</td>
</tr>
</tbody>
</table>

### Licensed indication

XELJANZ in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have inadequately responded to, or who are intolerant to, one or more disease-modifying antirheumatic drugs (DMARDs). XELJANZ can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.

### Class of drug

Janus kinase (JAK) inhibitor.

### Clinical trials

- **ORAL Scan** – MTX-inadequate response (IR); placebo control (N=797)
- **ORAL Standard** – MTX-IR; active control (adalimumab) (N=717)
- **ORAL Sync** – DMARD-IR; placebo control (N=792)
- **ORAL Solo** – DMARD-IR; placebo control (N=610)
- **ORAL Step** – tumour necrosis factor inhibitor (TNFi)-IR; placebo control (N=399)
- **ORAL Strategy** – MTX-IR; head-to-head (adalimumab) (N=1146)

### Dose

The recommended dose is 5 mg administered twice daily. No dose adjustment is required when used in combination with MTX.

### Administration

Oral use. XELJANZ is given orally with or without food.

### Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in the Summary of Product Characteristics
- Active tuberculosis (TB), serious infections such as sepsis, or opportunistic infections
- Severe hepatic impairment
- Pregnancy and lactation

### Cost

XELJANZ 5 mg, 56 film-coated tablets – £690.03 (MIMS, 2017).

For full prescribing and safety information, please see XELJANZ SmPC (Pfizer, 2017).
**XELJANZ**

**Mechanism of action**

JAK proteins control activation of signalling cascades for many cytokines important in the pathogenesis of immune-mediated inflammatory disease (O'Shea et al., 2015; McInnes and Liew, 2005), making JAK a candidate for targeted therapeutic interventions in RA.

XELJANZ is a novel oral JAK inhibitor that targets inflammation by reducing pro-inflammatory cytokines. It is an orally bioavailable small-molecule therapy that targets inflammation from inside the cell (Pfizer, 2017; O'Shea et al., 2015; Fleischmann, 2012; Tanaka and Yamaoka, 2013).

**Figure 1: Inhibition of JAK signalling with XELJANZ**

Figure adapted from: Shuai and Liu (2003); Jiang et al. (2008).

- **JAK signalling**
  - Cytokine binding to its cell surface receptor leads to receptor polymerisation and activation of associated JAKs
  - Activated JAKs phosphorylate the receptors that dock signal transducers and activators of transcription (STATs)
  - Activated JAKs phosphorylate STATs which dimerize and move to the nucleus to activate new gene transcription

- **JAK inhibition:**
Cytokine binding to its cell surface receptor leads to receptor polymerisation and activation of associated JAKs

- XELJANZ inhibits the autophosphorylation and activation of JAK
- JAKs cannot phosphorylate the receptors that therefore cannot dock STATs
- JAKs cannot phosphorylate STATs, which cannot dimerize and move to the nucleus to activate new gene transcription and produce more pro-inflammatory cytokines
The efficacy and safety of XELJANZ were assessed in six randomised, double-blind, controlled multicentre studies in patients greater than 18 years of age with active RA diagnosed according to American College of Rheumatology (ACR) criteria. Table 2 provides information regarding the pertinent study design and population characteristics.

Table 2: Phase III/IIIb clinical trials of XELJANZ 5 mg twice-daily doses in patients with RA

<table>
<thead>
<tr>
<th>Studies</th>
<th>ORAL Scan</th>
<th>ORAL Standard</th>
<th>ORAL Sync</th>
<th>ORAL Solo</th>
<th>ORAL Step</th>
<th>ORAL Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>MTX-IR</td>
<td>MTX-IR</td>
<td>DMARD-IR</td>
<td>DMARD-IR</td>
<td>TNFi-IR</td>
<td>MTX-IR</td>
</tr>
<tr>
<td>Control</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Adalimumab</td>
</tr>
<tr>
<td>Background treatment</td>
<td>MTX</td>
<td>MTX</td>
<td>csDMARDs</td>
<td>None</td>
<td>MTX</td>
<td>MTX</td>
</tr>
<tr>
<td>Key features</td>
<td>X-ray</td>
<td>Active control (adalimumab)</td>
<td>Various csDMARDs</td>
<td>Monotherapy</td>
<td>TNFi-IR</td>
<td>Head-to-head (adalimumab)</td>
</tr>
<tr>
<td>Number of patients treated</td>
<td>797</td>
<td>717</td>
<td>792</td>
<td>611</td>
<td>399</td>
<td>1146</td>
</tr>
<tr>
<td>Total study duration</td>
<td>24 months</td>
<td>12 months</td>
<td>12 months</td>
<td>6 months</td>
<td>6 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Co-primary efficacy endpoints†</td>
<td>Month 6: ACR20</td>
<td>Month 6: ACR20</td>
<td>Month 6: ACR20</td>
<td>Month 3: ACR50</td>
<td>Month 3: ACR20</td>
<td>Month 3: ACR20</td>
</tr>
<tr>
<td></td>
<td>mTSS DAS28-4(ESR)&lt;2.6</td>
<td>mTSS DAS28-4(ESR)&lt;2.6</td>
<td>mTSS DAS28-4(ESR)&lt;2.6</td>
<td>Non-inferiority</td>
<td>Non-inferiority</td>
<td>Non-inferiority</td>
</tr>
<tr>
<td></td>
<td>Month 3: HAQ-DI</td>
<td>Month 3: HAQ-DI</td>
<td>Month 3: HAQ-DI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>(van der Heijde et al., 2013)</td>
<td>(van Vollenhoven et al., 2012)</td>
<td>(Kremer et al., 2013)</td>
<td>(Fleischmann et al., 2012)</td>
<td>(Burmester et al., 2013)</td>
<td>(Fleischmann et al., 2017)</td>
</tr>
</tbody>
</table>

*Antimalarials were allowed; †Co-primary endpoints as follows: mean change from baseline in mTSS; percent of subjects achieving ACR20 or ACR70 responses; mean change from baseline in HAQ-DI; percent of subjects achieving a DAS28-4(ESR) <2.6 (remission).
## Baseline characteristics

Table 3: Baseline characteristics of Phase III clinical trials of XELJANZ 5 mg twice-daily doses in patients with RA

<table>
<thead>
<tr>
<th>Studies</th>
<th>ORAL Scan</th>
<th>ORAL Standard</th>
<th>ORAL Sync</th>
<th>ORAL Solo</th>
<th>ORAL Step</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria/</td>
<td>MTX-IR/MTX</td>
<td>MTX-IR/MTX</td>
<td>DMARD*-IR/DMARD*</td>
<td>DMARD-IR</td>
<td>TNFi-IR/MTX</td>
</tr>
<tr>
<td>background treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, %</td>
<td>85</td>
<td>82</td>
<td>81</td>
<td>87</td>
<td>84</td>
</tr>
<tr>
<td>Age, mean years</td>
<td>53</td>
<td>53</td>
<td>52</td>
<td>51</td>
<td>55</td>
</tr>
<tr>
<td>Duration of RA, mean</td>
<td>9.0</td>
<td>7.8</td>
<td>9.3</td>
<td>8.1</td>
<td>12.3</td>
</tr>
<tr>
<td>TJC, mean (total of 68)</td>
<td>23.3</td>
<td>27.2</td>
<td>25.2</td>
<td>29.1</td>
<td>28.1</td>
</tr>
<tr>
<td>SJC, mean (total of 66)</td>
<td>14.3</td>
<td>16.4</td>
<td>14.4</td>
<td>16.9</td>
<td>16.5</td>
</tr>
<tr>
<td>RF positive, %</td>
<td>77.0</td>
<td>66.7</td>
<td>73.0</td>
<td>65.0§</td>
<td>62.4</td>
</tr>
<tr>
<td>Anti-CCP positive, %</td>
<td>84.2</td>
<td>69.7</td>
<td>68.2</td>
<td>68.9§</td>
<td>69.2</td>
</tr>
<tr>
<td>CRP, mg/l, mean</td>
<td>15.0</td>
<td>16.3</td>
<td>17.2</td>
<td>19.9</td>
<td>17.2</td>
</tr>
<tr>
<td>ESR, mm/h, mean</td>
<td>50.70</td>
<td>48.52</td>
<td>50.68</td>
<td>52.03</td>
<td>46.57</td>
</tr>
<tr>
<td>HAQ-DI (0–3), mean</td>
<td>1.36</td>
<td>1.48</td>
<td>1.39</td>
<td>1.52</td>
<td>1.56</td>
</tr>
<tr>
<td>DAS28-4(ESR), mean</td>
<td>6.28</td>
<td>6.48</td>
<td>6.30</td>
<td>6.69</td>
<td>6.43</td>
</tr>
<tr>
<td>Reference</td>
<td>(van der Heijde et al., 2013)</td>
<td>(van Vollenhoven et al., 2012)</td>
<td>(Kremer et al., 2013)</td>
<td>(Fleischmann et al., 2012)</td>
<td>(Burmester et al., 2013)</td>
</tr>
</tbody>
</table>

*nbDMARDs; †bDMARDs and nbDMARDs; ‡Included MTX-IR patients; §Positive for RF, ACPA or both; values were grouped together.
Clinical response

ACR response

The percentages of XELJANZ-treated patients achieving American College of Rheumatology criteria – 20% improvement (ACR20), ACR50 and ACR70 responses in the ORAL Scan, ORAL Standard, ORAL Sync, ORAL Solo, and ORAL Step studies are shown in Table 4. In all placebo-controlled studies, ACR20, ACR50 and ACR70 response rates at Month 3 and Month 6 were statistically significantly higher in patients treated with 5 mg twice-daily XELJANZ (±MTX) compared with placebo-treated patients.

- The treatment effect was similar in patients independent of rheumatoid factor status, age, gender, race or disease status
- Time to onset was rapid (as early as Week 2 in ORAL Solo, ORAL Sync and ORAL Step) and the magnitude of response continued to improve with duration of treatment
- As with the overall ACR response in patients treated with 5 mg twice-daily XELJANZ, each of the components of the ACR response (including tender and swollen joint counts, patient and physician global assessment, disability index scores, pain assessment and C-reactive protein [CRP]) was consistently improved from baseline compared with patients receiving placebo plus MTX or other DMARDs in all studies

Figure 2: Proportion (%) of patients with an ACR20 response

ACR20 response was a primary endpoint for all studies.

*\( p<0.05 \);
\( ^{1} p<0.001 \);
\( ^{2} p<0.0001 \) vs placebo/MTX;
\( ^{3} \)Analyses for ORAL Scan, Standard and Sync included an advancement penalty; see published papers for further details (van der Heijde et al., 2013; van Vollenhoven et al., 2012; Kremer et al., 2013).

1. (van der Heijde et al., 2013); 2. (van Vollenhoven et al., 2012); 3. (Kremer et al., 2013); 4. (Fleischmann et al., 2012); 5. (Burmester et al., 2013)
Figure 3: Proportion (%) of patients with an ACR50 response

![Graph showing proportion of patients with an ACR50 response]

*\(p \leq 0.05; \) †\(p < 0.001; \) ‡\(p < 0.0001\) vs placebo/MTX; ‡‡Analyses for ORAL Scan, Standard and Sync included an advancement penalty; see published papers for further details (van der Heijde et al., 2013; van Vollenhoven et al., 2012; Kremer et al., 2013).

1. (van der Heijde et al., 2013); 2. (van Vollenhoven et al., 2012); 3. (Kremer et al., 2013); 4. (Fleischmann et al., 2012); 5. (Burmester et al., 2013).

Table 4: Proportion (%) of patients with an ACR response

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Time</th>
<th>Placebo + MTX N=156</th>
<th>XELJANZ 5 mg BID + MTX N=316</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>Month 3</td>
<td>27</td>
<td>55‡</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>25</td>
<td>50‡</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>NA</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Month 24</td>
<td>NA</td>
<td>40</td>
</tr>
<tr>
<td>ACR50</td>
<td>Month 3</td>
<td>8</td>
<td>28‡</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>8</td>
<td>32‡</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>NA</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Month 24</td>
<td>NA</td>
<td>28</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Time</td>
<td>Placebo N=105</td>
<td>XELJANZ 5 mg BID + MTX N=198</td>
</tr>
<tr>
<td>----------</td>
<td>--------</td>
<td>---------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>ACR70</td>
<td>Month 3</td>
<td>3</td>
<td>10**</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>1</td>
<td>14‡</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>NA</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Month 24</td>
<td>NA</td>
<td>17</td>
</tr>
</tbody>
</table>

**ORAL Standard: MTX inadequate responders (van Vollenhoven et al., 2012)**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Time</th>
<th>Placebo + DMARD(s) N=158</th>
<th>XELJANZ 5 mg BID + DMARD(s) N=312</th>
<th>Adalimumab 40 mg Q2W + MTX N=199</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>Month 3</td>
<td>26</td>
<td>59‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>28</td>
<td>51‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>NA</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>ACR50</td>
<td>Month 3</td>
<td>7</td>
<td>33‡</td>
<td>24‡</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>12</td>
<td>36‡</td>
<td>27†</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>NA</td>
<td>36</td>
<td>33†</td>
</tr>
<tr>
<td>ACR70</td>
<td>Month 3</td>
<td>2</td>
<td>12†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>2</td>
<td>19‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>NA</td>
<td>22</td>
<td></td>
</tr>
</tbody>
</table>

**ORAL Sync: DMARD inadequate responders (Kremer et al., 2013)**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Time</th>
<th>Placebo + DMARD(s) N=158</th>
<th>XELJANZ 5 mg BID + DMARD(s) N=312</th>
<th>Adalimumab 40 mg Q2W + MTX N=199</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>Month 3</td>
<td>27</td>
<td>56‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>31</td>
<td>53‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>NA</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>ACR50</td>
<td>Month 3</td>
<td>9</td>
<td>27‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>13</td>
<td>34‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>NA</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>ACR70</td>
<td>Month 3</td>
<td>2</td>
<td>8†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>3</td>
<td>13‡</td>
<td></td>
</tr>
</tbody>
</table>
DAS28-4(ESR) response

- Patients in the phase III studies had a mean Disease Activity Score (DAS28-4[ESR]) of 6.2–6.7 at baseline.
- At Month 3, significant reductions in DAS28-4(ESR) from baseline (mean improvement) of 1.8–2.0 were observed in patients treated with XELJANZ 5 mg twice daily compared with placebo-treated patients (0.7–1.1).
- The proportion of patients achieving a DAS28 clinical remission (DAS28-4[ESR] <2.6) in ORAL Standard, ORAL Sync and ORAL Step is shown in Table 5.
**Table 5: Proportion (%) of subjects achieving DAS28-4(ESR) <2.6 remission**

<table>
<thead>
<tr>
<th>Time Point</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORAL Standard: MTX inadequate responders (van Vollenhoven et al., 2012)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XELJANZ 5 mg BID + MTX Month 6</td>
<td>177</td>
<td>6*</td>
</tr>
<tr>
<td>Adalimumab 40 mg SC Q2W + MTX Month 6</td>
<td>178</td>
<td>7*</td>
</tr>
<tr>
<td>Placebo + MTX Month 6</td>
<td>92</td>
<td>1</td>
</tr>
<tr>
<td><strong>ORAL Sync: DMARD inadequate responders (Kremer et al., 2013)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XELJANZ 5 mg BID Month 6</td>
<td>284</td>
<td>9*</td>
</tr>
<tr>
<td>Placebo Month 6</td>
<td>153</td>
<td>3</td>
</tr>
<tr>
<td><strong>ORAL Step: TNF inhibitor inadequate responders (Burmester et al., 2013)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XELJANZ 5 mg BID + MTX Month 3</td>
<td>119</td>
<td>7</td>
</tr>
<tr>
<td>Placebo + MTX Month 3</td>
<td>120</td>
<td>2</td>
</tr>
</tbody>
</table>

*p<0.05 vs placebo.

**Radiographic response**

In ORAL Scan, inhibition of structural joint damage progression was assessed radiographically and expressed as mean change from baseline in modified total Sharp score (mTSS) and its components, the erosion score and joint space narrowing score, at Months 6 and 12 (Table 6).

In ORAL Scan, XELJANZ 5 mg twice daily plus MTX demonstrated numerical improvement in mTSS over time compared with placebo, but this was not statistically significant. Analysis of erosion and joint space narrowing scores were consistent with overall results.

In the placebo plus MTX group, 78% of patients experienced no radiographic progression (change in mTSS ≤0.5) at Month 6 compared with 89% of patients treated with XELJANZ 5 mg (plus MTX) twice daily (significant vs placebo plus MTX) (van der Heijde et al., 2013).
Table 6: Proportion (%) of patients achieving radiographic changes at Months 6 and 12

<table>
<thead>
<tr>
<th>ORAL Scan: MTX Inadequate Responders (van der Heijde et al., 2013)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + MTX</td>
</tr>
<tr>
<td>(N=139)</td>
</tr>
<tr>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

| mTSS           | 33 (42)                     | 31 (48)                     | –                     |
| Baseline       |                            |                            |                       |
| Month 6†       | 0.5 (2.0)                   | 0.1 (1.7)                   | –0.3 (–0.7–0.0)‡      |
| Month 12‡      | 1.0 (3.9)                   | 0.3 (3.0)                   | –0.6 (–1.3–0.0)‡      |

*Difference between least squares means XELJANZ minus placebo; †Data are mean change from baseline; ‡Endpoints were not statistically significant.

Figure 4: Radiographic progression at Months 6 and 12. Mean change from baseline in mTSS (LE)*. Primary endpoint not met (van der Heijde et al., 2013)

*Change from baseline (least squares mean [LSM]) – van der Heijde mTSS (imputation using LE); †Anticipated number for modelled placebo progression (based on available literature).
**Physical function response and health-related outcomes**

- XELJANZ, alone or in combination with MTX, has shown improvements in physical function, as measured by the health assessment questionnaire – disability index (HAQ-DI).

- In placebo-controlled studies, patients receiving XELJANZ 5 mg twice daily demonstrated significantly greater improvement from baseline in physical functioning compared with placebo at Month 3 (ORAL Solo, ORAL Sync, ORAL Standard and ORAL Step) and Month 6 (ORAL Sync and ORAL Standard).
  - Statistical significance could not be declared in ORAL Scan due to the step-down design of the study.

- In ORAL Solo and ORAL Sync, patients treated with XELJANZ 5 mg twice daily demonstrated significantly greater improvement in physical functioning compared with placebo as early as Week 2.

- Changes from baseline in HAQ-DI in studies ORAL Standard, ORAL Sync and ORAL Step are shown in Table 7.
Figure 6: LSM change from baseline in HAQ-DI scores at Month 3

*\( p \leq 0.001 \) vs placebo; †Statistical significance could not be declared in the ORAL Scan study due to the step-down procedure.

References: 1. (van der Heijde et al., 2013); 2. (van Vollenhoven et al., 2012); 3. (Kremer et al., 2013); 4. (Fleischmann et al., 2012); 5. (Burmester et al., 2013).

Table 7: LSM change from baseline in HAQ-DI at Month 3

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Drug Combination</th>
<th>N</th>
<th>LSM Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORAL Standard: MTX inadequate responders</strong> (van Vollenhoven et al., 2012)</td>
<td>Placebo + MTX</td>
<td>98</td>
<td>-0.24</td>
</tr>
<tr>
<td></td>
<td>XELJANZ 5 mg BID + MTX</td>
<td>188</td>
<td>-0.55*</td>
</tr>
<tr>
<td></td>
<td>Adalimumab 40 mg Q2W + MTX</td>
<td>190</td>
<td>-0.49*</td>
</tr>
<tr>
<td><strong>ORAL Sync: DMARD inadequate responders</strong> (Kremer et al., 2013)</td>
<td>Placebo + DMARD(s)</td>
<td>159</td>
<td>-0.16</td>
</tr>
<tr>
<td></td>
<td>XELJANZ 5 mg BID + DMARD(s)</td>
<td>315</td>
<td>-0.44*</td>
</tr>
<tr>
<td><strong>ORAL Step: TNF inhibitor inadequate responders</strong> (Burmester et al., 2013)</td>
<td>Placebo + MTX</td>
<td>118</td>
<td>-0.18</td>
</tr>
<tr>
<td></td>
<td>XELJANZ 5 mg BID + MTX</td>
<td>117</td>
<td>-0.43*</td>
</tr>
</tbody>
</table>

*\( p < 0.001 \) vs placebo + MTX.
Efficacy of XELJANZ after inadequate response to DMARDs

XELJANZ, alone or in combination with MTX, has shown significantly improved ACR responses compared to placebo. Biologic disease-modifying anti-rheumatic drug (bDMARD)-naive (N=2812) and bDMARD-IR (N=705) patients from four phase II studies and five phase III studies (ORAL Step, ORAL Scan, ORAL Solo, ORAL Sync and ORAL Standard) were analysed. The results of the analyses are shown in Figures 7 and 8.

Figure 7: Efficacy of XELJANZ after inadequate response to csDMARDs or bDMARDs; ACR20/50/70 at Month 3

No preservation of type I error was applied for secondary endpoints, no multiple-comparisons correction was applied to p-values, and statistical significance was defined as p≤0.05.

*p<0.0001; †p<0.05 vs placebo; ‡Non-responder imputation.

(Charles-Schoeman et al., 2016).
Figure 8: Efficacy of XELJANZ after inadequate response to nbDMARDs or one or multiple TNFis; ACR50 at Month 3

*<p><0.05 vs placebo.

(Charles-Schoeman et al., 2016).
HEAD-TO-HEAD STUDY

ORAL Strategy was a one-year, double-blind, phase IIIb/IV, head-to-head, non-inferiority, randomised control trial in adults with active RA despite methotrexate therapy. Patients were randomly assigned (1:1:1) to receive oral XELJANZ (5 mg BID) monotherapy, oral XELJANZ (5 mg BID) + MTX or subcutaneous (SC) adalimumab (40 mg Q2W) + MTX. The proportion of patients achieving ACR50 at Month 6 was the primary endpoint.

Non-inferiority comparisons at Month 6 were made between arms:

- XELJANZ + MTX vs adalimumab + MTX
- XELJANZ + MTX vs XELJANZ monotherapy
- XELJANZ monotherapy vs adalimumab + MTX

Baseline characteristics

Table 8: Baseline characteristics of ORAL Strategy

<table>
<thead>
<tr>
<th>Study</th>
<th>ORAL Strategy (Fleischmann et al., 2017)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria/ background treatment</td>
<td>MTX-IR/MTX</td>
</tr>
<tr>
<td>Female, %</td>
<td>83</td>
</tr>
<tr>
<td>Age, mean years</td>
<td>50</td>
</tr>
<tr>
<td>Duration of RA, mean years</td>
<td>5.8</td>
</tr>
<tr>
<td>TJC, mean (total of 68)</td>
<td>15.4</td>
</tr>
<tr>
<td>SJC, mean (total of 66)</td>
<td>11.3</td>
</tr>
<tr>
<td>RF positive, %</td>
<td>n/a</td>
</tr>
<tr>
<td>Anti-CCP positive, %</td>
<td>76.1</td>
</tr>
<tr>
<td>CRP, mg/l, mean</td>
<td>17.3</td>
</tr>
<tr>
<td>ESR, mm/h, mean</td>
<td>n/a</td>
</tr>
<tr>
<td>HAQ-DI (0–3), mean</td>
<td>1.6</td>
</tr>
<tr>
<td>DAS28-4(ESR), mean</td>
<td>6.53</td>
</tr>
</tbody>
</table>
Clinical response

ACR response

- The percentages of patients achieving ACR20, ACR50 and ACR70 responses in ORAL Strategy are shown in Figures 9 and 10.

- ORAL Strategy was designed as a non-inferiority study with a primary endpoint of ACR50 response rate at Month 6; p-values are not reported (Fleischmann et al., 2017)

- Non-inferiority was demonstrated for XELJANZ + MTX vs adalimumab + MTX; non-inferiority was not demonstrated for XELJANZ monotherapy vs adalimumab + MTX (see Figure 11)

Figure 9: Proportion (%) of patients with an ACR50 response at Month 6 (primary endpoint) (Fleischmann et al., 2017)
Figure 10: Proportion (%) of patients with an ACR20/70 response at Month 6 (Fleischmann et al., 2017)

Figure 11: Difference between groups in ACR50 response rates at Month 6. Non-inferiority declared for XELJANZ + MTX vs Adalimumab vs MTX (Fleischmann et al., 2017)

*Criteria for non-inferiority met. The dotted line represents the –13% non-inferiority margin and error bars represent 98.34% CIs.
**DAS28-4(ESR) response**

Patients in the phase IIIb study, ORAL Strategy, had a mean DAS28-4(ESR) of 6.5 at baseline. The proportion of patients achieving a DAS28 clinical remission (DAS28-4[ESR] <2.6) in ORAL Strategy is shown in Table 9.

### Table 9: Proportion (%) of patients achieving DAS28-4(ESR) <2.6 remission

<table>
<thead>
<tr>
<th>ORAL Strategy: <em>head-to-head (adalimumab) in MTX inadequate responders</em> (Fleischmann et al., 2017)</th>
<th>Time Point</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>XELJANZ 5 mg BID</td>
<td>Month 6</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>43</td>
<td>11</td>
</tr>
<tr>
<td>XELJANZ 5 mg BID + MTX</td>
<td>Month 6</td>
<td>45</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>55</td>
<td>15</td>
</tr>
<tr>
<td>Adalimumab 40 mg Q2W + MTX</td>
<td>Month 6</td>
<td>48</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>66</td>
<td>17</td>
</tr>
</tbody>
</table>

*ORAL Strategy was designed as a non-inferiority study; therefore p-values are not reported.

**Physical function response and health-related outcomes**

XELJANZ, alone or in combination with MTX, has shown improvements in physical function as measured by the HAQ-DI. Changes from baseline in HAQ-DI in ORAL Strategy are shown in Table 10 and Figure 12.
Table 10: LSM change from baseline in ORAL Strategy HAQ-DI at Month 3 (Fleischmann et al., 2017)

<table>
<thead>
<tr>
<th>ORAL Strategy:* head-to-head (adalimumab) in MTX inadequate responders (Fleischmann et al., 2017)</th>
<th>XELJANZ 5 mg BID</th>
<th>XELJANZ 5 mg BID + MTX</th>
<th>Adalimumab 40 mg Q2W + MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>–0.48</td>
<td>–0.54</td>
<td>–0.49</td>
</tr>
</tbody>
</table>

*ORAL Strategy was designed as a non-inferiority study; p-values are therefore not reported.

Figure 12: LSM change from baseline in ORAL Strategy HAQ-DI at Month 3 (Fleischmann et al., 2017)
Table 11: Summary of AEs, serious adverse events and discontinuations in the safety analysis set of ORAL Strategy

<table>
<thead>
<tr>
<th>ORAL Strategy:* head-to-head (adalimumab) in MTX inadequate responders (Fleischmann et al., 2017)</th>
<th>XELJANZ 5 mg BID</th>
<th>XELJANZ 5 mg BID + MTX</th>
<th>Adalimumab 40 mg Q2W + MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of AEs*</td>
<td>598</td>
<td>652</td>
<td>620</td>
</tr>
<tr>
<td>Patients with AEs</td>
<td>226 (595)</td>
<td>231 (61%)</td>
<td>253 (66%)</td>
</tr>
<tr>
<td>Patients with treatment-related AEs</td>
<td>101 (26%)</td>
<td>111 (30%)</td>
<td>133 (35%)</td>
</tr>
<tr>
<td>Patients with serious AEs</td>
<td>35 (9%)</td>
<td>27 (7%)</td>
<td>24 (6%)</td>
</tr>
<tr>
<td>Patients discontinuing due to AEs</td>
<td>23 (6%)</td>
<td>26 (7%)</td>
<td>37 (10%)</td>
</tr>
<tr>
<td>Patients with severe AEs (defined by the investigator)</td>
<td>24 (6%)</td>
<td>17 (5%)</td>
<td>23 (6%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>2 (1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AEs of special interest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious infections</td>
<td>6 (2%)</td>
<td>10 (3%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Herpes zoster (serious and non-serious)</td>
<td>4 (1%)</td>
<td>8 (2%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Herpes zoster (serious and non-serious in patients who were vaccinated)</td>
<td>1/69 (1%)</td>
<td>2/75 (3%)</td>
<td>0/72 (0%)</td>
</tr>
<tr>
<td>Opportunistic infections (excluding TB)</td>
<td>2 (1%)</td>
<td>1 (&lt;1%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>TB</td>
<td>0</td>
<td>2 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>MACE (non-fatal)</td>
<td>0</td>
<td>0</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Malignancy (excluding NMSC)</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NMSC</td>
<td>2 (1%)</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>

Data are n, n (%), or n/N (%).

*Patients could have had more than one AE.
XELJANZ SAFETY

Summary of the safety profile

- Safety data have been collated from six double-blind, controlled, multicentre studies varying in duration from 6–24 months (ORAL Scan, ORAL Standard, ORAL Sync, ORAL Solo, ORAL Step and ORAL Start), as well as earlier phase studies and a long-term extension study
- All patients in these studies had moderate to severe RA
- A total of 6194 patients were treated with any dose of XELJANZ, with a mean duration of 3.13 years
- The study XELJANZ population had a mean age of 52.1 years and 83.2% were female
- The findings of 19405.8 patient-years of accumulated total drug exposure have been published based on up to 8.5 years of continuous exposure to XELJANZ (Cohen et al., 2017)

Tabulated list of adverse reactions

The adverse drug reactions listed in the table below are presented by system organ class and frequency categories, defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100) and rare (≥1/10,000 to <1/1000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 12: Adverse drug reactions (Pfizer, 2017)

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>≥1/10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes zoster</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinusitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia pneumococcal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia bacterial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diverticulitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis bacterial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes simplex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroenteritis viral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB of central nervous system</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptococcal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urosepsis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disseminated TB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necrotizing fasciitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteraemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcal bacteraemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Pneumocystis jirovecii pneumonia**  
**Encephalitis**  
**Atypical mycobacterial infection**  
**Mycobacterium avium complex infection**  
**Cytomegalovirus infection**

<table>
<thead>
<tr>
<th>Neoplasms benign, malignant and unspecified (including cysts and polyps)</th>
<th>Non-melanoma skin cancers</th>
</tr>
</thead>
</table>
| Blood and lymphatic system disorders | Leukopenia  
Anaemia  
Lymphopenia  
Neutropenia |
| Metabolism and nutrition disorders | Dyslipidaemia  
Hyperlipidaemia  
Dehydration |
| Psychiatric disorders | Insomnia |
| Nervous system disorders | Headache  
Paraesthesia |
| Vascular disorders | Hypertension |
| Respiratory, thoracic and mediastinal disorders | Dyspnoea  
Cough  
Sinus congestion |
| Gastrointestinal disorders | Abdominal pain  
Vomiting  
Diarrhoea  
Nausea  
Gastritis  
Dyspepsia |
<table>
<thead>
<tr>
<th>Area of Disorders</th>
<th>Condition</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
<td>Hepatic steatosis</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Rash</td>
<td>Erythema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pruritus</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td>Musculoskeletal pain</td>
<td>Joint swelling</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>Tendonitis</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>Pyrexia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oedema peripheral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>Hepatic enzyme increased</td>
<td>Transaminases increased</td>
</tr>
<tr>
<td></td>
<td>Blood cholesterol increased</td>
<td>Liver function test abnormal</td>
</tr>
<tr>
<td></td>
<td>Weight increased</td>
<td>Gamma glutamyl-transferase increased</td>
</tr>
<tr>
<td></td>
<td>Blood creatine phosphokinase increased</td>
<td>Blood creatinine increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low density lipoprotein increased</td>
</tr>
<tr>
<td><strong>Injury, poisoning and procedural complications</strong></td>
<td></td>
<td>Ligament sprain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscle strain</td>
</tr>
</tbody>
</table>
**Description of selected adverse reactions**

**Serious infections**

**Figure 13: Potential risk factors for serious infection events following treatment with XELJANZ (pooled phase I-III and LTE data) (Cohen et al., 2017)**

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>HR and 95% CI</th>
<th>HR</th>
<th>Type 3 Wald p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline age, years</td>
<td></td>
<td>1.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline COPD*</td>
<td></td>
<td>1.5</td>
<td>0.0145</td>
</tr>
<tr>
<td>Baseline glucocorticoid use</td>
<td></td>
<td>1.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Baseline HAQ-DI score</td>
<td></td>
<td>1.1</td>
<td>0.0078</td>
</tr>
<tr>
<td>Baseline body mass index</td>
<td></td>
<td>1.1</td>
<td>0.0320</td>
</tr>
<tr>
<td>Prior confirmed post-baseline</td>
<td></td>
<td>2.5</td>
<td>0.0249</td>
</tr>
<tr>
<td>lymphopenia &lt;500 cells/μl</td>
<td></td>
<td>1.6</td>
<td>0.0009</td>
</tr>
<tr>
<td>Baseline diabetes</td>
<td></td>
<td>0.8</td>
<td>0.299</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td>1.2</td>
<td>0.0399</td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td>1.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time-varying XELJANZ dose, mg BID</td>
<td></td>
<td>1.4</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

*Medical history or complication of COPD; †In unit=x, ‘x’ is the change in the continuous variable corresponding to which the change in hazards is observed; ‡Based on exposure period before lymphopenia <500 cells/μl vs exposure period after lymphopenia <500 cells/μl.
Viral reactivation

Rates of HZ infection were increased with XELJANZ vs placebo, as well as with greater age and in Asian locations.

Figure 14: Potential risk factors for serious HZ infection following treatment with XELJANZ (pooled phase I-III and LTE data) (Cohen et al., 2017; Winthrop et al., 2014)

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>HR and 95% CI</th>
<th>HR</th>
<th>Type 3 Wald p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline age, years</td>
<td>Unit = 10^7</td>
<td>1.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline glucocorticoid use</td>
<td>≥7.5 mg/day vs 0 mg/day</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0–&lt;7.5 mg/day vs 0 mg/day</td>
<td>1.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Unknown dose vs 0 mg/day</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Baseline HAQ-DI score</td>
<td>Unit = 0.5^1</td>
<td>1.1</td>
<td>0.0539</td>
</tr>
<tr>
<td>Baseline methotrexate use</td>
<td>Yes vs No</td>
<td>1.1</td>
<td>0.3334</td>
</tr>
<tr>
<td>Prior confirmed post-baseline lymphopenia &lt;500 cells/μl</td>
<td>Unit = 1^†</td>
<td>0.9</td>
<td>0.6843</td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asia vs US/Canada</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Europe vs US/Canada</td>
<td>0.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>LA vs US/Canada</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ex-smoker vs never smoked</td>
<td>1.2</td>
<td>0.0014</td>
</tr>
<tr>
<td></td>
<td>Smoker vs never smoked</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Time-varying XELJANZ dose, mg BID</td>
<td>Unit = 5^†</td>
<td>1.4</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Medical history and/or complication of COPD; †In unit=x, ‘x’ is the change in the continuous variable corresponding to which the change in hazards is observed; ‡Based on exposure period before lymphopenia <500 cells/μl vs exposure period after lymphopenia <500 cells/μl.
**Safety in comparison to anti-TNFs**

**Table 13: Adverse events in XELJANZ treated groups vs adalimumab treated groups in the ORAL Standard trial (Pfizer, 2012)**

<table>
<thead>
<tr>
<th>AEs occurring in &gt;2% in any treatment group (all causality)</th>
<th>XELJANZ 5 mg BID, % (N=1216)</th>
<th>Placebo, % (N=681)</th>
<th>Adalimumab 40 mg Q2W, % (N=204)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>4.4</td>
<td>3.4</td>
<td>3.4</td>
</tr>
<tr>
<td>Headache</td>
<td>4.4</td>
<td>2.2</td>
<td>2.5</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>3.9</td>
<td>2.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3.7</td>
<td>2.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.6</td>
<td>2.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2.1</td>
<td>1.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Oedema peripheral</td>
<td>1.4</td>
<td>2.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>1.2</td>
<td>1.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Cough</td>
<td>0.9</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1.1</td>
<td>2.3</td>
<td>2.0</td>
</tr>
<tr>
<td>RA</td>
<td>1.4</td>
<td>2.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Rash</td>
<td>0.3</td>
<td>0.7</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Presented for AEs that occurred in over 2% of patients in at least one treatment group.
ORAL Standard was not designed as a head-to-head comparison between tofacitinib and adalimumab (40 mg every 2 weeks).
Figure 15: Meta-analysis of malignancies in tofacitinib and bDMARDs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Number of trials</th>
<th>Malignancies rate/100 PY (95% CI)</th>
<th>Patients (N)</th>
<th>Cumulative exposure (PY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept¹</td>
<td>12</td>
<td>0.76</td>
<td>5037</td>
<td>7087</td>
</tr>
<tr>
<td>Rituximab¹</td>
<td>2</td>
<td>1.06</td>
<td>683</td>
<td>577</td>
</tr>
<tr>
<td>Tocilizumab¹</td>
<td>10</td>
<td>1.02</td>
<td>4778</td>
<td>2742</td>
</tr>
<tr>
<td>Infliximab¹</td>
<td>7</td>
<td>0.90</td>
<td>1680</td>
<td>2313</td>
</tr>
<tr>
<td>Etanercept¹</td>
<td>11</td>
<td>1.03</td>
<td>3562</td>
<td>5093</td>
</tr>
<tr>
<td>Certolizumab pegol¹</td>
<td>8</td>
<td>0.61</td>
<td>5241</td>
<td>11046</td>
</tr>
<tr>
<td>Golimumab¹</td>
<td>8</td>
<td>0.96</td>
<td>3283</td>
<td>3303</td>
</tr>
<tr>
<td>Adalimumab¹</td>
<td>21</td>
<td>1.16</td>
<td>11108</td>
<td>10815</td>
</tr>
<tr>
<td>TNF inhibitors¹</td>
<td>54</td>
<td>0.95</td>
<td>25029</td>
<td>32631</td>
</tr>
<tr>
<td>Tofacitinib (constant) 5 mg bid²</td>
<td>19</td>
<td>0.80</td>
<td>2342</td>
<td>3623</td>
</tr>
<tr>
<td>Tofacitinib (average) 5 mg bid²</td>
<td>19</td>
<td>1.00</td>
<td>2239</td>
<td>6870</td>
</tr>
</tbody>
</table>

This table does not show a head-to-head comparison.

*Constant dosage without prior exposure to another tofacitinib dose or adalimumab during the study. Patients who switched doses were not included in this group; †Average dosing was based on average daily dose. Patients receiving <15 mg/day were assigned to the 5 mg twice daily group.

1. (Curtis et al., 2016); 2. (Cohen et al., 2017)

For full safety information, please refer to the XELJANZ (tofacitinib citrate) Summary of Product Characteristics, available at: https://www.medicines.org.uk/emc/medicine/33167
**Drug–drug interactions**

XELJANZ dose should be reduced to 5 mg once daily in patients receiving potent inhibitors of cytochrome (CYP) P450 3A4 (e.g. ketoconazole). XELJANZ dosage should be reduced to 5 mg once daily in patients receiving one or more concomitant medicinal products that result in both moderate inhibition of CYP3A4 as well as potent inhibition of CYP2C19 (e.g. fluconazole).

**Potential for other medicinal products to influence the PK of XELJANZ**

Since XELJANZ is metabolised by CYP3A4, interaction with medicinal products that inhibit or induce CYP3A4 is likely. XELJANZ exposure is increased when co-administered with potent inhibitors of CYP3A4 (e.g. ketoconazole) or when administration of one or more concomitant medications results in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole).

XELJANZ exposure is decreased when co-administered with potent CYP inducers (e.g., rifampicin). Inhibitors of CYP2C19 alone or P-glycoprotein are unlikely to significantly alter the pharmacokinetics (PK) of XELJANZ.

Co-administration with ketoconazole (strong CYP3A4 inhibitor), fluconazole (moderate CYP3A4 and potent CYP2C19 inhibitor), tacrolimus (mild CYP3A4 inhibitor) and ciclosporine (moderate CYP3A4 inhibitor) increased XELJANZ area under the curve (AUC), while rifampicin (potent CYP inducer) decreased XELJANZ AUC. Co-administration of XELJANZ with potent CYP inducers (e.g. rifampicin) may result in a loss of or reduced clinical response (see Figure 2). Co-administration of potent inducers of CYP3A4 with XELJANZ is not recommended. Co-administration with ketoconazole and fluconazole increased XELJANZ $C_{\text{max}}$, while tacrolimus, ciclosporine and rifampicin decreased XELJANZ $C_{\text{max}}$. Concomitant administration with MTX 15–25 mg once weekly had no effect on the PK of XELJANZ in RA patients (see Figure 16).
Figure 16: Impact of other drugs on PK of XELJANZ (Pfizer, 2017)

Note: Reference group is administration of XELJANZ alone.

**Potential for XELJANZ to influence the PK of other medicinal products**

_In vitro_ studies indicate that XELJANZ does not significantly inhibit or induce the activity of the major human–drug metabolising CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) at concentrations exceeding 160 and 268 times the respective steady state total and free $C_{\text{max}}$, respectively, of a 5 mg twice daily dose in RA patients. These _in vitro_ results were confirmed by a human–drug interaction study showing no changes in the PK of midazolam, a highly sensitive CYP3A4 substrate, when co-administered with XELJANZ.

_In vitro_ studies indicate that the potential for XELJANZ to inhibit transporters such as P-glycoprotein, organic anion transporting polypeptide, organic anionic or cationic transporters at therapeutic concentrations is also low.

Co-administration of XELJANZ did not have an effect on the PK of oral contraceptives, levonorgestrel and ethinyl estradiol, in healthy female volunteers.

In RA patients, co-administration of XELJANZ with MTX 15–25 mg once weekly decreased the AUC and $C_{\text{max}}$ of MTX by 10% and 13%, respectively. The extent of decrease in MTX exposure does not warrant modifications to the individualised dosing of MTX.

Co-administration of XELJANZ did not have an effect on the PK of metformin, indicating that XELJANZ does not interfere with the organic cationic transporter in healthy volunteers.
MONITORING

Each patient should be monitored for changes in laboratory parameters including lymphocytes, neutrophils, haemoglobin, lipids and hepatic enzymes.

Initiating treatment is not recommended in patients with:
- Low lymphocyte count (<0.75 cells x10⁹/l)
- Low absolute neutrophil count (<1.0 cells x10⁹/l)
- Low haemoglobin (<9 g/dl)

Caution should be exercised when considering initiation of XELJANZ treatment in patients with elevated ALT or AST, particularly when initiated in combination with potentially hepatotoxic medicinal products, such as MTX.

Table 14: Laboratory monitoring recommendations for XELJANZ (Pfizer, 2017)

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>At baseline</th>
<th>4–8 weeks</th>
<th>Every 3 weeks</th>
<th>Avoid XELJANZ treatment in patients with:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>Absolute lymphocyte count &lt;0.75 x 10⁹/l</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>Absolute neutrophil count &lt;1.00 x 10⁹/l</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>Haemoglobin levels &lt;9 g/dl</td>
</tr>
<tr>
<td>Lipids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver enzymes</td>
<td></td>
<td></td>
<td></td>
<td>Routine monitoring of liver tests and prompt investigation of the cause of liver enzyme elevation are also recommended†</td>
</tr>
</tbody>
</table>

*And as needed after original test; †Caution should be exercised when considering initiation of XELJANZ treatment in patients with elevated ALT or AST, particularly when initiated in combination with potentially hepatotoxic medicinal products such as MTX.

Dose interruption and discontinuation

XELJANZ treatment should be interrupted if a patient develops a serious infection until the infection is controlled.

Interruption of dosing may be needed for management of dose-related laboratory abnormalities including lymphopenia, neutropenia and anaemia. As described in Tables 15, 16 and 17 below,
recommendations for temporary dose interruption or permanent discontinuation of treatment are made according to the severity of laboratory abnormalities.

**Table 15: Low absolute lymphocyte count (Pfizer, 2017)**

<table>
<thead>
<tr>
<th>Lab value (cells/mm³)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALC ≥750</td>
<td>Dose should be maintained.</td>
</tr>
<tr>
<td>ALC 500–750</td>
<td>For persistent (2 sequential values in this range on routine testing) decrease in this range, dosing should be interrupted until ALC is &gt;750. When ALC is &gt;750, resume 5 mg twice daily.</td>
</tr>
<tr>
<td>ALC &lt;500</td>
<td>If lab value confirmed by repeat testing within 7 days, dosing should be discontinued.</td>
</tr>
</tbody>
</table>

**Table 16: Low absolute neutrophil count (Pfizer, 2017)**

<table>
<thead>
<tr>
<th>Lab value (cells/mm³)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC &gt;1000</td>
<td>Dose should be maintained.</td>
</tr>
<tr>
<td>ANC 500–1000</td>
<td>For persistent (2 sequential values in this range on routine testing) decreases in this range, dosing should be interrupted until ANC is &gt;1000. When ANC is &gt;1000, resume 5 mg twice daily.</td>
</tr>
<tr>
<td>ANC &lt;500</td>
<td>If lab value confirmed by repeat testing within 7 days, dosing should be discontinued.</td>
</tr>
</tbody>
</table>
Table 17: Low haemoglobin value (Pfizer, 2017)

<table>
<thead>
<tr>
<th>Lab value (g/dl)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2 g/dl decrease and ≥9.0 g/dl</td>
<td>Dose should be maintained.</td>
</tr>
<tr>
<td>&gt;2 g/dl decrease or &lt;8.0 g/dl</td>
<td>Dosing should be interrupted until haemoglobin values have normalised.</td>
</tr>
<tr>
<td>(Confirmed by repeat testing)</td>
<td></td>
</tr>
</tbody>
</table>

National health technology assessment

Pfizer have submitted evidence to NICE and the SMC. A decision from NICE is expected in December 2017.

Further information is available on request from: Medical Information at Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS, UK. Tel: +44 (0) 1304 616161.

Useful Links

The XELJANZ SmPC and RMP materials can be accessed at:
https://www.medicines.org.uk/emc/medicine/33167

The Risk Management Plan materials include:

- XELJANZ Healthcare Professional Brochure
- XELJANZ Initiation Checklist
- XELJANZ Maintenance Checklist
- XELJANZ Patient Alert Card

Additional information about XELJANZ can be found at www.xeljanz.eu

XELJANZ NHS List Price

Package quantities, marketing authorisation numbers and basic NHS price XELJANZ 5 mg, 56 film-coated tablets, EU/1/17/1178/003 £690.03.
© ▼ (XELJANZ) Prescribing Information:

Please refer to the Summary of Product Characteristics (SmPC) before prescribing XELJANZ.

Presentation: Film-coated tablets containing tofacitinib citrate, equivalent to 5 mg XELJANZ.

Indications In combination with methotrexate (MTX) 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. Can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate. Dosage The recommended dose is 5 mg orally twice daily, taken with or without food. It is recommended not to initiate dosing in patients with an absolute lymphocyte count (ALC) less than 0.75 x 10^9/l, an absolute neutrophil count (ANC) less than 1x10^9/l or in patients with haemoglobin less than 9 g/dl. Renal impairment: No dose adjustment is required in patients with mild or moderate renal impairment. XELJANZ dose should be reduced to 5 mg once daily in patients with severe renal impairment. Patients with severe renal impairment should remain on a reduced dose of 5 mg once daily even after haemodialysis. Hepatic impairment: No dose adjustment is required in patients with mild hepatic impairment. The dose should be reduced to 5 mg once daily in patients with moderate hepatic impairment. XELJANZ is contraindicated in patients with severe hepatic impairment Elderly: No dose adjustment is required in patients aged 65 years and older. Use with caution as increased risk and severity of adverse events. Drug–drug Interactions: XELJANZ dose should be reduced to 5 mg once daily in patients receiving potent inhibitors of cytochrome (CYP) P450 3A4 (e.g., ketoconazole). XELJANZ dosage should be reduced to 5 mg once daily in patients receiving one or more concomitant medicinal products that result in both moderate inhibition of CYP3A4 as well as potent inhibition of CYP2C19 (e.g., fluconazole) Coadministration of XELJANZ with potent CYP inducers (e.g., rifampicin) may result in a loss of or reduced clinical response. Coadministration of potent inducers of CYP3A4 with XELJANZ is not recommended. Contraindications: Hypersensitivity to any of the ingredients, active tuberculosis (TB), serious infections such as sepsis, or opportunistic infections, severe hepatic impairment, pregnancy and lactation. Warnings and Precautions: XELJANZ should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of RA. Patients treated with XELJANZ should be given a patient alert card. There is a higher incidence of adverse events when XELJANZ is prescribed in combination with methotrexate versus XELJANZ as monotherapy. XELJANZ should be avoided in RA patients in combination with biological disease-modifying antirheumatic drugs (bDMARDs) and potent immunosuppressants such as azathioprine, ciclosporin and tacrolimus. Infections: Serious and sometimes fatal infections have been reported in RA patients in patients administered XELJANZ. Patients should be closely monitored for infections, with prompt diagnosis and treatment. Treatment should be interrupted if a serious infection develops. Use carefully in elderly or patients predisposed to, or with a history of infection (e.g. diabetes). Tuberculosis: Patients should be evaluated for both active and latent TB prior to being treated with XELJANZ, patients who test positive for latent TB should be treated with standard antmycobacterial therapy before administering XELJANZ. Viral Reactivation: In clinical studies viral reactivation and cases of herpes zoster have been observed. Screening for viral hepatitis should be performed in accordance with clinical guidelines prior to starting therapy with XELJANZ the impact on chronic viral hepatitis is not known. Vaccinations: Prior to initiating XELJANZ, it is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines. Live vaccines should not be given concurrently with XELJANZ Malignancy: Lymphomas and other malignancies have been observed in patients treated with XELJANZ. Patients with highly active disease may be at higher risk than the general population the effect of XELJANZ on the development and course of malignancies is not known. NMSCs have been reported, periodic skin examination is recommended in patients at increased risk. Interstitial lung disease: Caution is recommended in patients with a history of chronic lung disease as they may be
more prone to infection. Asian patients are known to be at higher risk of ILD caution should be exercised with these patients. *Gastrointestinal perforations:* XELJANZ should be used with caution in patients who may be at increased risk e.g. diverticulitis or concomitant use of corticosteroids or NSAIDs. *Cardiovascular risk:* risk factors should be managed as part of usual standard of care. *Laboratory Parameters:* increased incidence of lymphopenia and neutropenia have been reported and decreases in haemoglobin and should be monitored in accordance with the SmPC. Monitor ANC and haemoglobin at baseline, 4-8 weeks and 3 monthly, ALC at baseline and 3 monthly. XELJANZ has been associated with increases in lipid parameters maximal effects are observed at 6 weeks monitoring should be performed 8 weeks after initiation and managed according to hyperlipidemia guidelines. Increases in liver enzymes greater than 3x ULN were uncommonly reported, use caution when initiating with potential hepatotoxic medicinal products. *Pregnancy & Lactation:* Use of XELJANZ during pregnancy and breast-feeding is contraindicated. Side Effects: The most common serious adverse reactions were serious infections; pneumonia, cellulitis, herpes zoster, UTIs, diverticulitis, appendicitis and opportunistic infections. The most commonly reported adverse reactions during the first 3 months in controlled clinical trials were headache, upper respiratory tract infections, nasopharyngitis, diarrhoea, nausea and hypertension. Very common adverse reactions (≥1/10) were nasopharyngitis. Commonly reported adverse reactions (≥1/100 to <1/10), were pneumonia, influenza, herpes zoster, urinary tract infection, sinusitis, bronchitis, pharyngitis, leukopenia, anaemia, dyslipidaemia, hyperlipidaemia, insomnia, headache, hypertension, dyspnea, cough, abdominal pain, vomiting, diarrhoea, nausea, gastritis, dyspepsia, rash, musculoskeletal pain, arthralgia, pyrexia, oedema peripheral, fatigue, hepatic enzyme increased, blood cholesterol increased, weight increased, blood creatine phosphokinase increased. Refer to SmPC for further information on side effects. Legal Category: POM. Marketing Authorisation Holder: Pfizer Ltd, Ramsgate Road, Sandwich, Kent, CT13 9NJ, UK. Package quantities, Marketing Authorisation Numbers and Basic NHS Price XELJANZ 5 mg, 56 film-coated tablets, EU/1/17/1178/003 £690.03. Further information is available on request from: Medical Information at Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS, UK. Tel: +44 (0) 1304 616161

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Pfizer Medical Information on 01304 616161.

Last revised: 03/2017

Ref: XJ 1_0
### Glossary

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20/50/70</td>
<td>American College of Rheumatology ≥20/50/70% improvement</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ALC</td>
<td>Absolute lymphocyte count</td>
</tr>
<tr>
<td>ANC</td>
<td>Absolute neutrophil count</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>bDMARD</td>
<td>Biologic disease-modifying antirheumatic drug</td>
</tr>
<tr>
<td>BID</td>
<td>Twice daily</td>
</tr>
<tr>
<td>CCP</td>
<td>Cyclic citrullinated peptide</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum drug concentration</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>csDMARD</td>
<td>Conventional synthetic disease-modifying antirheumatic drug</td>
</tr>
<tr>
<td>DAS28</td>
<td>Disease Activity Scale 28 joints</td>
</tr>
<tr>
<td>DMARD</td>
<td>Disease-modifying antirheumatic drug</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>HAQ-DI</td>
<td>Health assessment questionnaire disability index</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>HZ</td>
<td>Herpes zoster</td>
</tr>
<tr>
<td>IR</td>
<td>Inadequate response</td>
</tr>
<tr>
<td>JAK</td>
<td>Janus kinase</td>
</tr>
<tr>
<td>LE</td>
<td>linear extrapolation</td>
</tr>
<tr>
<td>LS</td>
<td>least squares</td>
</tr>
<tr>
<td>LSM</td>
<td>least squares mean</td>
</tr>
<tr>
<td>MACE</td>
<td>Major cardiovascular event</td>
</tr>
<tr>
<td>MCID</td>
<td>Minimum clinically important difference</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------</td>
</tr>
<tr>
<td>mTSS</td>
<td>Modified total Sharp score</td>
</tr>
<tr>
<td>MTX</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>N</td>
<td>Number of patients</td>
</tr>
<tr>
<td>NA</td>
<td>Not applicable</td>
</tr>
<tr>
<td>nbDMARDs</td>
<td>Non-biologic disease-modifying antirheumatic drug</td>
</tr>
<tr>
<td>NMSC</td>
<td>Non-melanoma skin cancer</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
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REFERENCES


