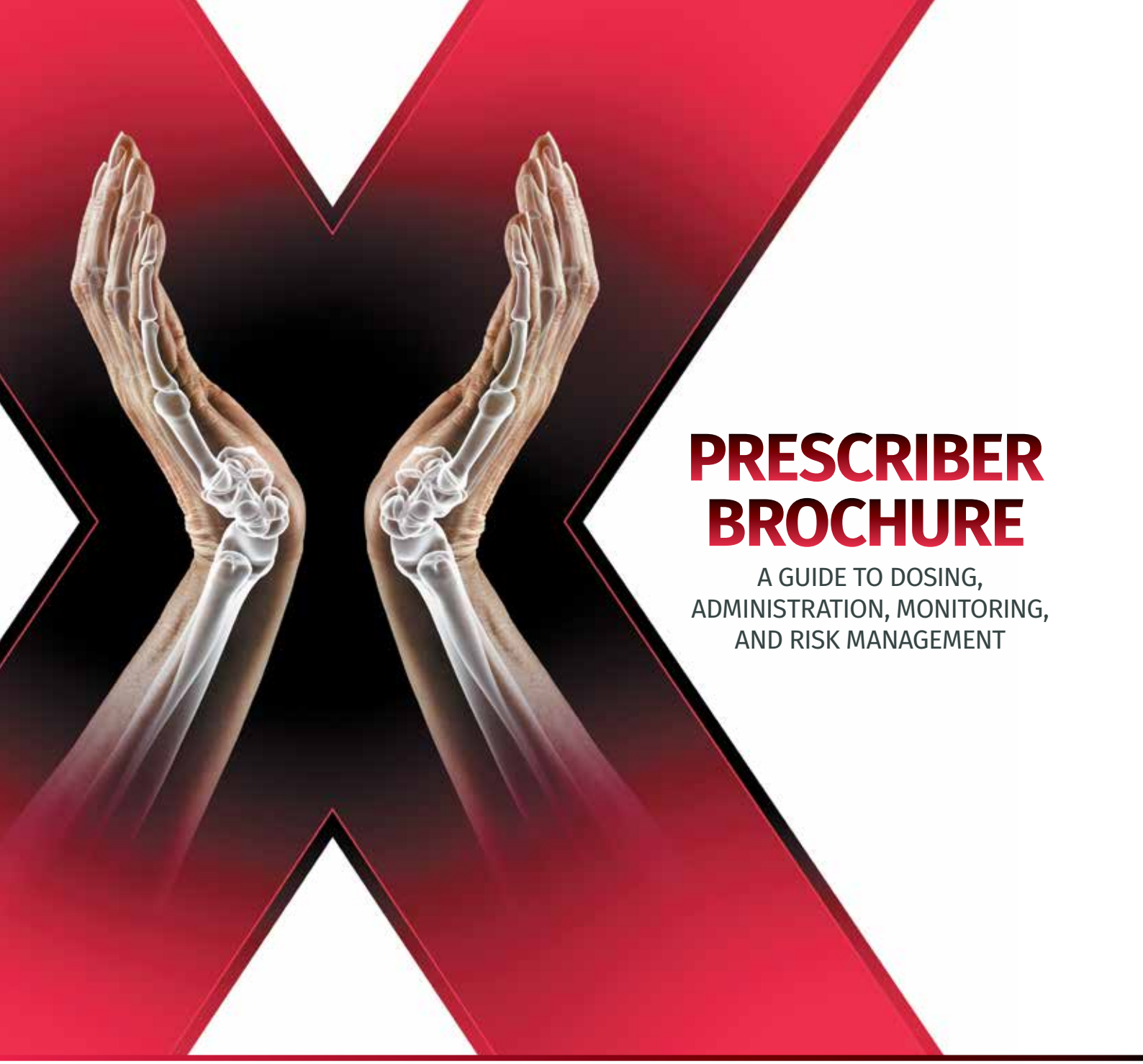

PRESCRIBER BROCHURE

A GUIDE TO DOSING, ADMINISTRATION, MONITORING, AND RISK MANAGEMENT

XELJANZ®
(tofacitinib citrate)

Version: XELJ-MT-EM-V2.0
Date of approval: 17 Sep 2018

PRESCRIBER BROCHURE

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

This Prescriber Brochure intends to provide guidance on tofacitinib to the prescribing physicians with respect to therapeutic indications, dosing and administration including considerations for administration, instruction on monitoring laboratory parameters, precautions and warnings, patient counseling, reporting of adverse events, and a summary of the risk management plan.

Therapeutic indications

Rheumatoid arthritis

XELJANZ, 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. XELJANZ can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.

Psoriatic arthritis

XELJANZ in combination with MTX is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying anti-rheumatic drug (DMARD) therapy.

Ulcerative colitis

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

Posology and method of administration

The recommended posology for RA and PsA is 5 mg administered orally twice daily.

The proposed recommended dose for UC is 10 mg given orally twice daily for induction for 8 weeks and 5 mg given twice daily for maintenance. For patients who do not achieve adequate therapeutic benefit by week 8, the induction dose of 10 mg twice daily can be extended for an additional 8 weeks (16 weeks total), followed by 5 mg twice daily for maintenance. XELJANZ induction therapy should be discontinued in any patient who shows no evidence of therapeutic benefit by week 16. For some patients, such as those who have failed prior tumour necrosis factor (TNF) antagonist therapy, consideration should be given to continuation of the 10 mg twice daily dose for maintenance in order to maintain therapeutic benefit. Patients who experience a decrease in response on XELJANZ 5 mg twice daily maintenance therapy may benefit from an increase to XELJANZ 10 mg administered twice

daily. In patients who have responded to treatment with XEJLANZ, corticosteroids may be reduced and/or discontinued in accordance with standard of care. If therapy is interrupted, restarting treatment with XELJANZ may be considered. If there has been a loss of response, reinduction with XELJANZ 10 mg twice daily may be considered. The treatment interruption period in clinical studies extended up to 1 year. Efficacy may be regained by 8 weeks of 10 mg twice daily therapy.

XELJANZ treatment of rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis patients should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of these respective conditions.

XELJANZ should be avoided in combination with biologics and potent immunosuppressants because of the possibility of increased immunosuppression and increased risk of infection.

XELJANZ dose should be reduced by half in patients receiving potent inhibitors of cytochrome (CYP) P450 3A4 (e.g., ketoconazole) and 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) as follows:

- XELJANZ dose should be reduced to 5 mg once daily in patients receiving 5 mg twice daily.
- XELJANZ dose should be reduced to 5 mg twice daily in patients with UC receving 10 mg twice daily.

Considerations for administration

Contraindications

- Must not administer XELJANZ in patients with:
  - Hypersensitivity to the active substance(s) or to any of the excipients listed in Summary of Product Characteristics (SmPC)
  - Active tuberculosis (TB) or other severe infections such as sepsis or opportunistic infections
  - Severe hepatic impairment
  - Pregnancy and lactation

Prior to administering XELJANZ

- Discuss the risks with patients using the **patient alert card** and **XELJANZ treatment initiation checklist** (see enclosed checklist for more details).
- Consider the risk and benefits of XELJANZ treatment carefully in patients who are at higher risk of developing serious infections including patients:
  - with recurrent infections,
  - who have been exposed to TB,
  - with a history of a serious or an opportunistic infection,
  - who have resided or travelled in areas of endemic TB or endemic mycoses,
  - who have underlying conditions that may predispose them to infection, such as diabetes mellitus.
- Evaluate and test the patient for latent or active TB infection. Patients with latent TB should be treated with standard antimycobacterial therapy before administering XELJANZ.
- All patients should be brought up to date with all immunisations in agreement with current immunisation guidelines. Viral reactivation and cases of herpes virus reactivation (e.g., herpes zoster) were observed in clinical studies with XELJANZ. The risk of herpes zoster appears to be higher in Japanese and Korean patients treated with XELJANZ.

- Screening for viral hepatitis should be performed in accordance with clinical guidelines.
- Consider the risks and benefits of XELJANZ treatment prior to initiating therapy in patients with current or a history of malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ in patients who develop a malignancy
- Check patients' laboratory parameters including lymphocytes, neutrophils, haemoglobin, lipids, and hepatic enzymes. Initiating treatment is not recommended in patients with:
  - Low absolute lymphocyte count (<750 cells/mm^3)
  - Low absolute neutrophil count (<1000 cells/mm^3)
  - Low haemoglobin (<9 g/dL)

Patients treated with XELJANZ should be given a patient alert card. An adequate supply will be provided to prescribers for distribution to patients (through Pfizer local country office distribution channels). Additional copies can be downloaded via the prescriber website (see section Risk Communication for more details). **Patients should be advised to keep this card with them for at least 2 months after taking the last dose of XELJANZ.**

Monitoring of laboratory parameters:

Laboratory parameters	Routine Monitoring	Laboratory value	Recommended Actions
Lymphocytes (ALC)	At baseline, then every 3 months	Greater than or equal to 750 cells/mm^3	Dose should be maintained
		Between 500 and 750 cells/mm^3 (confirmed by repeat testing	Dosing should be reduced or interrupted until lymphocyte count is greater than 750 cells/mm^3 For patients receiving XELJANZ 5 mg twice daily, dosing should be interrupted. For patients with UC receiving XELJANZ 10 mg twice daily, dosing should be reduced to XELJANZ 5 mg twice daily. When ALC is greater than 750, resume treatment as clinically appropriate.
		Less than 500 cells/mm^3 (confirmed by repeat testing)	Dosing should be discontinued.

Laboratory parameters	Routine Monitoring	Laboratory value	Recommended Actions
Neutrophils (ANC)	At baseline, after 4 to 8 weeks of treatment, and then every 3 months	ANC greater than 1000 cells/mm^3	Dose should be maintained
		ANC 500–1000 cells/mm^3	For persistent decreases in this range, reduce or interrupt dosing until ANC is greater than 1000 cells/mm^3. For patients receiving XELJANZ 5 mg twice daily, dosing should be interrupted. For patients with UC receiving XELJANZ 10 mg twice daily, dosing should be reduced to XELJANZ 5 mg twice daily. When ANC is greater than 1000 cells/mm^3 resume treatment as clinically appropriate.
		ANC less than 500 cells/mm^3	Dosing should be discontinued
Haemoglobin	At baseline, after 4 to 8 weeks of treatment, and then every 3 months	Less than or equal to 2 g/dL decrease and greater than or equal to 9.0 g/dL	Dose should be maintained
		Greater than 2 g/dL decrease or less than 8.0 g/dL (confirmed by repeat testing)	Interrupt dosing until haemoglobin values have normalised
Lipids	After 8 weeks following initiation of therapy	NA	Managed according to clinical guidelines for the management of hyperlipidaemia
Liver enzymes	Routine monitoring	NA	Following initiation, routine monitoring of liver tests and prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury

ALC=absolute lymphocyte count; ANC=absolute neutrophil count; NA=not applicable

Special warnings and precautions for use

Combination with other therapies

XELJANZ has not been studied and its use should be avoided in patients in combination with biologics such as TNF antagonists, IL-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies, IL17 antagonists, IL12/IL23 antagonists, anti-integrins, and selective co-stimulation modulators and potent immunosuppressants such as azathioprine, 6-mercaptopurine, cyclosporine and tacrolimus because of the possibility of increased immunosuppression and increased risk of infection.

There is a higher incidence of adverse events for the combination of XELJANZ plus MTX versus XELJANZ as monotherapy in RA clinical trials.

Serious infections

The most common serious infections reported with XELJANZ were pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Among opportunistic infections, TB and other mycobacterial infections, cryptococcus, histoplasmosis, oesophageal candidiasis, multidermatomal herpes zoster, cytomegalovirus, BK virus infections and listeriosis were reported with XELJANZ. Some patients have presented with disseminated rather than localised disease, and patients were often taking concomitant immunomodulating agents such as MTX or corticosteroids which, in addition to rheumatoid arthritis or psoriatic arthritis, may predispose them to infections. Other serious infections that were not reported in clinical studies may also occur (e.g., coccidioidomycosis). The risk of opportunistic infections is higher in Asian geographic regions.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ. Treatment must be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with XELJANZ should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

Caution is recommended when XELJANZ treatment is used in the following patients:

- Elderly and diabetic patients given there is a higher incidence of infections in general
- Patients with a history of chronic lung disease as they may be more prone to infections.
- Patients with lymphopenia

Tuberculosis

The risks and benefits of treatment should be considered prior to initiating XELJANZ in patients:

- who have been exposed to TB
- who have resided or travelled in areas of endemic TB or endemic mycoses

Patients should be evaluated and tested for latent or active infection prior to and per applicable guidelines during administration of XELJANZ.

Viral reactivation

Viral reactivation and cases of herpes virus reactivation (e.g., herpes zoster) were observed in clinical studies with XELJANZ. In patients treated with XELJANZ, the incidence of herpes zoster appears to be increased in:

- Japanese and Korean patients.
- Patients with an absolute lymphocyte count (ALC) less than 1000 cells/mm.^{3}
- Patients with long standing RA who have previously received two or more biologic DMARDs.
- Patients with UC treated with 10 mg twice daily.

Malignancies and lymphoproliferative disorder [Excluding Non-melanoma Skin Cancer (NMSC)]

The risks and benefits of XELJANZ treatment should be considered prior to initiating therapy in patients with current or a history of malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ in patients who develop a malignancy. The possibility exists for XELJANZ to affect host defences against malignancies.

Lymphomas have been observed in patients treated with XELJANZ. Patients with RA, particularly those with highly active disease may be at a higher risk (up to several-fold) than the general population for the development of lymphoma. The role of XELJANZ in the development of lymphoma is uncertain.

Other malignancies were observed in clinical studies and the post-marketing setting, including, but not limited to, lung cancer, breast cancer, melanoma, prostate cancer, and pancreatic cancer.

The effect of XELJANZ on the development and course of malignancies is not known.

Non-melanoma skin cancer

Non-melanoma skin cancers (NMSCs) have been reported in patients treated with XELJANZ. The risk of NMSC may be higher in patients treated with XELJANZ 10 mg twice daily than in patients treated with 5 mg twice daily. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Interstitial Lung Disease

Events of interstitial lung disease (some of which had a fatal outcome) have been reported in patients treated with XELJANZ in RA clinical trials and in the post-marketing setting although the role of Janus kinase (JAK) inhibition in these events is not known. Asian RA patients are known to be at higher risk of interstitial lung disease, thus caution should be exercised in treating these patients.

Gastrointestinal perforations

Events of gastrointestinal perforation have been reported in clinical trials although the role of Janus- kinase inhibition in these events is not known.

XELJANZ should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis and patients with concomitant use of corticosteroids and/or nonsteroidal anti-inflammatory medicinal products). Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Vaccination

- Prior to initiating XELJANZ it is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines.
- It is recommended that live vaccines not be given concurrently with XELJANZ. The decision to use live vaccines prior to XELJANZ treatment should take into account the pre-existing immunosuppression in a given patient.
- Prophylactic zoster vaccination should be considered in accordance with vaccination guidelines. Particular consideration should be given to patients with longstanding rheumatoid arthritis who have received two or more prior biological DMARDs. If live zoster vaccine is administered; it should only be administered to patients with a known history of chickenpox or those that are seropositive for varicella zoster virus (VZV). If the history of chickenpox is considered doubtful or unreliable it is recommended to test for antibodies against VZV.
- Vaccination with live vaccines should occur at least 2 weeks but preferably 4 weeks prior to initiation of XELJANZ or in accordance with current vaccination guidelines regarding immunomodulatory medicinal products.

Use in Special Populations

Patients with renal impairment

- No dose adjustment is required in patients with mild (creatinine clearance 50-80 mL/min) or moderate renal impairment (creatinine clearance 30-49 mL/min).
- Severe renal impairment (creatinine clearance <30 mL/min): Dose should be reduced to 5 mg once daily when the indicated dose in the presence of normal renal function is 5 mg twice daily. Dose should be reduced to 5 mg twice daily when the indicated dose in the presence of normal renal function is 10 mg twice daily in patients with UC. Patients with severe renal impairment should remain on a reduced dose even after haemodialysis.

Patients with hepatic impairment

- No dose adjustment is required in patients with mild hepatic impairment (Child Pugh A).
- Moderate hepatic impairment (Child Pugh B): Dose should be reduced to 5 mg once daily when the indicated dose in the presence of normal hepatic function is 5 mg twice daily. Dose should be reduced to 5 mg twice daily when the indicated dose in the presence of normal hepatic function is 10 mg twice daily in patients with UC.
- XELJANZ should not be used in patients with severe hepatic impairment (Child Pugh C).

Pediatric patients

The safety and efficacy of XELJANZ in children aged from 0 to less than 18 years of age have not yet been established. No data are available.

Pregnancy and lactation

- Use of XELJANZ during pregnancy is contraindicated.
- Use of XELJANZ during breastfeeding is contraindicated.

Women of childbearing potential

- Women of childbearing potential should be advised to use effective contraception during treatment with XELJANZ and for at least 4 weeks after the last dose.

FOR MORE DETAILS ON PRESCRIBING XELJANZ, PLEASE REFER TO THE SUMMARY OF PRODUCT CHARACTERISTICS.

Patient Counseling

It is important for you to discuss the risks associated with use of XELJANZ with your patients, and in applicable instances, with their caregivers.

A patient alert card has been developed to help patients understand the risks associated with XELJANZ, and remind them to seek immediate medical attention if they experience any listed signs and symptoms.

It is important for physicians to:

- provide the patient alert card to each patient who is prescribed with XELJANZ.
- remind patients to use the patient alert card.
- discuss the risks with each patient and ensure patient understanding of the treatment potential risks.
- ensure patients to carry the patient alert card with them, particularly when they visit doctors' office and/or the emergency room.

You should remind patients to seek immediate medical attention if they experience any of the following signs and symptoms.

- Experience possible symptoms of allergic reactions such as chest tightness, wheezing, severe dizziness or lightheadedness, swelling of the lips, tongue or throat, itching or skin rash when taking XELJANZ, or soon after taking XELJANZ.
- Develop symptoms of an infection, such as fever, persistent cough, weight loss, or excessive tiredness.
- Develop symptoms of herpes zoster, such as painful rash or blisters.
- Have been in close contact with a person with TB.
- Notice any new growth on the skin or any changes in existing moles or spots.
- Develop symptoms of interstitial lung diseases, such as shortness of breath
- Develop abdominal signs and symptoms such as stomach pain, abdominal pain, blood in stool, or any change in bowel habits with fever.
- Develop yellow skin, nausea, or vomiting.

- Are due to receive any vaccine. Patients should not receive certain types of vaccines while taking XELJANZ.
- Become pregnant or plan on becoming pregnant.

To order more copies of the patient alert card, please call Pfizer's Local Representative, Vivian Corporation Ltd.: 00356 22588600 or visit the website: **www.tofacitinib-rmp.com.mt**

Reporting of Adverse Events

If you become aware of any suspected adverse reactions in association with use of XELJANZ, please report the event promptly to

ADR Reporting

www.medicinesauthority.gov.mt/adrportal

Malta Medicines Authority
Sir Temi Żammit Buildings,
Malta Life Sciences Park,
San Ġwann,
SĠN 3000,
Malta Website: www.medicinesauthority.gov.mt/adrportal
e-mail: postlicensing.medicinesauthority@gov.mt

Also, please contact Pfizer Hellas S.A. Medical Information at +30 210 67 85 800.

Local Representative: Vivian Corporation Ltd.: Tel. +00356 22588600.

Risk Management Plan (RMP)

A risk management system, described in the risk management plan (RMP), is a set of pharmacovigilance activities and interventions required by the European Medicine Agency (EMA) to ensure that the benefits of the medicinal product outweigh its risks.

The XELJANZ RMP is developed:

- to identify, characterise, prevent or minimise risks relating to XELJANZ including the assessment of the effectiveness of those activities and interventions.

Risk Communication

In order to communicate certain risks about XELJANZ, Pfizer has worked with the EMA to develop a detailed communication plan to communicate the risks described in the summary of product characteristics, including the following items:

- patient alert card
- prescriber brochure
- prescriber treatment initiation checklist
- prescriber treatment maintenance checklist

Two treatment checklists: initiation checklist and maintenance checklists, are developed for you to be used prior to and during XELJANZ treatment. They intend to remind you of the risks associated with use of XELJANZ and the recommended tests before and during the XELJANZ treatment.

Prescriber website

All the educational materials including patient alert card and treatment initiation/maintenance checklist are available at www.tofacitinib-rmp.com.mt .
Please visit this website for more details.

Ongoing Risk Assessment

In order to continue to characterise the risks relating to XELJANZ in treatment of RA, Pfizer has committed to participate in 4 established European RA registries including one in UK (i.e., BSRBR), one in Germany (i.e., RABBIT), one in Sweden (i.e., ARTIS), and one in Spain (i.e., BIOBADASER).

The purpose of the registry surveillance studies is to collect additional longitudinal safety data from the clinical practice setting regarding the use of XELJANZ in patients with rheumatoid arthritis.

Physicians from those countries can register their patients treated with XELJANZ by contacting the registries via the following contact information:

- BSRBR: http://www.rheumatology.org.uk/resources/bsr_biologics_registers/bsrbr_rheumatoid_arthritis_register/default.aspx.

- RABBIT – Rheumatoide Arthritis: Beobachtung der Biologika-Therapie:
  The internet address is http://www.biologika-register.de; contact form available at http://www.biologika-register.de/index.php?page=kontakt&lang=de, and
  information can be retrieved/requested via Info@biologika-register.de.

- ARTIS
  Johan.Askling@ki.se
  Clinical Epidemiology Unit and Rheumatology Unit
  Dept of Medicine
  Karolinska Institute

- BIOBADASER: https://biobadaser.ser.es/biobadaser/eng/

In order to continue to characterize the risks relating to XELJANZ in treatment of UC, a prospective, non-interventional comparative safety study using 1 or more European UC registries is proposed (options being considered include Spanish ENEIDA Inflammatory Bowel Disease Registry, Swedish National Quality Registry for Inflammatory Bowel Disease [SWIGREG], and the United Kingdom Inflammatory Bowel Disease Registry).

Please contact Pfizer medical information at +30 210 6785800,
Local Representative: Vivian Corporation Ltd., +00356 21344610.

Pfizer

XELJANZ®
(tofacitinib citrate)