TOFAXEL® (TOFACITINIB) F. C. TABLET AND TOFAXEL® ER (TOFACITINIB) EXTENDED RELEASE TABLET

TOFAXEL® and TOFAXEL® ER
TOFACITINIB

Tofaxel® and Tofaxel® ER F. C. Tablets for Oral Use
Read this patient information carefully before you start taking Tofaxel® and Tofaxel® ER because it answers some common questions about Tofaxel® and Tofaxel® ER. This medication is prescribed for your current condition, therefore do not use it in similar cases and do not recommend it to others.
To report SUSPECTED ADVERSE REACTIONS, contact Noavaran Daroui Kimia Co. at +982166433514 or send email to medical@kimia-pharma.co
Read this patient information carefully before you start taking Tofaxel® and Tofaxel® ER because it contains important information for you. This leaflet does not take the place of talking with your healthcare provider about your medical condition or treatment.

Composition
Each film coated tablet Tofaxel® 5 mg contains: Tofacitinib (as citrate) 5 mg.
Each film coated tablet Tofaxel® 10 mg contains: Tofacitinib (as citrate) 10 mg.
Each film coated tablet Tofaxel® ER 11 mg contains: Tofacitinib (as citrate) 11 mg.

Mechanism of action
Tofacitinib is a Janus kinase (JAK) inhibitor.

Pharmacokinetic
Absorption
The absolute oral bioavailability of Tofaxel® is 74%. Tofaxel® half-life is about 3 hours and Tofaxel® ER half-life is about 6 to 8 hours.
Distribution
The protein binding of tofacitinib is approximately 40%.
Metabolism and Excretion
The metabolism of tofacitinib is primarily mediated by CYP3A4. Clearance mechanisms for tofacitinib are approximately 70% hepatic metabolism and 30% renal excretion of the parent drug.

Indication
Tofaxel®/ Tofaxel® ER are indicated for:
- Rheumatoid Arthritis: 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*.
- Psoriatic Arthritis: the treatment of adult patients with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers*.
- Ankylosing Spondylitis: the treatment of adult patients with active ankylosing spondylitis who have had an inadequate response or intolerance to one or more TNF blockers*.
- Ulcerative Colitis: the treatment of adult patients with moderately to severely active ulcerative colitis (UC), who have had an inadequate response or intolerance to one or more TNF blockers**.
- Polyarticular Course Juvenile Idiopathic Arthritis: Tofaxel® is indicated for the treatment of active polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older who have had an inadequate response or intolerance to one or more TNF blockers*.

* Limitations of Use: Use of Tofaxel®/ Tofaxel® ER in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.
** Limitations of Use: Use of Tofaxel®/ Tofaxel® ER in combination with biological therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

It is not known if Tofaxel® ER is safe and effective in children.

Dosage and administration
Administration Instructions
- Changes between Tofaxel® and Tofaxel® ER should be made by the healthcare provider.
- Do not initiate Tofaxel®/ Tofaxel® ER if absolute lymphocyte count <500 cells/mm³, an absolute neutrophil count (ANC) <1000 cells/mm³ or hemoglobin <9 g/dL.

Recommended Dosage
Rheumatoid Arthritis
- Tofaxel® 5 mg twice daily or Tofaxel® ER 11 mg once daily with or without food.
- Recommended dosage in patients with moderate and severe renal impairment or moderate hepatic impairment is Tofaxel® 5 mg once daily.

Psoriatic Arthritis (in combination with nonbiologic DMARDs)
- Tofaxel® 5 mg twice daily or Tofaxel® ER 11 mg once daily with or without food.
- Recommended dosage in patients with moderate and severe renal impairment or moderate hepatic impairment is Tofaxel® 5 mg once daily.

Ankylosing Spondylitis
- Tofaxel® 5 mg twice daily or Tofaxel® ER 11 mg once daily with or without food.
- Recommended dosage in patients with moderate and severe renal impairment or moderate hepatic impairment is Tofaxel® 5 mg once daily.

Ulcerative Colitis
- Induction: Tofaxel® 10 mg twice daily for 8 weeks; evaluate patients and transition to maintenance therapy depending on therapeutic response. If needed, continue Tofaxel® 10 mg twice daily for a maximum of 16 weeks. Discontinue Tofaxel® 10 mg twice daily after 16 weeks if adequate therapeutic response is not achieved.
- Maintenance: Tofaxel® 5 mg twice daily or Tofaxel® ER 11 mg once daily. For patients with loss of response during maintenance treatment, Tofaxel® 10 mg twice daily may be considered and limited to the shortest duration, with careful consideration of the benefits and risks for the individual patient. Use the lowest effective dose needed to maintain response.
- Dosage adjustment is needed in patients with moderate and severe renal impairment or moderate hepatic impairment.

Polyarticular Course Juvenile Idiopathic Arthritis
- Tofaxel® 5 mg twice daily or weight-based equivalent twice daily with or without food.
- Dosage adjustment is needed in patients with moderate and severe renal impairment or moderate hepatic impairment.

Dosage Adjustment
- Use of Tofaxel®/ Tofaxel® ER in patients with severe hepatic impairment is not recommended in any patient population.

Side effects / Adverse reactions
It should be noted that these side effects do not occur in all patients. These are not all the possible side effects of Tofaxel® and Tofaxel® ER. For more information, ask your healthcare provider or pharmacist.

Tofaxel® and Tofaxel® ER may cause serious side effects including:
- **Serious infections.** Some people can have serious infections while taking Tofaxel® and Tofaxel® ER, including tuberculosis (TB). These infections can be life threatening.
  - Your healthcare provider should test you for TB before starting Tofaxel® and Tofaxel® ER and during treatment. You should not start taking Tofaxel® and Tofaxel® ER if you have any kind of infection unless your healthcare provider tells you it is okay. You may be at a higher risk of developing shingles (herpes zoster).

  People with ulcerative colitis taking the higher dose of Tofaxel® (10 mg twice daily) have a higher risk of serious infections and shingles.

  Before starting Tofaxel® and Tofaxel® ER, tell your healthcare provider if you:
  - think you have an infection or have symptoms of an infection such as: fever, sweating, or chills, muscle aches, cough, shortness of breath, blood in phlegm, weight loss, warm, red, or painful skin or sores on your body, diarrhea or stomach pain, burning when you urinate or urinating more often than normal, and feeling very tired.
  - have diabetes, chronic lung disease, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
  - get a lot of infections or have infections that keep coming back.
  - are being treated for an infection.
  - have TB, or have been in close contact with someone with TB.
  - have or have had hepatitis B or C.

- **Increased risk of death in people 50 years of age and older who have at least 1 heart disease (cardiovascular) risk factor and are taking Tofaxel® 5 mg twice daily or Tofaxel® 10 mg twice daily.**
- **Cancer and immune system problems.**
  - lymphoma and other cancers including lung and skin cancers can happen in patients taking Tofaxel® and Tofaxel® ER. Tell your healthcare provider if you have ever had any type of cancer.
  - Some people who have taken Tofaxel® with certain other medicines to prevent kidney transplant rejection have had Epstein Barr Virus-associated post-transplant lymphoproliferative disorder.
- **Increased risk of major cardiovascular events such as heart attack, stroke or death in people 50 years of age and older who have at least 1 heart disease (cardiovascular) risk factor and are taking Tofaxel® 5 mg twice daily or Tofaxel® 10 mg twice daily, especially if you are a current or past smoker.**
  Get emergency help right away if you have any symptoms of a heart attack or stroke while taking Tofaxel®, including:
  - shortness of breath with or without chest discomfort
  - breaking out in a cold sweat
  - nausea or vomiting
  - feeling lightheaded
  - weakness in one part or on one side of your body
  - slurred speech
  - discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
  - severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw
  - pain or discomfort in your arms, back, neck, jaw, or stomach
- **Blood clots in the lungs, veins of the legs or arms, and arteries.** Stop taking Tofaxel® and Tofaxel® ER and tell your healthcare provider right away if you develop signs and symptoms of a blood clot, such as sudden shortness of breath or difficulty breathing, chest pain, swelling of the leg or arm, leg pain or tenderness, or redness or discoloration in the leg or arm. These blood clots can be life threatening.
- **Tears (perforation) in the stomach or intestines.**
  This happens most often in people who also take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.

  Tell your healthcare provider right away if you have fever and stomach-area pain that does not go away, and a change in your bowel habits.
- **Allergic reactions.**
  Symptoms including swelling of your lips, tongue, or throat, or hives (raised, red patches of skin that are often very itchy). If any of these symptoms occur, stop Tofaxel® and Tofaxel® ER and call your healthcare provider right away.
- **Changes in certain laboratory test results.** Your healthcare provider should do blood and liver tests before and while you take Tofaxel® and Tofaxel® ER to check for the following side effects:
  - changes in lymphocyte counts.
  - low neutrophil counts.
  - low red blood cell count.

  Your healthcare provider should do blood tests to check your cholesterol levels 4 to 8 weeks after you start taking Tofaxel® and Tofaxel® ER, and as needed after that.
- **Hepatitis B or C activation infection.** If you are a carrier of the hepatitis B or C virus, the virus may become active while you use Tofaxel® and Tofaxel® ER. Tell your healthcare provider if you have any of the following symptoms of a possible hepatitis B or C infection:
  - Feel very tired
  - skin or eyes look yellow
  - little or no appetite
  - dark urine
  - vomiting
  - clay-colored bowel movements
  - fevers
  - skin rash
  - chills
  - stomach discomfort
  - muscle aches

Call your healthcare provider right away if you have aforementioned symptoms.

Common side effects
Common side effects of Tofaxel® and Tofaxel® ER in people with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis include:
- Upper respiratory tract infections (common cold, sinus infections)
- Nasal congestion, sore throat and runny nose (nasopharyngitis)
- High blood pressure (hypertension)
- Headache
- Diarrhea

Common side effects of Tofaxel® and Tofaxel® ER in patients with ulcerative colitis include:
- Nasal congestion, sore throat and runny nose (nasopharyngitis)
- Increased cholesterol levels
- Upper respiratory tract infections (common cold, sinus infections)
- Increased muscle enzyme levels
- Headache
- Shingles (herpes zoster)
- Rash
- Diarrhea

Common side effects of Tofaxel® in people with polyarticular course juvenile arthritis include:
- Upper respiratory tract infections (common cold, sinus infections)
- Nasal congestion, sore throat, and runny nose (nasopharyngitis)
- Nausea
- Headache
- Fever
- Vomiting

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

Drug interaction
- **Strong CYP3A4 Inhibitors (e.g., ketoconazole)**
  - Increased exposure to tofacitinib.
  - Dosage adjustment of Tofaxel® and Tofaxel® ER is recommended.
- **Moderate CYP3A4 Inhibitors Coadministered with Strong CYP2C19 Inhibitors (e.g., fluconazole)**
  - Increased exposure to tofacitinib.
  - Dosage adjustment of Tofaxel® and Tofaxel® ER is recommended.
- **Strong CYP3A4 Inducers (e.g., rifampin)**
  - Decreased exposure to tofacitinib and may result in loss of or reduced clinical response.
  - Coadministration with Tofaxel® and Tofaxel® ER is not recommended.
- **Immunosuppressive Drugs (e.g., azathioprine, tacrolimus, cyclosporine)**
  - Risk of added immunosuppression; coadministration with biologic DMARDs or potent immunosuppressants has not been studied in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, UC, or pcJIA.
  - Coadministration with Tofaxel® and Tofaxel® ER is not recommended.

Warnings
Before you take Tofaxel® and Tofaxel® ER, tell your healthcare provider about all of your medical conditions, including if you:
- have an infection.
- have had a heart attack, other heart problems or stroke.
- plan to become pregnant or are pregnant.
- plan to breastfeed or are breastfeeding.
- have had blood clots in the veins of your legs, arms, or lungs, or clots in the arteries in the past.
- have had a reaction to tofacitinib or any of the ingredients in Tofaxel® and Tofaxel® ER.
- have any stomach area (abdominal) pain or been diagnosed with diverticulitis or ulcers in your stomach or intestines.
- have recently received or are scheduled to receive a vaccine. People who take Tofaxel® and Tofaxel® ER should not receive live vaccines.
- are a current or past smoker.
- have had any type of cancer.
- have liver problems.
- have kidney problems.

Tell your healthcare provider about all the medicines you take, including prescription medicines and over-the-counter medicines, vitamins, and herbal supplements. Tofaxel® and Tofaxel® ER and other medicines may affect each other causing side effects.

Especially tell your healthcare provider if you take:
- any other medicines to treat your rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis or polyarticular course juvenile arthritis. You should not take tocilizumab, etanercept, adalimumab, infliximab, rituximab, abatacept, anakinra, certolizumab, golimumab, ustekinumab, secukinumab, vedolizumab, ixekizumab, azathioprine, cyclosporine, or other immunosuppressive drugs while you are taking Tofaxel® and Tofaxel® ER. Taking Tofaxel® and Tofaxel® ER with these medicines may increase your risk of infection.
- medicines that affect the way certain liver enzymes work.

Missed dose
If a dose of Tofaxel® and Tofaxel® ER is missed, do not make up the missed dose and take the next dose as scheduled.

Overdose
If you take too much Tofaxel® or Tofaxel® ER, call your healthcare provider or go to the nearest hospital emergency room right away.

Pregnancy and lactation
Tofaxel® and Tofaxel® ER must not be used during pregnancy. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking Tofaxel® and Tofaxel® ER. Tell your doctor right away if you become pregnant while taking Tofaxel® and Tofaxel® ER.

If you are a woman of childbearing age, you should use effective birth control during treatment with Tofaxel® and Tofaxel® ER and for at least 4 weeks after the last dose.
Based on animal studies, Tofaxel® and Tofaxel® ER may impair fertility in females of reproduction potential. It is not known if this effect is reversible.
It is not known whether Tofaxel® and Tofaxel® ER is secreted in human milk. If you are taking Tofaxel® and Tofaxel® ER and breast-feeding, you must stop breast-feeding until you talk to your doctor about stopping treatment with Tofaxel® and Tofaxel® ER. Breastfeeding is not recommended during treatment and for at least 18 hours after the last dose of Tofaxel® and 36 hours after the last dose of Tofaxel® ER.

Patient information
- Try to take Tofaxel® and Tofaxel® ER at the same time every day.
- Swallow Tofaxel® ER tablets whole and intact. Do not crush, split, or chew.
- Tofaxel® contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
- For the treatment of psoriatic arthritis, take Tofaxel® and Tofaxel® ER in combination with methotrexate, sulfasalazine or leflunomide as instructed by your healthcare provider.
- Tofaxel® ER should not be used instead of Tofacitinib Oral Solution.
- When you take Tofaxel® ER, you may see something in your stool that looks like a tablet. This is the empty shell from the tablet after the medicine has been absorbed by your body.
- Tofaxel® ER tablets contain sorbitol. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

Storage
- Keep away from light and moisture. Store below 30°C.
- Store in the original package.
- Keep out of the reach of children.
- Keep the desiccant in the bottle. Do not eat or throw away desiccant pack.
- Safely throw away medicine that is out of date or that you no longer need.

Packaging
Bottle of 30 F. C. Tablets.

Last revision date: August 2022.

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BNF 83 (British National Formulary) March 2022