For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory only

Tofacitinib Ointment 2% w/w
Tofadoz®
Ointment

1. GENERIC NAME
Tofacitinib Ointment 2% w/w

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each gm Contains:
Tofacitinib Citrate IP
Eq. to Tofacitinib 20 mg
In an Ointment Base q.s.

3. DOSAGE FORM AND STRENGTH
Ointment, 20mg/gm

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Mild to moderate atopic dermatitis (AD)

4.2 Posology and method of administration
Posology
Twice a day apply to affected area in a dose and duration as directed by the Physician
Method of administration: For external use only.

4.3 CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients
- Active tuberculosis (TB), serious infections such as sepsis, or opportunistic infections.
- Severe hepatic impairment.
- Pregnancy and lactation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Serious Infections
Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving Tofacitinib 2 %. The most common serious infections reported with Tofacitinib 2 % included pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcosis, histoplasmosis, esophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus infections, BK virus infection, and listeriosis will aggravated with Tofacitinib 2 %. Some patients have presented with disseminated rather than localized disease and were often taking concomitant immunomodulating agents such as methotrexate or corticosteroids.

Avoid use of Tofacitinib 2 % in patients with an active, serious infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating Tofacitinib 2 % in patients:
- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Tofacitinib 2 %. It should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with Tofacitinib 2 % 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 also recommended in patients with a history of chronic lung disease, or in those who develop interstitial lung disease, as they may be more prone to infections. Risk of infection may be higher with increasing degrees of lymphopenia and consideration should be given to lymphocyte counts when assessing individual patient risk of infection. Discontinuation and monitoring criteria for lymphopenia are recommended

Tuberculosis
Patients should be evaluated and tested for latent or active infection prior to and per applicable guidelines during administration of Tofacitinib 2 %. Anti-tuberculosis therapy should also be considered prior to administration of Tofacitinib 2 % in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but who have risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision about whether initiating anti-tuberculosis therapy is appropriate for an individual patient. Patients should be closely monitored for the development of signs and symptoms of tuberculosis, including patients who tested negative for latent tuberculosis infection prior to initiating therapy. Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before administering Tofacitinib 2 %.

Viral Reactivation
Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical trials with Janus kinase inhibitors used to treat inflammatory conditions including Tofacitinib 2 % w/w. If a patient develops herpes zoster, consider interrupting Tofacitinib 2 % w/w treatment until the episode resolves.

Hepatitis B and C
Patients who screened positive for hepatitis B or C were excluded from clinical trials. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with Tofacitinib 2 %. The risk of herpes zoster is increased in patients treated with Tofacitinib 2%

Hypersensitivity
Reactions such as angioedema and urticaria that may reflect drug hypersensitivity have been observed in patients receiving Tofacitinib 2 %. Some events were serious. If a serious hypersensitivity reaction occurs, promptly discontinue tofacitinib while evaluating the potential cause or causes of the reaction

Lymphocyte Abnormalities
Lymphocyte counts less than 500 cells/mm3 were associated with an increased incidence of treated and serious infections.
Avoid initiation of Tofacitinib 2 % treatment in patients with a low lymphocyte count (i.e., less than 500 cells/mm3). In patients who develop a confirmed absolute lymphocyte count less than 500 cells/mm3, treatment with Tofacitinib 2 % is not recommended.
Monitor lymphocyte counts at baseline and every 3 months thereafter. For recommended modifications based on lymphocyte counts.

Neutropenia
Avoid initiation of Tofacitinib 2 % treatment in patients with a low neutrophil count (i.e., ANC less than 1000 cells/mm3). For patients who develop a persistent ANC of 500 to 1000 cells/mm3, interrupt Tofacitinib 2 % dosing until ANC is greater than or equal to 1000 cells/mm3. In patients who develop an ANC less than 500 cells/mm3, treatment with Tofacitinib 2 % is not recommended.

Monitor neutrophil counts at baseline and after 4–8 weeks of treatment and every 3 months thereafter. For recommended modifications based on ANC results.

Anemia
Avoid initiation of Tofacitinib 2 % treatment in patients with a low hemoglobin level (i.e., less than 9 g/dL). Treatment with Tofacitinib 2 % should be interrupted in patients who develop hemoglobin levels less than 8 g/dL or whose hemoglobin level drops greater than 2 g/dL on treatment.
Monitor hemoglobin at baseline and after 4–8 weeks of treatment and every 3 months thereafter. For recommended modifications based on hemoglobin results.

Liver Enzyme Elevations
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. If drug-induced liver injury is suspected, the administration of Tofacitinib 2 % should be interrupted until this diagnosis has been excluded.

Lipid Elevations
There were no clinically relevant changes in LDL/HDL cholesterol ratios. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Assessment of lipid parameters should be performed approximately 4–8 weeks following initiation of Tofacitinib 2 %. Manage patients according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP)] for the management of hyperlipidemia.

Mortality
A higher rate of all-cause mortality, including sudden cardiovascular death was observed in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Tofacitinib 2 % w/w.

Malignancy and Lymphoproliferative Disorders
Malignancies, including lymphomas, were observed in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Tofacitinib 2 % w/w, particularly in patients with a known malignancy (other than successfully treated non-melanoma skin cancers), patients who develop a malignancy, and patients who are current or past smokers.

4.5 DRUG INTERACTIONS
Potential for other medicinal products to influence the pharmacokinetics (PK) of tofacitinib
Since tofacitinib is metabolised by CYP3A4, interaction with medicinal products that inhibit or induce CYP3A4 is likely. Tofacitinib exposure is increased when coadministered with potent inhibitors of CYP3A4 (e.g., ketoconazole) or when administration of one or more concomitant medicinal products results in both moderate inhibitions of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole). Tofacitinib exposure is decreased when coadministered with potent CYP inducers (e.g., rifampicin). Inhibitors of CYP2C19 alone or P-glycoprotein are unlikely to significantly alter the PK of tofacitinib. Coadministration with ketoconazole (strong CYP3A4 inhibitor), fluconazole (moderate CYP3A4 and potent CYP2C19 inhibitor), tacrolimus (mild CYP3A4 inhibitor) and ciclosporin (moderate CYP3A4 inhibitor) increased tofacitinib AUC, while rifampicin (potent CYP inducer) decreased tofacitinib AUC. Coadministration of tofacitinib with potent CYP inducers (e.g., rifampicin) may result in a loss of or reduced clinical response. Coadministration of potent inducers of CYP3A4 with tofacitinib is not recommended. Coadministration with ketoconazole and fluconazole increased tofacitinib Cmax, while tacrolimus, cyclosporine and rifampicin decreased tofacitinib Cmax. Concomitant administration with MTX 15-25 mg once weekly had no effect on the PK of tofacitinib in RA patients

Potential for tofacitinib to influence the PK of other medicinal products
Coadministration of tofacitinib did not have an effect on the PK of oral contraceptives, levonorgestrel and ethinyl estradiol, in healthy female volunteers. In RA patients, coadministration of tofacitinib with MTX 15-25 mg once weekly decreased the AUC and Cmax of MTX by 10% and 13%, respectively. The extent of decrease in MTX exposure does not warrant modifications to the individualised dosing of MTX.

Paediatric population
Interaction studies have only been performed in adults.

4.6 USE IN SPECIFIC POPULATIONS
Pregnancy
There are no adequate and well-controlled studies on the use of tofacitinib in pregnant women. Tofacitinib has been shown to be teratogenic in rats and rabbits, and to affect parturition and peri/postnatal development as a precautionary measure, the use of tofacitinib during pregnancy is contraindicated

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

Breast-feeding It is not known whether tofacitinib is secreted in human milk. A risk to the breast-fed child cannot be excluded. Tofacitinib was secreted in the milk of lactating rats. As a precautionary measure, the use of tofacitinib during breast-feeding is contraindicated

Fertility Formal studies of the potential effect on human fertility have not been conducted. Tofacitinib impaired female fertility but not male fertility in rats.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Tofacitinib has no or negligible influence on the ability to drive and use machines.

4.8 UNDESIRABLE EFFECTS
The following clinically significant adverse reactions are described elsewhere in the labeling:
- Serious Infections
- Malignancy and Lymphoproliferative Disorders
- Gastrointestinal Perforations
- Laboratory Abnormalities

Other adverse reactions occurring in controlled and open-label extension studies included:
- Blood and lymphatic system disorders: Anemia
- Infections and infestations: Diverticulitis
- Metabolism and nutrition disorders: Dehydration
- Psychiatric disorders: Insomnia
- Nervous system disorders: Paresthesia
- Respiratory, thoracic and mediastinal disorders: Dyspnea, cough, sinus congestion, interstitial lung disease (cases were limited to patients with rheumatoid arthritis and some were fatal)
- Gastrointestinal disorders: Abdominal pain, dyspepsia, vomiting, gastritis, nausea
- Hepatobiliary disorders: Hepatic steatosis
- Skin and subcutaneous tissue disorders: Rash, erythema, pruritus
- Musculoskeletal, connective tissue and bone disorders: Musculoskeletal pain, arthralgia, tendonitis, joint swelling
- Neoplasms benign, malignant and unspecified (including cysts and polyps): Non-melanoma skin cancers
- General disorders and administration site conditions: Pyrexia, fatigue, peripheral edema

4.9 OVERDOSE
There is no specific antidote for overdose with tofacitinib. In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. In a study in subjects with end stage renal disease (ESRD) undergoing hemodialysis, plasma tofacitinib concentrations declined more rapidly during the period of hemodialysis and dialyzer efficiency, calculated as dialyzer clearance/blood flow entering the dialyzer, was high [mean (SD) = 0.73 (0.15)]. However, due to the significant non-renal clearance of tofacitinib, the fraction of total elimination occurring by hemodialysis was small, and thus limits the value of hemodialysis for treatment of overdose with tofacitinib.

5. PHARMACOLOGICAL PROPERTIES
5.1 Mechanism of action
Tofacitinib is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Tofacitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs. JAK enzymes transmit cytokine signaling through pairing of JAKs (e.g., JAK1/JAK3, JAK1/JAK2, JAK1/TyK2, JAK2/JAK2). Tofacitinib inhibited the *in vitro* activities of JAK1/JAK2, JAK1/JAK3, and JAK2/JAK2 combinations with IC50 of 406, 56, and 1377 nM, respectively. However, the relevance of specific JAK combinations to therapeutic effectiveness is not known.

5.2 Pharmacodynamic properties
The Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway is utilized by numerous cytokines and growth factors for signal transduction. Tofacitinib is a small-molecule JAK inhibitor. Tofacitinib has been shown to inhibit cytokines such as IL-4 directly and leads to rapid attenuation of JAK–STAT signaling in keratinocytes.

5.3 Pharmacokinetic properties
Tofacitinib ointment or vehicle was applied twice daily (BID) to all areas affected by AD, except areas of hair-bearing scalp, which was excluded as a treatment-eligible area due to the cosmetic unacceptability of an ointment for treating hair-bearing scalp. Local tolerability data for the ointment formulation on the groin and genitals was not available at the time this study was conducted; therefore, the presence of AD on the groin or genitals at baseline was exclusionary. However, patients were permitted to treat new AD lesions on the groin or genitals occurring post-Day 1 with study drug to avoid the need for a concomitant therapy for groin or genitals. In this study, the maximum observed concentration of 2.72 ng/ml, which was observed post-dosing at Week 2, has a margin of approximately 4.6-fold relative to the 10th percentile C_{av} (12.4 ng/mL) of 5 mg BID oral tofacitinib based on the observed concentrations in the Phase 3 clinical trials of patients with moderate-to-severe plaque psoriasis. Based on an exposure-response analysis of oral tofacitinib psoriasis data, C_{av} of 12.4 ng/mL was not associated with increased incidence rates of serious infections and herpes zoster infections when compared to patients treated with placebo (unpublished observations). Serious infections and herpes zoster infections were associated with tofacitinib treatment in Phase 3 studies of oral tofacitinib in patients with moderate to severe psoriasis. In the current study, 76% of tofacitinib levels measured in plasma from patients in the active treatment group were <1.0 ng/mL, which represents a >12-fold margin to the exposure levels for oral tofacitinib (10^{th} percentile C_{av}) with no increased incidence rates for serious and herpes zoster infections relative to placebo observed in the oral tofacitinib Phase 3 psoriasis program.

6. NONCLINICAL PROPERTIES
6.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 39-week toxicology study in monkeys, tofacitinib at exposure levels approximately 6 times the recommended dose of 5 mg twice daily, and approximately 3 times the 10 mg twice daily dose (on an AUC basis at oral doses of 5 mg/kg twice daily) produced lymphomas. No lymphomas were observed in this study at exposure levels 1 times the recommended dose of 5 mg twice daily, and approximately 0.5 times the 10 mg twice daily dose (on an AUC basis at oral doses of 1 mg/kg twice daily).

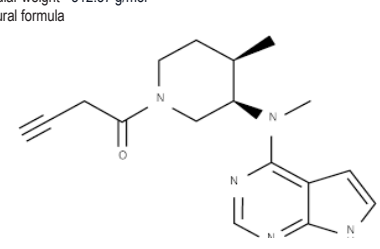
The carcinogenic potential of tofacitinib was assessed in 6-month rasH2 transgenic mouse carcinogenicity and 2-year rat carcinogenicity studies. Tofacitinib, at exposure a levels approximately 34 times the recommended dose of 5 mg twice daily, and approximately 17 times the 10 mg twice daily dose (on an AUC basis at oral doses of 200 mg/kg/day) was not carcinogenic in mice.

In the 24-month oral carcinogenicity study in Sprague-Dawley rats, tofacitinib caused benign Leydig cell tumors, hibernomas (malignancy of brown adipose tissue), and benign thymomas at doses greater than or equal to 30 mg/kg/day (approximately 42 times the exposure levels at the recommended dose of 5 mg twice daily, and approximately 21 times the 10 mg twice daily dose on an AUC basis). The relevance of benign Leydig cell tumors to human risk is not known.

Tofacitinib was not mutagenic in the bacterial reverse mutation assay. It was positive for clastogenicity in the in vitro chromosome aberration assay with human lymphocytes in the presence of metabolic enzymes, but negative in the absence of metabolic enzymes. Tofacitinib was negative in the in vivo rat micronucleus assay and in the in vitro CHOHGPRT assay and the in vivo rat hepatocyte unscheduled DNA synthesis assay.

In rats, tofacitinib at exposure levels approximately 17 times the recommended dose of 5 mg twice daily, and approximately 8.3 times the 10 mg twice daily dose (on an AUC basis at oral doses of 10 mg/kg/day) reduced female fertility due to increased postimplantation loss. There was no impairment of female rat fertility at exposure levels of tofacitinib equal to the recommended dose of 5 mg twice daily, and approximately 0.5 times the 10 mg twice daily dose (on an AUC basis at oral doses of 1 mg/kg/day). Tofacitinib exposure levels at approximately 133 times the recommended dose of 5 mg twice daily, and approximately 67 times the 10 mg twice daily dose (on an AUC basis at oral doses of 100 mg/kg/day) had no effect on male fertility, sperm motility, or sperm concentration.

7. DESCRIPTION
This product (ointment) contains tofacitinib as active ingredient and it is indicated for the treatment of Mild to moderate atopic dermatitis (AD). Tofacitinib is an inhibitor of Janus kinases, a group of intracellular enzymes involved in signalling pathways that affect hematopoiesis and immune cell function.
Molecular formula- $C_{16}H_{20}N_6O$
Molecular weight - 312.37 g/mol
Structural formula



8. PHARMACEUTICAL PARTICULARS
8.1 Incompatibilities
Not applicable.

8.2 Shelf-life
See on the Carton

8.3 Packaging information
Available in 15g Aluminium tube.

8.4 Storage and handling instructions
Store at a temperature not exceeding 30ºC. Do not freeze.
Keep out of reach of children.

9. PATIENT COUNSELLING INFORMATION
Read this entire leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

10. MANUFACTURED BY
Pure & Cure Healthcare Pvt. Ltd.
(A subsidiary of
Akums Drugs & Pharmaceuticals Ltd.)
Plot No. 26A, 27-30, Sector-8A, I.I.E.,
SIDCUL, Ranipur, Haridwar-249 403,
Uttarakhand.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE
31/UA/2013 on Dated 03/06/2023

12. DATE OF REVISION
September – 2023

13. Marketed by :
MSN Laboratories Private Limited.
MSN HOUSE, Plot No. C-24,
Industrial Estate, Sanath Nagar,
Hyderabad-500 018. Telangana, India.

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