Summary of Product Characteristics
RITRI 10
(Tofacitinib 10 mg film-coated tablets)

1. Name of the medicinal product

RITRI 10 (Tofacitinib Tablets 10 mg)

2. Qualitative and quantitative composition

Each film-coated tablet contains tofacitinib citrate equivalent to 10 mg of tofacitinib.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet.

A white-coloured, round, biconvex film-coated tablet, plain on both sides.

4. Clinical particulars

4.1 Therapeutic indications

Tofacitinib is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to, or who are intolerant of, methotrexate. It may be used as monotherapy or in combination with methotrexate or other non-biologic disease-modifying antirheumatic drugs (DMARDs).

4.2 Posology and method of administration

Treatment should be initiated and supervised by a specialist physician experienced in the diagnosis and treatment of rheumatoid arthritis. The recommended dose is 5 mg twice daily; the 10 mg tablet is intended to allow administration of dosing regimens that require a 10 mg unit dose where approved. Tofacitinib may be used as monotherapy or in combination with methotrexate. Dose interruption and reduction, and management of laboratory abnormalities (lymphocyte, neutrophil and haemoglobin values, and liver enzymes), should follow the recommendations in the full prescribing information.

Special populations

A reduced dose is recommended in patients with moderate or severe renal impairment and in those with moderate hepatic impairment; tofacitinib should not be used in severe hepatic impairment. Dose adjustment is also recommended when co-administered with potent CYP3A4 inhibitors or with medicines that are both moderate CYP3A4 and potent CYP2C19 inhibitors.

Paediatric population

The safety and efficacy of tofacitinib in children below 18 years of age with rheumatoid arthritis have not been established.

Method of administration

For oral use, with or without food. Tablets should be swallowed whole and not crushed or split.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- Active tuberculosis, serious active infections including localised infections, or opportunistic infections.
- Severe hepatic impairment.
- Pregnancy and breast-feeding.

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. Tofacitinib should not be initiated in patients with active infections, including localised infections. Patients should be screened for latent and active tuberculosis before, and monitored during, treatment; anti-tuberculosis therapy should be considered prior to tofacitinib in patients with a history of latent or active tuberculosis. Viral reactivation, including herpes zoster, has been reported.

Malignancy and lymphoproliferative disorders

Lymphoma and other malignancies, including non-melanoma skin cancer and lung cancer, have been observed. In a large randomised study in rheumatoid-arthritis patients aged 50 years and older with at least one cardiovascular risk factor, a higher rate of malignancies (particularly lung cancer and lymphoma) was observed with tofacitinib compared with TNF inhibitors. Tofacitinib should be used in these patients only if no suitable alternatives are available.

Major adverse cardiovascular events (MACE)

In the same study, major adverse cardiovascular events (including myocardial infarction) occurred more frequently with tofacitinib than with TNF inhibitors, particularly in current or past smokers and in patients with other cardiovascular risk factors. Tofacitinib should be used in these patients only if no suitable alternatives are available.

Venous thromboembolism

Serious venous thromboembolic events, including deep vein thrombosis and pulmonary embolism (some fatal), have occurred in patients treated with tofacitinib, and a dose-dependent increased risk was observed. Tofacitinib should be used with caution in patients with known risk factors for thromboembolism, and patients with symptoms should be evaluated promptly and treatment discontinued.

Gastrointestinal perforation and laboratory monitoring

Gastrointestinal perforations have been reported; caution is advised in patients at risk (e.g. those with a history of diverticulitis). Tofacitinib is associated with decreases in lymphocyte, neutrophil and haemoglobin values and with increases in lipid parameters and liver enzymes; complete blood counts and lipid profiles should be monitored, and dose interruption or discontinuation applied according to the recommended thresholds. Live vaccines should not be given concurrently with tofacitinib.

4.5 Interaction with other medicinal products and other forms of interaction

Tofacitinib is metabolised principally by CYP3A4, with a minor contribution from CYP2C19. Co-administration with potent CYP3A4 inhibitors (e.g. ketoconazole), or with medicines that are both moderate CYP3A4 and potent CYP2C19 inhibitors (e.g. fluconazole), increases tofacitinib exposure and requires dose reduction. Potent CYP3A4 inducers (e.g. rifampicin) reduce tofacitinib exposure and may reduce efficacy. Tofacitinib should not be combined with biologic DMARDs or potent immunosuppressants such as azathioprine and ciclosporin, owing to the risk of added immunosuppression.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data on the use of tofacitinib in pregnant women. Studies in animals have shown reproductive toxicity. Tofacitinib is contraindicated during pregnancy. Women of childbearing potential should use effective contraception during treatment and for at least 4 weeks after the last dose.

Breast-feeding

Tofacitinib is excreted in the milk of lactating animals. A risk to breast-fed infants cannot be excluded, and tofacitinib is contraindicated during breast-feeding.

Fertility

Impaired female fertility was observed in rats; the effect on human fertility has not been studied.

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 most common serious adverse reactions are serious infections. The adverse reactions are listed below by System Organ Class and frequency, defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Very common	Nasopharyngitis, upper respiratory tract infection
	Common	Pneumonia, bronchitis, influenza, urinary tract infection, sinusitis, herpes zoster, herpes simplex
	Uncommon	Tuberculosis, diverticulitis, pyelonephritis, cellulitis, viral infection
	Not known	Serious and opportunistic infections (including sepsis, cryptococcosis, oesophageal candidiasis, cytomegalovirus, atypical mycobacterial infection)
Neoplasms benign, malignant and unspecified	Uncommon	Non-melanoma skin cancers
	Not known	Lymphoma, lung cancer and other malignancies
Blood and lymphatic system disorders	Common	Anaemia
	Uncommon	Leukopenia, neutropenia, lymphopenia
Metabolism and nutrition disorders	Common	Dyslipidaemia, hyperlipidaemia
	Uncommon	Dehydration
Psychiatric disorders	Uncommon	Insomnia
Nervous system disorders	Common	Headache
	Uncommon	Paraesthesia
Vascular disorders	Common	Hypertension
	Not known	Venous thromboembolism (deep vein thrombosis, pulmonary embolism)
Cardiac disorders	Not known	Major adverse cardiovascular events including myocardial infarction
Respiratory, thoracic and mediastinal disorders	Common	Cough
	Uncommon	Dyspnoea, sinus congestion
Gastrointestinal disorders	Common	Abdominal pain, vomiting, diarrhoea, nausea, gastritis, dyspepsia
	Not known	Gastrointestinal perforation
Hepatobiliary disorders	Uncommon	Hepatic steatosis, transaminases increased, liver function test abnormal
Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	Erythema, pruritus
Musculoskeletal and	Common	Arthralgia

System Organ Class	Frequency	Adverse reaction
connective tissue disorders		
	Uncommon	Musculoskeletal pain, joint swelling, tendonitis
General disorders and administration site conditions	Common	Pyrexia, peripheral oedema, fatigue
Investigations	Common	Blood creatine phosphokinase increased, hepatic enzyme increased, blood cholesterol increased, weight increased
	Uncommon	Blood creatinine increased, low-density lipoprotein increased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the National Regulatory Authority.

4.9 Overdose

There is no specific antidote for overdose with tofacitinib. In the event of overdose, the patient should be monitored for signs and symptoms of adverse reactions and given appropriate symptomatic and supportive treatment. Pharmacokinetic data indicate that a substantial proportion of a dose can be removed by dialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants; Janus kinase (JAK) inhibitors. ATC code: L04AA29.

Tofacitinib is a potent, selective inhibitor of the Janus kinase (JAK) family of intracellular enzymes, with a preference for JAK1 and JAK3 over JAK2. By inhibiting JAK1 and JAK3, tofacitinib modulates the signalling of several cytokines integral to lymphocyte activation, proliferation and function, and the production of inflammatory mediators, thereby reducing the inflammation that characterises rheumatoid arthritis.

5.2 Pharmacokinetic properties

Tofacitinib is rapidly absorbed, with peak plasma concentrations reached within about 0.5 to 1 hour and an absolute oral bioavailability of approximately 74%; food does not affect overall exposure. It is about 40% bound to plasma proteins. Approximately 70% of hepatic metabolism is mediated by CYP3A4 and 30% by CYP2C19. Elimination is by hepatic metabolism (about 70%) and renal excretion of unchanged drug (about 30%); the terminal elimination half-life is approximately 3 hours.

5.3 Preclinical safety data

In non-clinical studies, effects were observed on the immune and haematopoietic systems, consistent with the pharmacology of tofacitinib. Secondary effects of immunosuppression, such as bacterial and viral infections and lymphoma, were seen in animals. Tofacitinib was not mutagenic or clastogenic; it impaired female fertility in rats and was associated with teratogenicity and effects on parturition and peri/postnatal development.

6. Pharmaceutical particulars

6.1 List of excipients

The full quantitative list of excipients should be confirmed from the applicant's finished-product formulation (3.2.P.1); for the tablet core this typically includes microcrystalline cellulose, lactose

monohydrate, croscarmellose sodium and magnesium stearate, with a film coat containing hypromellose, titanium dioxide, macrogol, triacetin and colourants. Any excipient of known effect present (e.g. lactose) must additionally be declared in section 2 and warned in section 4.4.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

To be confirmed from the applicant's stability data.

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture. Keep out of the reach and sight of children.

6.5 Nature and contents of container

1 x 10 tablets in an Alu-Alu blister pack, presented in a printed carton together with the package insert.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

Omilife Limited.

Manufacturer

4Care Lifescience Pvt. Ltd., Survey No. 23/3P & 24, Opp. Jeans Factory, Daduram Vistar, Village Bagdol, Taluka Kathalal, District Kheda, Pin 387630, India.

8. Marketing Authorisation Number

H2022/CTD10720/24417

9. Date of first authorisation / renewal of the authorisation

10. Date of revision of the text