

Available online on 15.09.2016 at <http://jddtonline.info>**Journal of Drug Delivery and Therapeutics***An International Peer Reviewed Journal*

Open access to Pharmaceutical and Medical research

© 2016, publisher and licensee JDDT, This is an Open Access article which permits unrestricted noncommercial use, provided the original work is properly cited

REVIEW ARTICLE**TERIFLUNOMIDE: A NOVEL ORAL DISEASE-MODIFYING AGENT UNDER INVESTIGATION FOR THE TREATMENT OF MULTIPLE SCLEROSIS****Singh Asheesh ^{1*}, Singh Parul ²**¹ Glenmark pharmaceutical Limited Plot No.2 Pharma Zone Pithampur-454775²Department of Pharmacy, Guru Ghasidas University, Bilaspur (India)-495009

Received 19 July 2016; Review Completed 06 Sep 2016; Accepted 06 Sep 2016, Available online 15 Sep 2016

ABSTRACT:

Treatment of multiple sclerosis (MS) is challenging: disease-modifying treatments (DMTs) must both limit unwanted immune responses associated with disease initiation and propagation (as T and B lymphocytes are critical cellular mediators in the pathophysiology of relapsing MS), and also have minimal adverse impact on normal protective immune responses. There are a number of oral agents emerging as potential disease-modifying agents in multiple sclerosis (MS). Among these investigational agents, teriflunomide has shown promise in large, multicenter, phase III clinical trials with respect to safety and efficacy in relapsing MS patients, and is the latest disease-modifying agent approved for use in MS patients in the United States. Teriflunomide selectively and reversibly inhibits dihydro-orotate dehydrogenase, a key mitochondrial enzyme in the de novo pyrimidine synthesis pathway, leading to a reduction in proliferation of activated T and B lymphocytes without causing cell death. Results from animal experiments modelling the immune activation implicated in MS demonstrate reductions in disease symptoms with teriflunomide treatment, accompanied by reduced central nervous system lymphocyte infiltration, reduced axonal loss, and preserved neurological functioning. Teriflunomide is an immunomodulatory drug that received FDA approval for the treatment of relapsing forms of multiple sclerosis (MS) in September 2012. Its primary mode of action is inhibition of dihydroorotate dehydrogenase which inhibits the proliferation of activated T cells, but it also has a number of other actions that may be important contributors to its efficacy in MS. This review will summarize teriflunomide's historical development, clinical pharmacology, studies in animals, clinical trials, and safety data, and will end with a discussion of the role of teriflunomide in MS in the context of existing treatment options.

Keywords: teriflunomide, multiple sclerosis, clinical trials, disease-modifying treatments.**DOI:** <http://dx.doi.org/10.22270/jddt.v6i5.1303>**URI:** <http://jddtonline.info/index.php/jddt/article/view/1303>**INTRODUCTION:**

Teriflunomide is an effective and safe oral treatment option for relapsing MS. It can be used as monotherapy or added to interferon or glatiramer acetate. Teriflunomide reduces the rate of relapse and may slow disease progression. The advantages of this drug are the convenience of oral administration and good tolerability. The disadvantages are the lack of long-term safety data and data on the benefit of combination therapy¹.

Teriflunomide is the principal active metabolite of leflunomide, which has been licensed for use in the treatment of rheumatoid arthritis (RA) for over a decade.² Leflunomide was discovered in the 1980s during a chemical compound-screening process intended to identify agricultural pesticides, and was inadvertently found to have both anti-inflammatory and immunosuppressive properties and was thus developed for use in RA. Due to its efficacy, safety, and tolerability in RA, leflunomide was later tested in animal models of other inflammatory disorders,

including experimental autoimmune encephalitis, the animal model of MS. Upon oral ingestion, leflunomide is rapidly converted into its primary active metabolite, teriflunomide. Since teriflunomide is able to avoid the first-pass metabolism that leflunomide undergoes, it has become the focus of development in MS patients³. Teriflunomide may cause major birth defects or fetal death if used during pregnancy. Do not take teriflunomide if you are pregnant. Do not take it if you may become pregnant and are not using an effective form of birth control. You must make sure you are not pregnant before you start teriflunomide. Do not become pregnant while you take teriflunomide or for as long as any medicine remains in your body after you stop treatment. Teriflunomide may stay in the body for as long as 2 years after you stop it. Women who may become pregnant must use effective birth control while they take teriflunomide and for as long as any medicine remains in the body^{4,5}.

Additionally, teriflunomide has been shown in in vitro and in animal studies to inhibit tyrosine kinases,

nuclear factor- κ B, cyclooxygenase-2, and other proteins, but the drug's binding affinity for these targets is much lower than its affinity for DHODH.⁶ As a result, the mechanisms of teriflunomide appear to be concentration dependent. At drug concentrations achievable with therapeutic doses of teriflunomide, it is likely that DHODH inhibition is the predominant mechanism.⁷

Protein-tyrosine kinase inhibitors have been useful in defining the role of these enzymes in signal transduction events. Herbimycin A, a benzoquinonoid ansamycin antibiotic, increases the turnover of p56^{lck} and p59^{fn}, which in turn decreases tyrosine kinase activity in human T lymphocytes, and thus impairs signal transduction by the TCR complex. Tyrosine

phosphorylation, PLC- γ 1 activity, phosphatidylinositol 4, 5-bisphosphate hydrolysis, and $[Ca^{2+}]$ mobilization, as well as the expression of distal markers of T cell activation, such as interleukin-2 (IL-2) and IL-2 receptor (IL-2R), are all inhibited by herbimycin A.⁸ Genistein, a natural isoflavone, also inhibits tyrosine phosphorylation of PLC- γ 1 and other substrates, although it is less effective than herbimycin A and has only marginal effects on the generation of inositol 1,4,5-trisphosphate and Ca^{2+} mobilization. However, genistein still efficiently blocks IL-2 production and IL-2 receptor expression. Both herbimycin A and genistein are capable of blocking proliferation of T cells stimulated by phytohemagglutinin or by anti-TCR antibody, but neither has yet been tested in any *in vivo* animal models for immunosuppression.⁹

Table 1: Food and Drug Administration-Approved Agents for Relapsing Forms of Multiple Sclerosis.

Drug (Brand Name)	Dose	Route of Administration	Comments
Dimethyl fumarate, delayed release (Tecfidera)	240 mg twice daily	Oral	30% decrease in lymphocytes during therapy, flushing common
Fingolimod (Gilenya)	0.5 mg once daily	Oral	Requires extensive monitoring including varicella zoster immunity evaluation, pulse, blood pressure, ophthalmology examination, dermatologic examination
Glatiramer acetate (Copaxone)	20 mg once daily	Subcutaneous	First-line therapy, skin reactions common
Natalizumab (Tysabri)	300 mg every 4 weeks	Intravenous	Requires registration of patient, pharmacy, and prescriber before use because of concerns
Teriflunomide (Aubagio)	7 mg or 14 mg once daily	Oral	Hepatotoxicity and teratogenicity risk

ACTIVE SUBSTANCE:

The chemical name of teriflunomide is (Z)-2-Cyano-3-hydroxy-but-2-enoic acid-(4-trifluoromethylphenyl) amide with molecular formula $C_{12}H_{9}F_{3}N_{2}O_{2}$ and relative molecular mass 270.2 g/mol. Its structural formula is shown below:

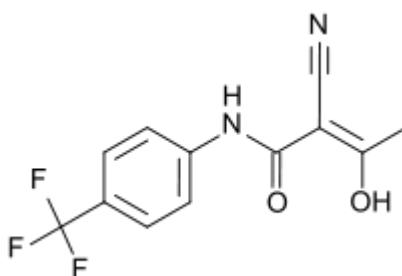


Figure 1: Structure of Teriflunomide

Teriflunomide appears as a white to almost white, odourless, non-hygroscopic powder. It is a biopharmaceutical classification system (BCS) Class 2 compound, which is practically insoluble in water; sparingly soluble in acetone; and slightly soluble in ethanol, acetonitrile and methylene chloride.

Teriflunomide contains no asymmetric centres, therefore no enantiomers are possible.

The presence of polymorphs of teriflunomide has been evaluated using DSC and X-ray powder diffraction and recrystallization from different solvents and only one polymorphic form has been observed. In addition, single crystal X-ray diffraction analysis studies have demonstrated that teriflunomide in the solid state (crystalline phase) is only the Z-isomer.

The structure of teriflunomide has been elucidated by elemental analysis (C, H and N), spectroscopic analyses (IR, UV, 1H -NMR, ^{13}C -NMR, ^{15}N -NMR, F-NMR and mass spectrometry) and single X-ray diffraction analysis. All data are consistent with the proposed structure.

PHARMACOKINETICS:

Leflunomide is rapidly converted to teriflunomide in the gastrointestinal tract wall and/or the liver and the pharmacokinetics of the 2 compounds are similar.¹⁰ The half-life of teriflunomide is more than 2 weeks and steady-state serum concentrations are reached in approximately 3 months. The concentration-dose relationship is linear with doses of 7 to 100 mg.

The pharmacokinetic characteristics after single p.o. or i.v. administration of teriflunomide were evaluated in male mice, rats, rabbits and dogs using formulations that were subsequently also analysed in toxicological investigations. These results were complemented with toxicokinetic data, which document teriflunomide pharmacokinetics following repeated dosing. Protein binding properties of teriflunomide were investigated *in vitro*. Teriflunomide was maximally absorbed in mice, rats, rabbits and dogs within 1 hrs, 6 hrs, 4-8 hrs or 1-4 hrs post dose culminating in levels of 36 μ g/ml, 48.4 μ g/ml, 25.9 μ g/ml or 58.9 μ g/ml, respectively. Teriflunomide showed almost 100% oral bioavailability in mice, rats and dogs, whereas it showed clearly lower levels (~66 %) in rabbits. Extensive protein binding between 96 and more than 99 % was determined in animals and man¹¹.

Following repeated oral administration of teriflunomide to mice and rats for up to 3 and 6 months, respectively, systemic exposure generally increased linearly with dose. The exposure increased in a greater than dose-proportional manner in dogs after repeated oral administration for up to 12 months and in pregnant rabbits treated orally for up to 7 days. Accumulation of teriflunomide was noted in all species after repeated doses reaching steady-state after approximately 1 month in mice and dogs and after 3 months in rats. There were no gender differences across test species¹²⁻¹³.

CLINICAL PHARMACOLOGY: MECHANISM OF ACTION OF TERIFLUNOMIDE

The precise mechanisms by which teriflunomide exerts immunomodulatory effects in MS are incompletely understood. Teriflunomide primarily acts as an inhibitor of dihydroorotate dehydrogenase (DHODH), a key mitochondrial enzyme involved in the de novo synthesis of pyrimidines in rapidly proliferating cells. By reducing the activity of high-avidity proliferating T lymphocytes and B lymphocytes, teriflunomide likely attenuates the inflammatory response to autoantigens in MS.¹⁴ Of note, DHODH blockade does not affect resting or homeostatically proliferating hematopoietic cell lines, as pyrimidine pools in these cells can be generated through an alternate "salvage pathway," which is independent of the DHODH. As a result, basic homeostatic functions of resting and slowly dividing cells appear to be preserved, and lymphocytes remain available for immune surveillance. Thus, teriflunomide can be considered a cytostatic rather than a cytotoxic drug to leukocytes. In addition to DNA and RNA synthesis, pyrimidines are involved in a myriad of cellular functions, including protein and lipid glycosylation, phospholipid synthesis, and DNA strand repair, together which lead to a variety of downstream immunomodulatory effects (Figure 2)¹⁵⁻¹⁷.

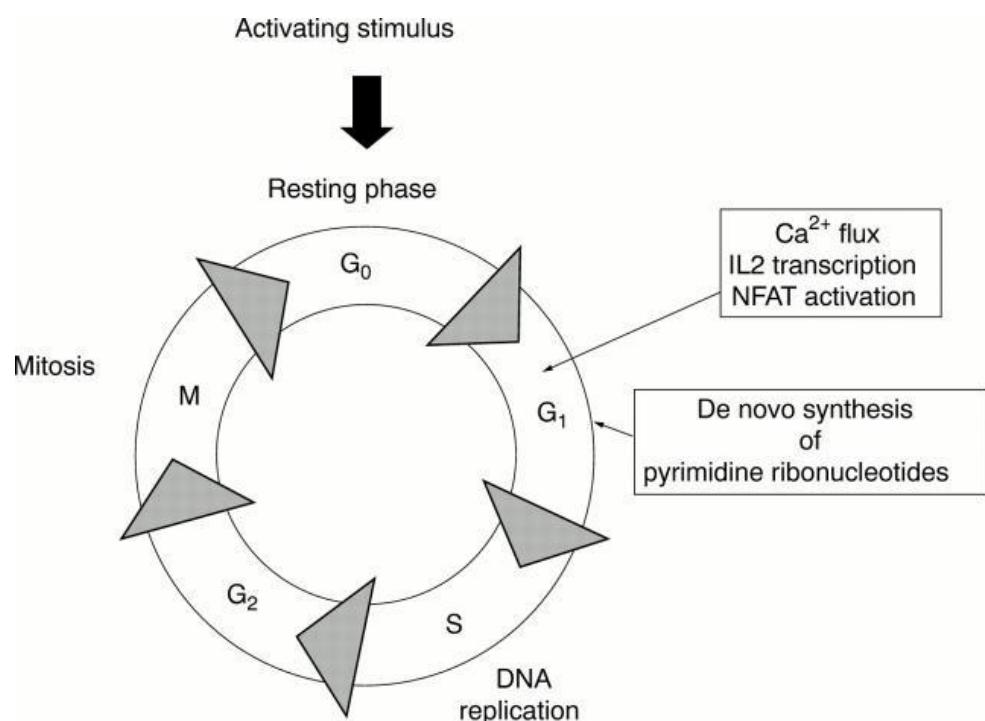


Figure 2: Cell cycle modulations. Some agents block signal transduction events in the resting G₀ phase. Other agents interfere with ribonucleotide biosynthesis in the G₁ phase. In either case, transition into the DNA replication phase, or S phase, of the cell cycle is blocked. NFAT = nuclear factor of activated T cells.

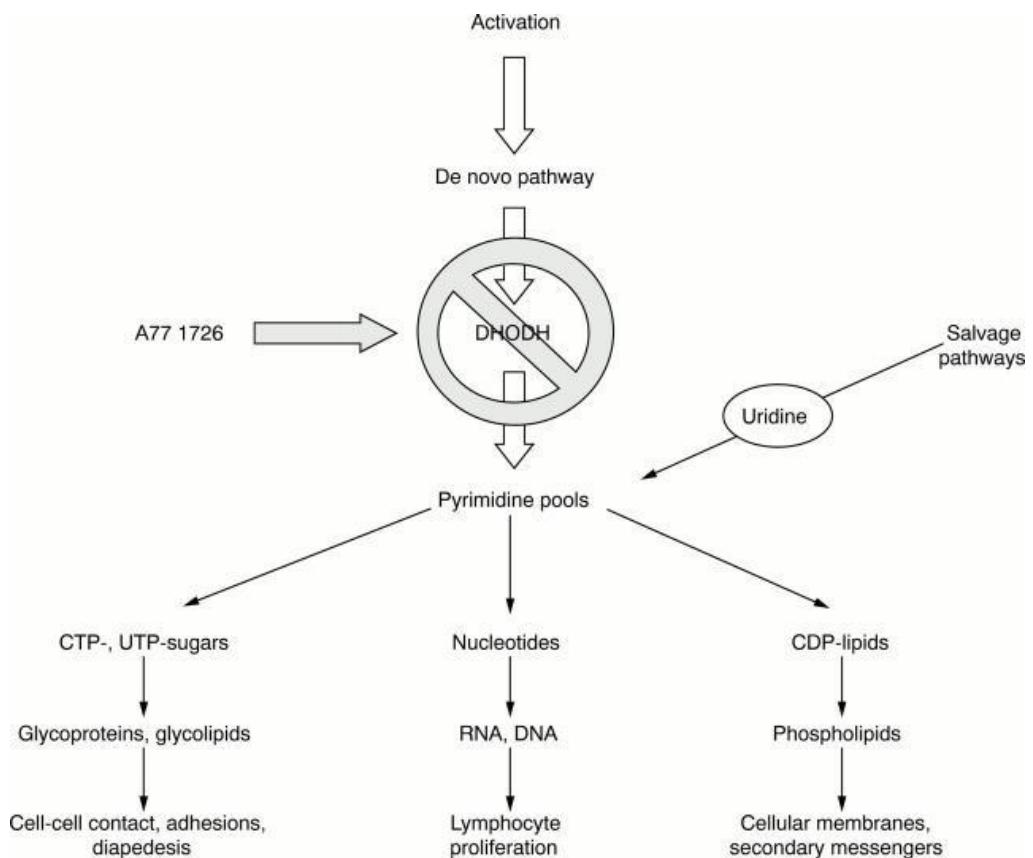


Figure 3: Effect of inhibition of de novo pyrimidine synthesis on various mechanisms of activated lymphocytes.
(Adapted from Herrmann et al.¹⁸)

TERIFLUNOMIDE IS USED FOR:

Treating certain forms of multiple sclerosis (MS). It may also be used for other conditions as determined by your doctor. Teriflunomide is a pyrimidine synthesis inhibitor. Exactly how teriflunomide works to treat MS is not known.

BEFORE USING TERIFLUNOMIDE:

Some medical conditions may interact with teriflunomide. Tell your doctor or pharmacist if you have any medical conditions, especially if any of the following apply to you:

- if you are pregnant, planning to become pregnant, or are breast-feeding
- if you are taking any prescription or nonprescription medicine, herbal preparation, or dietary supplement
- if you have allergies to medicines, foods, or other substances
- if you have a weakened immune system, a fever or an infection, a history of an infection that keeps coming back, or you have recently received or are scheduled to receive a vaccination
- if you have a history of lung or breathing problems, tuberculosis (TB) or a positive TB test, high blood pressure, blood or bone marrow problems, diabetes, liver problems, or abnormal

liver function tests, or if you drink alcoholic beverages

- if you have unusual numbness or tingling in your hands or feet that is different from your MS symptoms, or if you have had serious skin problems from taking other medicine
- if you have or have had a history of kidney problems or you are on dialysis
- if you take or have recently taken other medicine for MS, medicine to treat cancer, or any other medicine that may suppress your immune system
- if you take cholestyramine.¹⁹⁻²¹

DRUG- INTERACTION:

Some Medicines may interact with teriflunomide. Tell your health care provider if you are taking any other medicines, especially any of the following:

- Leflunomide because it may increase the risk of teriflunomide's side effects.
- Atorvastatin, cefaclor, cimetidine, ciprofloxacin, furosemide, ketoprofen, nateglinide, oral contraceptives (birth control pills), paclitaxel, penicillin G, pioglitazone, pravastatin, repaglinide, rosiglitazone, rosuvastatin, simvastatin, or zidovudine because the risk of their side effects may be increased by teriflunomide.

- Alosetron, anticoagulants (eg, warfarin), duloxetine, theophylline, or tizanidine because their effectiveness may be decreased by teriflunomide.
- Methotrexate because the risk of liver problems, blood problems, or infection may be increased.
- Rifampin because it may increase the risk of teriflunomide's side effects.
- Anticoagulants (eg, warfarin) because the risk of its side effects, including bleeding, may be increased by teriflunomide.
- Medicines that may suppress the immune system because the risk of infection or unusual bruising or bleeding may be increased. Ask your doctor if you are unsure if any of your medicines may suppress the immune system.
- Medicines that may cause nerve problems, because the risk of a certain nerve side effect (burning, numbness, or tingling sensation) may be increased. Ask your doctor if you are unsure if any of your medicines may cause nerve problems.
- Medicines that may harm the liver (eg, acetaminophen, methotrexate, ketoconazole, isoniazid, certain medicines for HIV infection) because the risk of liver side effects may be increased. Ask your doctor if you are unsure if any of your medicines might harm the liver.²²

HOW TO USE TERIFLUNOMIDE:

Use teriflunomide as directed by your doctor. Check the label on the medicine for exact dosing instructions.

- Teriflunomide comes with an extra patient information sheet called a Medication Guide. Read it carefully. Read it again each time you get teriflunomide refilled.
- Take teriflunomide by mouth with or without food.

REFERENCES:

1. Gever John. "Teriflunomide Modest Help but Safe for MS". Joint meeting of the Consortium of Multiple Sclerosis Centers and the Americas Committee for Treatment and Research in Multiple Sclerosis. Retrieved June 4, 2012.
2. Breedveld FC, Dayer JM. Leflunomide: mode of action in the treatment of rheumatoid arthritis. *Annual Rheumatoid Disorder*, 2000, 59 (11), 841-849.
3. Osiri M, Shea B, Robinson V, et al. Leflunomide for treating rheumatoid arthritis. *Cochrane Database Systematic Review*, 2003, 1, CD002047.
4. Bartlett RR, Schleyerbach R. Immunopharmacological profile of a novel isoxazol derivative, HWA 486, with potential antirheumatic activity -I. Disease modifying action on adjuvant arthritis of the rat. *International Journal of Immunopharmacology*, 1985, 7, 7-18.
5. Korn T, Magnus T, Toyka K, Jung S. Modulation of effector cell functions in experimental autoimmune encephalomyelitis by leflunomide – mechanisms independent of pyrimidine depletion. *Journal of Leukocyte Biology*, 2004, 76, 950-960.
6. Davis JP, Cain GA, Pitts WJ, Magolda RL, Copeland RA. The immunosuppressive metabolite of leflunomide is a potent inhibitor of human dihydroorotate dehydrogenase. *Biochemistry*, 1996, 35, 1270-1273.
7. Fox RI, Herrmann ML, Frangou CG, et al. Mechanism of action for leflunomide in rheumatoid arthritis. *Clinical Immunology*, 1999, 93, 198-208.
8. June CH, Fletcher MC, Ledbetter JA, Schieven GL, et al. Inhibition of tyrosine phosphorylation prevents T-cell receptor-mediated signal transduction. *Proceedings of the National Academy Science USA*.1990, 87, 7722-7726.
9. Renaud A, Du Pasquier DD, Pinschewer, Doron M. Immunological Mechanism of Action and Clinical Profile of Disease-Modifying Treatments in Multiple Sclerosis. *CNS Drugs*, 2014, 28:535-558.

CONCLUSION:

Teriflunomide is an effective and safe oral treatment option for relapsing MS. It can be used as monotherapy or added to interferon or glatiramer acetate. It reduces the rate of relapse and may slow disease progression. The advantages of this drug are the convenience of oral administration and good tolerability. The disadvantage is the lack of long-term safety data and data about the benefit of combination therapy.

For decades, patients with MS and health care providers managing treatment have awaited oral disease-modifying agents. With 3 oral drugs now available and more in development, there are several treatment options. Teriflunomide also is well tolerated and requires less patient monitoring when compared with some other treatments for MS such as mitoxantrone, natalizumab, and fingolimod. This tolerability and patient preference for oral therapy are likely reflected in the relatively low discontinuation rates. In addition, the long washout period of teriflunomide may have implications for the use of other immunosuppressive agents in individuals with breakthrough disease on this drug, although rapid-elimination procedures may mitigate this concern. Most importantly, as with any novel pharmacological agent, post marketing surveillance will be essential in more definitively characterizing the long-term safety and efficacy of teriflunomide in the treatment of MS in the real world.

ACKNOWLEDGEMENT

Authors are thankful to Glenmark Pharmaceutical limited Pithampur to provide necessary facilities to complete the review paper. Especial thanks to Guru Ghasidas Vishwavidyalaya for providing the necessary facilities and guidance to carry out this review.

10. Aubagio (teriflunomide) [product information]. Cambridge, MA: Genzyme Corp; September 2012.
11. Limskun T, Menguy-Vacheron F. Pharmacokinetics of oral teriflunomide, a novel oral disease-modifying agent under investigation for the treatment of multiple sclerosis. *Neurology*, 2010, 74(2), 415-425.
12. Rozman B. Clinical pharmacokinetics of Leflunomide, *Clinical Pharmacokinetic*, 2002, 41, 421-430.
13. Chisholm-Burns MA, Wells BG, Schwinghammer TL. *Pharmacotherapy: Principles and Practice*. 3rd ed. New York: McGraw-Hill Medical; 2013.443-456.
14. Bruneau JM, Yea CM, Spinella-Jaegle S, et al. Purification of human dihydro-orotate dehydrogenase and its inhibition by A77 1726, the active metabolite of leflunomide. *Biochemistry Journal*, 1998, 336:299-303.
15. Cherwinski HM, Cohn RG, Cheung P, et al. The immunosuppressant leflunomide inhibits lymphocyte proliferation by inhibiting pyrimidine biosynthesis. *Journal of Pharmacology Experimental Therapeutics*. 1995; 275:1043-1049.
16. Fox RI, Herrmann ML, Frangou CG, et al. Mechanism of action for leflunomide in rheumatoid arthritis. *Clinical Immunology*, 1999, 93, 198-208.
17. Ruckemann K, Fairbanks LD, Carrey EA, et al. Leflunomide inhibits pyrimidine de novo synthesis in mitogen-stimulated T-lymphocytes from healthy humans. *Journal of Biological Chemistry*, 1998, 273, 21682-21691.
18. Herrmann ML, Schleyerbach R, Kirschbaum BJ. Leflunomide: an immunomodulatory drug for the treatment of rheumatoid arthritis and other autoimmune diseases. *Immunopharmacology*, 2000, 47, 273-289.
19. Fairbanks LD, Bofill M, Ruckemann K, Simmonds HA. Importance of ribonucleotide availability to proliferating T-lymphocytes from healthy humans. Disproportionate expansion of pyrimidine pools and contrasting effects of de novo synthesis inhibitors. *Journal of Biological Chemistry*, 1995, 270, 29682-29689.
20. Herrmann ML, Schleyerbach R, Kirschbaum BJ. Leflunomide: an immunomodulatory drug for the treatment of rheumatoid arthritis and other autoimmune diseases. *Immunopharmacology*, 2002, 48 (2-3), 147-157.
21. O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *New England Journal of Medicine*, 2011, 365, 1293-1303.
22. O'Connor PW, Wolinsky JS, Confavreux C, et al. Extension of a phase III trial (TEMSO) of oral teriflunomide in multiple sclerosis with relapses: clinical and MRI data 5 years after initial randomisation. ECTRIMS/ACTRIMS. Amsterdam, the Netherlands. P9242011.
23. Cristina C, Kenneth G, Wilhelm Jr, Andrew G, and Allan MW. T cell Antigen Receptor Ubiquitination Is A Consequence Of Receptor-Mediated Tyrosine Kinase Activation. *The Journal of Biological Chemistry*, 1996, 271, 15, 8709-8713.

***Corresponding Author:**

Asheesh Singh, Research Officer, Department of Analytical Research Formulation, Glenmark pharmaceutical Limited, Plot No.2 Pharma Zone Pithampur-454775, (B) 91 07292667986 +91-9893737249, Email: asheesh_parihar@yahoo.com

Cite this article as:

Singh A, Singh P, TERIFLUNOMIDE: A NOVEL ORAL DISEASE-MODIFYING AGENT UNDER INVESTIGATION FOR THE TREATMENT OF MULTIPLE SCLEROSIS, Journal of Drug Delivery & Therapeutics. 2016; 6(5):97-102.

DOI: <http://dx.doi.org/10.22270/jddt.v6i5.1303>