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REVIEW ARTICLE

Teriflunomide in Patients with Relapsing–Remitting Forms of Multiple Sclerosis

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Abstract Teriflunomide is a once-daily oral agent that has been licensed in the EU since August 2013 for the treatment of adult patients with relapsing–remitting multiple sclerosis (RRMS). More recently (September 2014), the EU summary of product characteristics (SmPC) was updated to include data from patients with a first clinical demyelinating event. This review examines the EU SmPC for teriflunomide, with reference to key clinical and safety outcomes and practical considerations for prescribing physicians. In two phase III trials (TEMSO and TOWER) in patients with relapsing forms of MS, teriflunomide 14 mg significantly reduced the annualized relapse rate and the risk of confirmed disability progression sustained for at least 12 weeks. Magnetic resonance imaging (MRI) total lesion volume, gadolinium-enhancing lesions, and unique active lesions were reduced with teriflunomide treatment in TEMSO. In the TOPIC study, in patients with a first clinical demyelinating event, teriflunomide treatment significantly reduced the time to a second clinical episode (relapse). Across the clinical studies, teriflunomide was generally well tolerated; adverse events reported in ≥10 % of teriflunomide-treated patients were diarrhea, nausea, increased alanine aminotransferase, and alopecia. Data from the clinical development program support the use of teriflunomide in a broad spectrum of patients with RRMS.

Key Points

Teriflunomide is a once-daily oral treatment approved for relapsing–remitting multiple sclerosis.

Teriflunomide has pleiotropic and novel mechanisms of action, specifically targeting activated T and B cells.

Teriflunomide demonstrated consistent efficacy in reducing the risk of disability progression and the annualized relapse rate in two independent phase III trials (TEMSO, TOWER) as well as positive outcomes on several magnetic resonance imaging (MRI) parameters of disease activity (TEMSO).

1 Introduction

Teriflunomide (Aubagio®, sanofi-aventis groupe, Paris, France) is a once-daily oral agent that was approved in the EU in August 2013 for the treatment of adult patients with relapsing–remitting multiple sclerosis (RRMS) [1]. It was the second oral disease-modifying therapy (DMT), following fingolimod (Gilenya®, Novartis Europharm Ltd, UK), approved in the EU for the treatment of RRMS in March 2011 [2]. Fingolimod is approved for use in patients with high disease activity despite treatment with at least one DMT, or in patients with rapidly evolving severe RRMS. The 14-mg dose of teriflunomide is licensed in the

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EU and several other countries. BG-12 (Tecfidera®, Biogen Idec Ltd, UK) has also been approved for patients with RRMS [3].

Teriflunomide's mechanism of action is considered to be related to its effect on rapidly dividing lymphocytes. Teriflunomide selectively and reversibly inhibits a key mitochondrial enzyme, dihydroorotate dehydrogenase (DHODH), required for de novo pyrimidine synthesis. As a consequence of limited de novo pyrimidine production, teriflunomide reduces the proliferation of activated T and B cells, which are thought to participate in the inflammatory process in the central nervous system [4]. In vitro, teriflunomide causes cell-cycle arrest without cell death [5, 6], and the cytostatic effects of teriflunomide can be reversed by the addition of exogenous uridine [6], which supports DHODH inhibition as the primary mechanism. However, pleiotropic effects independent from DHODH inhibition have also been reported [4]. Investigation of the effects of teriflunomide on peripheral blood mononuclear cells in vitro have shown little or no impact on lymphocyte activation and no cytotoxicity associated with teriflunomide [7]. Resting lymphocytes rely on the salvage pathway, which is unaffected by teriflunomide, to meet their pyrimidine needs, thereby preserving these cells for normal immune surveillance. In a study of teriflunomide's effect on the immune response to seasonal influenza vaccine, patients with relapsing forms of MS (RMS) receiving teriflunomide generally mounted appropriate memory immune responses to influenza vaccination [8]. In a separate study, teriflunomide-treated healthy volunteers were able to make a seroprotective response to neoantigen (rabies vaccine) [9]. Together, these results argue against a clinically relevant immunosuppressive effect.

Teriflunomide is the active metabolite of leflunomide (ARAVA®, Sanofi-Aventis Deutschland GmbH, Germany), a disease-modifying antirheumatic drug (DMARD) licensed in the EU since 1999 for the treatment of adult patients with active rheumatoid arthritis (RA) [10]. Postmarketing experience with leflunomide has informed the EU summary of product characteristics (SmPC) for teriflunomide, specifically regarding safety as reflected in warnings and precautions for use. However, there are a number of challenges when comparing the safety of teriflunomide with its parent compound; leflunomide has only been evaluated in patients with RA, who often have comorbidities and are prescribed concomitant medications, which may impact the safety observations on leflunomide and confound comparisons with teriflunomide. There are also pharmacological differences between leflunomide and teriflunomide, which are discussed below.

This review summarizes key efficacy and safety data that supported the approval of teriflunomide 14 mg for the once-daily treatment of RRMS. It specifically focuses on recommendations in the EU SmPC in the context of clinical practice, with the aim of providing a practical reference for treatment.

2 Key Data from Teriflunomide Trials

2.1 Efficacy Outcomes

The efficacy of teriflunomide was demonstrated in three phase III, placebo-controlled trials, TEMSO (NCT00134563) [1, 11], TOWER (NCT00751881) [1, 12], and TOPIC (NCT00622700) [1, 13] (Table 1), and in one active comparator phase III trial, TENERE (NCT00883337) [1, 14]. Data pertaining to the 14-mg dose have been emphasized here as it is the dose licensed in the EU.

In the TEMSO trial, 1088 patients with RMS (McDonald 2001 criteria [15]) were randomized to receive once-daily oral teriflunomide 14 mg, teriflunomide 7 mg, or placebo for 108 weeks [1, 11]. Teriflunomide 14 mg significantly reduced annualized relapse rate (ARR) (primary endpoint) by 31.5 % ($p < 0.001$) and reduced the risk of disability progression (key secondary endpoint) by 30.0 % ($p < 0.05$) versus placebo (Table 2). Teriflunomide 14 mg also reduced total lesion volume [key magnetic resonance imaging (MRI) endpoint] by 67 % versus placebo at week 108 ($p < 0.001$), the mean number of T1 gadolinium (Gd)-enhancing lesions per scan by a change relative to placebo of 0.80 ($p < 0.0001$) and the number of unique active lesions per scan by 69 % ($p < 0.0001$) (Table 2).

In a post hoc analysis of a subgroup of patients from the TEMSO study with high disease activity (two or more relapses in 1 year and with one or more Gd-enhancing lesion on baseline brain MRI; $n = 127$), a consistent treatment effect of teriflunomide 14 mg compared with placebo was observed for ARR and disability progression [1, 16].

In TOWER, 1169 patients with RMS (McDonald 2005 criteria [17]) were randomized to receive teriflunomide 14 mg, 7 mg, or placebo (Table 1) [1, 12]. The 14-mg dose significantly reduced ARR by 36.0 % ($p < 0.0001$) and the risk of confirmed disability progression sustained for 3 months by 32.0 % ($p < 0.05$) versus placebo (Table 2).

In TOPIC, 618 patients with a first clinical demyelinating event were randomized to receive teriflunomide 14 mg, 7 mg, or placebo for up to 108 weeks. Teriflunomide 14 mg significantly reduced the risk of a second relapse by 43 % compared with placebo ($p = 0.0087$), and the risk of relapse or new MRI lesion, whichever occurred first, by 35 % ($p = 0.0003$). Significant efficacy on MRI outcomes (total lesion volume, number and volume of Gd-enhancing lesions, and volume of post-Gd T1 lesion component) was also demonstrated [1, 13].

Table 1 Overview of placebo-controlled trials for teriflunomide

	Phase II POC [18]	TEMSO [11]	TOWER [12]	TOPIC [13]
Study design	Randomized (1:1:1), double-blind, placebo-controlled			
Study duration	36 weeks	108 weeks	48 weeks after the last patient randomized	Up to 108 weeks
Study population	• Poser criteria for MS [23] • Aged 18–65 years • EDSS ≤6.0 • Two documented relapses in the previous 3 years and one relapse in the past year	• McDonald 2001 criteria for MS with relapsing course ± progression [15] • Aged 18–55 years • EDSS ≤5.5 • ≥2 clinical relapses in the previous 2 years or ≥1 relapse in the past year • No relapse in 60 days prior to randomization	• McDonald 2005 criteria for MS with relapsing course ± progression [17] • Aged 18–55 years • EDSS ≤5.5 • ≥2 clinical relapses in the previous 2 years or ≥1 relapse in the past year • No relapse in 30 days prior to randomization	• First acute or subacute, well-defined neurological event consistent with demyelination (optic neuritis confirmed by an ophthalmologist, spinal cord syndrome, brainstem/cerebellar syndromes) • Onset of MS symptoms occurring within 90 days of randomization • ≥2 T2 lesions ≥3 mm in diameter that are characteristic of MS
Treatment arms[a]	• Teriflunomide 14 mg/day ($n = 57$) • Teriflunomide 7 mg/day ($n = 61$) • Placebo ($n = 61$)	• Teriflunomide 14 mg/day ($n = 358$) • Teriflunomide 7 mg/day ($n = 365$) • Placebo ($n = 363$)	• Teriflunomide 14 mg/day ($n = 370$) • Teriflunomide 7 mg/day ($n = 407$) • Placebo ($n = 388$)	• Teriflunomide 14 mg/day ($n = 216$) • Teriflunomide 7 mg/day ($n = 205$) • Placebo ($n = 197$)
Primary endpoint	Mean number of combined unique active lesions per MRI scan	Annualized relapse rate		Time to relapse indicating conversion to clinically definite MS
Key secondary endpoint(s)	• Other MRI measures[b] • Annualized relapse rate • Disability progression	• Confirmed disability progression sustained ≥3 months • MRI total lesion volume • Mean number of Gd-enhancing lesions on T1-weighted images per MRI scan	• Confirmed disability progression sustained ≥3 months	• Time to relapse or new MRI lesion, whichever occurred first

EDSS Expanded Disability Status Scale, *Gd* gadolinium, *MRI* magnetic resonance imaging, *MS* multiple sclerosis, *POC* proof of concept

[a] All randomized patients who received one or more dose of study medication

[b] Other MRI outcomes measured: number of T1 enhancing lesions and T2 active lesions, the number of patients with combined unique active lesions, and the percentage change from baseline in the T2 lesion volume

The effectiveness of teriflunomide was compared with that of subcutaneous interferon (IFN)-β-1a in the phase III TENERE study, in which 324 randomized patients were treated for at least 48 weeks. No difference was found between teriflunomide and IFNβ on the primary endpoint of time to failure, defined as confirmed relapse or permanent treatment discontinuation, whichever came first. Overall, patients reported greater treatment satisfaction and less fatigue with teriflunomide than with IFNβ [1, 14, 16].

2.2 Safety and Tolerability Outcomes

The safety analysis included 2047 teriflunomide-treated patients from four placebo-controlled trials: phase II (NCT00475865) [18], TEMSO, TOWER, and TOPIC. Adverse events reported in ≥10 % of patients treated with teriflunomide were diarrhea, nausea, increased alanine aminotransferase (ALT), and alopecia (reported as hair thinning). In general, diarrhea, nausea, and hair thinning were mild to moderate in intensity, transient, and only infrequently led to treatment discontinuation (Table 3) [1].

Mild increases in ALT ≤3× the upper limit of normal (ULN) were more frequently observed in patients receiving teriflunomide (49.6 %) than in those receiving placebo (29.5 %). According to study protocols, patients with confirmed ALT >3× ULN were required to discontinue treatment permanently [14]. The frequency of ALT increase >3× ULN was similar across treatment groups. Increases

Table 2 Efficacy outcomes from key registration trials

	TEMSO		TOWER	
	Teriflunomide 14 mg ($n = 358$)	Placebo ($n = 363$)	Teriflunomide 14 mg ($n = 370$)	Placebo ($n = 388$)
Annualized relapse rate	0.37	0.54	0.32	0.50
Relative reduction vs. placebo (%)	31.5***	–	36.0****	–
Patients remaining relapse free at week 108 (%)	56.5	45.6	57.1	46.8
Hazard ratio vs. placebo	0.72**	–	0.63****	–
Patients with 3-month sustained disability progression at week 108 (%)	20.2	27.3	15.8	19.7
Hazard ratio vs. placebo	0.70*	–	0.68*	–
Risk reduction vs. placebo (%)	30.0	–	32.0	–
Patients free of MRI activity[a] at week 108 (%)	37.6****[b] OR 2.26 (1.61–3.17)	21.1	–	–
Patients with no evidence of disease activity[c] at week 108 (%)	21.2***[b] OR 2.06 (1.35–3.13)	11.6	–	–
Change from baseline in total lesion volume (ml)[d] at week 108	0.72	2.21	–	–
Relative reduction vs. placebo (%)	67.0***	–	–	–
Mean number of T1 Gd-enhancing lesions per scan	0.38	1.18	–	–
Change relative to placebo	−0.80****	–	–	–
Number of unique active lesions per scan	0.75	2.46	–	–
Relative reduction vs. placebo (%)	69.0****	–	–	–

Data in parentheses are 95 % confidence intervals

Gd gadolinium, *MRI* magnetic resonance imaging, *OR* odds ratio

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$

[a] MRI activity was defined as no Gd-enhancing T1 lesions and no new/enlarging T2 lesions. Evaluable patients must have at least one valid MRI scan for assessment over the study duration; Placebo, $n = 346$; 14 mg, $n = 340$

[b] Data on file

[c] No evidence of disease activity was defined as no Gd-enhancing T1 lesions, no new/enlarging T2 lesions, no confirmed clinical relapse, and no 3-month sustained disability progression. Evaluable patients must have both valid MRI and clinical activity assessments over the study duration; Placebo, $n = 346$; 14 mg, $n = 340$

[d] Total volume of all abnormal brain tissue and calculated as the sum of the total volume of T2 lesion component and T1 hypointense lesion component

in ALT occurred mainly within the first 6 months of treatment, and the majority of these increases were reversible following discontinuation of treatment [1].

Minor reductions (<15 % decrease from baseline levels) in white blood cells (WBCs), mainly neutrophils and lymphocytes, have been observed in patients receiving teriflunomide in clinical trials. Most reductions were observed during the first 6 weeks of treatment with no further decrease while patients remained on therapy [1].

No increase in the incidence of serious infections was observed for teriflunomide (2.7 %) compared with placebo (2.2 %); serious opportunistic infections occurred in 0.2 % of patients per group [1]. There was no increased risk of malignancy with teriflunomide treatment [1].

Peripheral neuropathy, including both polyneuropathy and mononeuropathy (e.g., carpal tunnel syndrome), was reported more frequently in patients receiving teriflunomide than in placebo patients. In the pivotal studies, the incidence of peripheral neuropathy confirmed by nerve conduction studies was 1.4 % (13 of 1002 patients) in the teriflunomide group compared with 0.4 % (4 of 997 patients) in the placebo group [1].

Systolic blood pressure >140 and >160 mmHg was observed in 19.9 and 3.8 % of patients receiving teriflunomide compared with 15.5 and 2.0 % of those receiving placebo, respectively. Diastolic blood pressure >90 mmHg was observed in 21.4 % of patients receiving teriflunomide compared with 13.6 % of patients receiving placebo [1].

3 Practical Considerations for Physicians Prescribing Teriflunomide

Physicians must be aware of required assessments before initiation of treatment and monitoring requirements during teriflunomide therapy, as well as contraindications for its use (Tables 4, 5). In addition to

Table 3 Frequency of adverse reactions in patients treated with teriflunomide in placebo-controlled trials

System organ class[a]	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10,000 to <1/1000)	Very rare (<1/10,000)
Investigations	ALT increase	Increase: GGT and AST Decrease: weight, neutrophil count, WBC count			
Gastrointestinal disorders	Diarrhea, nausea	Abdominal pain upper, vomiting, toothache			Pancreatitis[b]
Skin and subcutaneous tissue disorders	Alopecia (hair thinning)	Rash, acne			
Infections and infestations		Influenza, upper respiratory tract infection, urinary tract infection, bronchitis, sinusitis, pharyngitis, cystitis, gastroenteritis viral, oral herpes, tooth infection, laryngitis, tinea pedis			
Blood and lymphatic system disorders		Neutropenia, anemia	Mild thrombocytopenia (platelets <100 G/l)		
Immune system disorders		Mild allergic reactions			
Psychiatric disorders		Anxiety			
Nervous system disorders		Paraesthesia, sciatica, carpal tunnel syndrome	Hyperesthesia, neuralgia, peripheral neuropathy		
Vascular disorders		Hypertension			
Respiratory, thoracic and mediastinal disorders					Interstitial lung disease[b]
Musculoskeletal and connective tissue disorders		Musculoskeletal pain, myalgia			
Renal and urinary disorders		Pollakiuria			
Reproductive system and breast disorders		Menorrhagia			
General disorders and administration site conditions		Pain			
Injury, poisoning and procedural complications			Post-traumatic pain		

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *GGT* gamma-glutamyltransferase, *WBC*, white blood cell

[a] Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness

[b] Based on leflunomide data only

the EU SmPC recommendations referred to in this article, national recommendations and guidelines have been issued.

3.1 Considerations Before Initiation of Teriflunomide Therapy

Elevations in liver enzymes have been observed in patients receiving teriflunomide in clinical trials, and teriflunomide treatment is contraindicated in patients with severe hepatic impairment [Child–Pugh class C, where A (5–6 points) is the least severe and C (10–15 points) is the most severe] [1, 19]. ALT/serum glutamic pyruvic transaminase (SGPT) should be assessed before initiation of teriflunomide treatment [1].

Due to the effect of teriflunomide on WBC counts, a complete blood count, including differential WBC and platelet count, should be assessed [1].

Teriflunomide treatment was associated with increases in systolic and diastolic blood pressure in clinical trials [1, 11, 12] and, therefore, blood pressure should be checked [1].

Table 4 Recommendations before initiation of teriflunomide and during therapy

Before starting teriflunomide	During teriflunomide treatment
• Measure liver enzymes	• Assess liver enzymes every 2 weeks during the first 6 months of treatment
• Exclude pregnancy and confirm use of reliable contraception	– Monitor every 8 weeks thereafter or as indicated by signs and symptoms (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine)
• Screen for latent tuberculosis infection	• If ALT/SGPT is 2–3× ULN, monitor weekly
– For positive tuberculosis tests, treat by standard medical practice prior to therapy	
• Check baseline blood pressure	• Check blood pressure periodically
• Obtain a recent complete blood count including differential WBC and platelets	• Do not use live attenuated vaccines
• Wait until resolution of any severe, active infection	• Confirm patient uses reliable contraception

ALT alanine aminotransferase, *SGPT* serum glutamic pyruvate transaminase, *ULN* upper limit of normal, *WBC* white blood cell

Teriflunomide is contraindicated in women who are pregnant or of childbearing potential if not using reliable contraception, or breast feeding (Table 5). Pregnancy must be excluded before initiation of teriflunomide in women of childbearing potential [1].

For a full list of considerations before initiating teriflunomide, see Table 4.

3.2 Recommendations During Teriflunomide Therapy

During treatment with teriflunomide, liver enzymes should be assessed every 2 weeks during the first 6 months of treatment and every 8 weeks thereafter. In the US prescribing information, monitoring is required at least monthly for 6 months after starting treatment [20]. If ALT/SGPT increases 2–3× ULN, weekly monitoring is advised. Patients with pre-existing liver disease may be at increased risk of developing elevated liver enzymes when receiving teriflunomide and should be monitored closely for signals of liver disease; therapy should be discontinued if liver injury is suspected and/or if elevated liver enzymes >3× ULN are confirmed [1]. It is advised to check patients' blood pressure periodically during treatment and any blood pressure elevation should be appropriately managed [1]. Teriflunomide treatment should be delayed in patients with severe active infection. Two clinical studies have demonstrated that vaccination with inactive neoantigen (rabies vaccine) or recall antigen (influenza vaccine) were safe and effective during treatment with teriflunomide. The use of live attenuated vaccines may carry an infection risk and should therefore be avoided, as is generally suggested in MS (Table 5) [1].

Women of childbearing age must be advised to use effective contraception during teriflunomide treatment and after treatment until teriflunomide plasma concentration is below 0.02 mg/l [1].

3.3 Recommendations for Treatment-Emergent Situations During Teriflunomide Therapy

A list of recommended management approaches for treatment-emergent clinical situations during teriflunomide therapy is summarized in Table 5.

3.3.1 Pregnancy

Teriflunomide is contraindicated in pregnant women, or women of childbearing potential not using reliable contraception, based on observations of teratogenicity and embryolethality in the offspring of teriflunomide-treated rats and rabbits. However, in vitro teriflunomide studies showed no evidence for increased frequency of mutations, and teriflunomide did not cause chromosome breakage in vivo [1]. In rats, teriflunomide administration resulted in a lower sperm count, but fertility was unaffected. No external malformations were observed in the offspring of male rats administered teriflunomide before mating with untreated female rats [1].

In a prospective trial conducted by The Organization of Teratology Information Specialists (OTIS) comparing pregnancies in leflunomide-treated RA patients, RA patients not exposed to leflunomide, and healthy volunteers, leflunomide did not demonstrate any evidence of increased risk for major birth defects, a specific pattern of major or minor anomalies, or an increased risk of spontaneous abortions [21]. Global teriflunomide pregnancy registries are collecting prospective data from pregnancies in the post-marketing setting.

During teriflunomide treatment, women of childbearing potential should discuss plans to stop or change contraception with their treating physician and notify their physician if pregnancy is suspected. If the pregnancy test is positive, the physician and patient must discuss the risk to the pregnancy, and should discuss initiation of the accelerated elimination procedure [1]. Teriflunomide US prescribing information recommends that men wishing to

Table 5 Recommendations/considerations for treatment-emergent situations during teriflunomide therapy

Treatment-emergent situations	Recommendations	Rationale
Hepatic		Leflunomide/teriflunomide clinical trials
Contraindications		
Patients with severe hepatic impairment (Child–Pugh class C)		
Warnings and precautions		
Mild to moderate hepatic impairment	No dosage adjustment necessary	
Liver injury is suspected	Discontinue teriflunomide	
Elevated liver enzymes (>3 × ULN) are confirmed	Consider discontinuing teriflunomide	
Clinical signs and symptoms, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia or jaundice, and/or dark urine occur	Assess liver enzymes	
Blood pressure		Leflunomide/teriflunomide clinical trials
Warnings and precautions		
Blood pressure increases	Manage elevations appropriately	
Infections		Leflunomide/teriflunomide immunomodulation
Contraindications		
Patients with severe, active infection until resolution		
Warnings and precautions		
Serious infection develops	Consider suspending treatment; consider accelerated elimination; re-assess benefits and risks prior to re-initiation of therapy	
Respiratory		Leflunomide
Warnings and precautions		
Pulmonary symptoms, such as persistent cough and dyspnea, develop	Consider discontinuing teriflunomide; investigate further as appropriate	
Hematologic		Leflunomide/teriflunomide immunomodulation
Contraindications		
Patients with significantly impaired bone marrow function or significant anemia, leucopenia, neutropenia, or thrombocytopenia		
Patients with severe immunodeficiency states (e.g., AIDS)		
Warnings and precautions		
Clinical signs and symptoms (e.g. infection) warrant further investigation	Perform complete blood cell count as indicated	
Severe hematological reactions, including pancytopenia, occur	Discontinue teriflunomide and any concomitant myelosuppressive treatment	
Anemia, leucopenia, thrombocytopenia, impaired bone marrow function or bone marrow suppression occur	Consider accelerated elimination	
Hypersensitivities		Leflunomide
Contraindications		
Patients with severe hypersensitivity to the active substance or to any of the excipients		
Warnings and precautions		
Skin and/or mucosal reactions that raise suspicions of severe generalized major skin reactions (Stevens-Johnson syndrome or toxic epidermal necrolysis—Lyell's syndrome) occur	Discontinue teriflunomide and perform accelerated elimination; do not re-expose patient to teriflunomide	
Ulcerative stomatitis occurs	Discontinue teriflunomide	

Table 5 continued

Treatment-emergent situations	Recommendations	Rationale
Peripheral neuropathy		Leflunomide/teriflunomide clinical trials
Warnings and precautions		
Peripheral neuropathy is confirmed	Consider discontinuing teriflunomide and performing accelerated elimination	
Renal		Teriflunomide clinical trials
Contraindications		
Patients with severe renal impairment undergoing dialysis		
Patients with severe hypoproteinemia (e.g. nephrotic syndrome)		
Warnings and precautions		
Mild, moderate or severe renal impairment not undergoing dialysis	No dosage adjustment necessary	
Vaccination		Immunomodulatory action of teriflunomide
Warnings and precautions		
Live attenuated vaccines may carry risk of infections	Avoid use of live attenuated vaccines	
Fertility, pregnancy and lactation		Leflunomide/teriflunomide pre-clinical toxicology
Contraindications		
Pregnant women or women of childbearing potential who are not using reliable contraception during treatment with teriflunomide and thereafter as long as its plasma levels are above 0.02 mg/l		
Breast-feeding women		
Warnings and precautions		
A woman has plans to stop or change contraception	Discuss risks and contraception options	
Pregnancy is suspected	Conduct pregnancy testing	
Pregnancy test is positive	Discuss risk to pregnancy; rapidly lowering blood level of teriflunomide by accelerated elimination may decrease risk to the fetus	
A woman wishes to become pregnant	Recommend accelerated elimination	
Overdose		Safety precautions
Warnings and precautions		
Overdose of teriflunomide	Accelerated elimination	
Other		Leflunomide
Warnings and precautions		
Patient experiences adverse reaction, such as dizziness	Advise to refrain from driving cars and using machines	

AIDS acquired immunodeficiency syndrome, *ULN* upper limit of normal

father a child should discontinue and undergo an accelerated elimination procedure [20], although no such recommendation is made in the EU SmPC.

4 Pharmacokinetics of Teriflunomide

There are pharmacological differences between leflunomide and its major metabolite teriflunomide, which also form the basis for the designation of teriflunomide as a new active substance by the European Medicines Agency [16]. Metabolism of leflunomide does not only generate teriflunomide, but other metabolites that may contribute to the leflunomide-specific safety profile. Teriflunomide is only moderately metabolized and is the only component detected in plasma. The primary biotransformation pathway for teriflunomide is hydrolysis, with oxidation as a minor pathway [1]; therefore, no dosage adjustment is necessary for patients with mild, moderate, or severe renal impairment not undergoing dialysis, or patients with mild or moderate hepatic impairment [mild, Child–Pugh class A (score 5–6); moderate, Child–Pugh class B (score 7–9)] [1].

A population pharmacokinetic analysis demonstrated that there is a slow approach to steady-state concentration (~100 days). In patients with MS, the median half-life of teriflunomide was approximately 19 days after repeated 14-mg doses. Teriflunomide is extensively bound to plasma protein (>99 %) and is mainly distributed in plasma. Severe hypoproteinemia (e.g., due to nephrotic syndrome) is therefore a contraindication for treatment with teriflunomide. Food does not have a clinically relevant effect on the pharmacokinetics of teriflunomide [1].

5 Accelerated Elimination of Teriflunomide

Teriflunomide is slowly eliminated from plasma; it takes an average of 8 months to reach plasma concentration less than 0.02 mg/L, although individual variation means it may take up to 2 years. Teriflunomide undergoes enterohepatic circulation, and the accelerated elimination process is thought to interrupt reabsorption of teriflunomide at the intestinal level [1].

Several clinical situations may warrant accelerated elimination of teriflunomide. It should be implemented after discontinuation of teriflunomide in instances where (1) pregnancy is confirmed or (2) skin and/or mucosal reactions develop that raise suspicions of severe generalized major skin reactions (e.g., Stevens–Johnson syndrome or toxic epidermal necrolysis), which have been reported with leflunomide but not in clinical trials with teriflunomide [1]. Accelerated elimination of teriflunomide should also be considered after discontinuation of teriflunomide in cases where a serious infection develops, hematologic disorders or severe hematologic reactions occur, confirmed peripheral neuropathy develops, a woman wishes to become pregnant, or a clinically significant overdose or toxicity of teriflunomide occurs [1].

Table 6 Pharmacokinetic interactions of teriflunomide on other substances [1]

Drug category	Example(s)	Effect of teriflunomide	Recommendation while on teriflunomide therapy
CYP1A2 substrate	Caffeine, duloxetine, alosetron, theophylline, tizanidine	• Decrease in mean caffeine C_{max} by 18 % • Decrease in mean caffeine AUC by 55 %	• Use CYP1A2 substrates with caution • Monitor for decreased efficacy
CYP2C8 substrate	Repaglinide, paclitaxel, pioglitazone, rosiglitazone	• Increase in mean repaglinide C_{max} by 1.7-fold • Increase in mean repaglinide AUC by 2.4-fold	• Use CYP2C8 substrates with caution
CYP2C9 substrate	Warfarin	• 25 % decrease in peak INR	• INR follow-up and monitoring required[a]
OAT3 substrate	Cefaclor, benzylpenicillin, ciprofloxacin, indomethacin, ketoprofen, furosemide, cimetidine, methotrexate, zidovudine	• Increase in mean cefaclor C_{max} by 1.43-fold • Increase in mean cefaclor AUC by 1.54-fold	• Use OAT3 substrates with caution
BCRP and/or OATP1B1/B3 substrates	BCRP: rosuvastatin, methotrexate, topotecan, sulfasalazine, daunorubicin, doxorubicin OATP: simvastatin, atorvastatin, pravastatin, methotrexate, nateglinide, repaglinide, rifampicin	• Increase in mean rosuvastatin C_{max} by 2.65-fold • Increase in mean rosuvastatin AUC by 2.51-fold	• Rosuvastatin: reduce dose by 50 % • All other BCRP and OATP1B1/B3 substrates: use with caution
Combined oral contraceptives	Ethinylestradiol/levonorgestrel	• Increase in mean ethinylestradiol C_{max} by 1.58-fold • Increase in mean ethinylestradiol $AUC_{0–24}$ by 1.54-fold • Increase in mean levonorgestrel C_{max} by 1.33-fold • Increase in mean levonorgestrel $AUC_{0–24}$ by 1.41-fold	• No adverse impact expected • Consider when selecting or adjusting oral contraceptives treatment used in combination with teriflunomide

AUC area under the curve, *$AUC_{0–24}$* area under the 24-h concentration–time curve, *BCRP* breast cancer resistant protein, C_{max} maximum concentration, *CYP* cytochrome P450, *INR* international normalized ratio, *OAT* organic anion transporter, *OATP* organic anion transporting polypeptide

[a] There are no data on interaction with phenprocoumon, which is more commonly used in the EU. Given its similarities to warfarin, close INR monitoring is also advisable during concomitant phenprocoumon use

For accelerated elimination, use of cholestyramine 8 g administered three times daily for 11 days or 50 g of activated powdered charcoal every 12 h for 11 days are recommended. Cholestyramine 4 g three times daily can be used if the higher dose is not well tolerated. All described regimens have been shown to decrease teriflunomide plasma concentrations by >98 %, with cholestyramine being faster than charcoal.

It should be noted that patients receiving oral contraceptives while undergoing accelerated elimination should use alternative contraceptive methods because cholestyramine and activated charcoal may negatively affect the absorption of estrogens and progestogens [1].

6 Interaction with Other Medicinal Products

Metabolism studies conducted in vitro have demonstrated that teriflunomide is not directly metabolized by cytochrome P450 (CYP) or flavine monoxidase enzymes [1], which limits the potential for drug–drug interactions. This is a significant factor differentiating teriflunomide from leflunomide. Furthermore, polymorphisms in CYP 2C19 in patients with RA were associated with different levels of metabolism of leflunomide, and poor metabolizers frequently discontinued their treatment due to adverse events [16, 22]. However, teriflunomide co-administration with potent CYP and transport inducers may decrease the amount of teriflunomide exposure and therefore should be used with caution [1]. A list of pharmacokinetic interactions of teriflunomide on other substances is shown in Table 6.

No waiting period is required when initiating teriflunomide after IFNβ or glatiramer acetate, provided there are no laboratory abnormalities. Due to the relatively long-lasting biological activity of natalizumab, concomitant exposure could occur for up to 2–3 months following discontinuation of natalizumab if teriflunomide therapy were initiated immediately. Therefore, caution is required when switching patients from natalizumab to teriflunomide. Based on the half-life of fingolimod, a 6-week interval is needed for clearance from the circulation, and a period of 1–2 months is commonly needed for lymphocytes to return to normal range. Starting teriflunomide within this interval will result in concomitant exposure to fingolimod, which may lead to an additive effect on the immune system [1].

7 Conclusions

Data from the teriflunomide clinical development program support the positive benefit : risk profile of teriflunomide 14 mg in patients with RRMS when prescribed according to the SmPC. Teriflunomide demonstrated significant and consistent efficacy in TEMSO and TOWER. In addition, positive outcomes on several MRI parameters were observed in the TEMSO study. In the TOPIC study, teriflunomide significantly reduced the risk of relapse in patients with a first clinical episode suggestive of MS. These data support the use of teriflunomide in patients in the early stages of relapsing MS. Teriflunomide has a well-characterized safety and tolerability profile. An understanding of pre-treatment evaluations and on-treatment monitoring will ensure optimal outcomes when using teriflunomide in the clinical setting and facilitate identification of potential safety concerns as well as provide guidance for treatment-emergent clinical situations.

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Compliance with Ethical Standards

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Conflicts of interest A. Chan has received compensation for consulting services and speaking honoraria from Allmiral, Bayer Schering Pharma, Biogen Idec, Genzyme, Merk Serono, Novartis Pharma, Sanofi-Aventis, and Teva Pharmaceuticals, and he currently receives research funds from Biogen Idec, Genzyme, and Novartis Pharma. He has served as the country lead investigator (Germany) for TEMSO and TENERE trials (sponsor: Sanofi).
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