Attachment 1: Product information for AusPAR Aubagio/Teriflunomide Winthrop/Teriflunomide Sanofi Teriflunomide Sanofi-Aventis Australia Pty Ltd PM-2011-02772-3-1 Final 21 May 2013. This Product Information was approved at the time this AusPAR was published.

PRODUCT INFORMATION

AUBAGIO

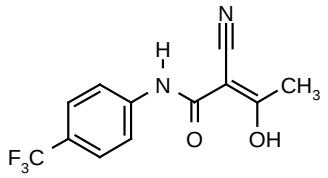
NAME OF THE MEDICINE

AUSTRALIAN APPROVED NAME

Teriflunomide

CHEMICAL STRUCTURE

The chemical structure of teriflunomide is



Molecular formula: $C_{12}H_9F_3N_2O_2$

Molecular weight: 270.21

Chemical name: (Z)-2-Cyano-3-hydroxy-but-2-enoic acid-(4-trifluoromethylphenyl)-amide

CAS REGISTRY NUMBER: 163451-81-8

DESCRIPTION

Teriflunomide, is an oral *de novo* pyrimidine synthesis inhibitor of the dihydroorotate dehydrogenase (DHO-DH) enzyme.

Teriflunomide is a white to almost white powder that is sparingly soluble in acetone, slightly soluble in polyethylene glycol and ethanol, very slightly soluble in isopropanol and practically

insoluble in water. Teriflunomide has a pKa of 3.1 at room temperature and its aqueous solubility is pH dependent and decreases with lowering pH. Teriflunomide is Class 2 in the Biopharmaceutics Classification System.

Teriflunomide is formulated as film-coated tablets for oral administration. Each tablet contains 14 mg of teriflunomide and the following inactive ingredients: lactose, maize starch, hydroxypropylcellulose, microcrystalline cellulose, sodium starch glycollate, and magnesium stearate. The film coating (OPADRY complete film coating system 03F20651 BLUE) is made of hypromellose, titanium dioxide, purified talc, macrogol 8000 and indigo carmine aluminium lake.

PHARMACOLOGY

PHARMACODYNAMICS

Mechanism of Action

Teriflunomide is an immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), required for the *de novo* pyrimidine synthesis. As a consequence teriflunomide blocks the activation and proliferation of stimulated lymphocytes which need *de novo* synthesis of pyrimidine to expand. Slowly dividing or resting cells which rely on the salvage pathway for pyrimidine synthesis are unaffected by teriflunomide. The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood, but may include reduced number of activated lymphocytes in CNS. It is likely that teriflunomide diminishes in periphery the numbers of activated lymphocytes available to migrate into the CNS.

Immune system

Effects on immune cell numbers in the blood

In the placebo controlled studies, teriflunomide 14 mg once a day led to a mild mean reduction in lymphocyte count, of 0.3 x 10^9/L, most of which occurred over the first 3 months of treatment following which levels were maintained until the end of the treatment.

Potential to prolong the QT interval

In a placebo controlled thorough QT study performed in healthy subjects, teriflunomide at mean steady state concentrations did not show any potential for prolonging the QTcF interval compared with placebo: the largest time matched mean difference between teriflunomide and placebo was

3.46 ms with the upper bound of the 90% CI being 6.45 ms. In addition, no QTcF values were ≥480 ms and no changes from baseline were >60 ms.

Effect on renal tubular functions

In the placebo controlled studies, mean decreases in serum uric acid at a range of 20 to 30% were observed in patients treated with teriflunomide compared to placebo. Mean decrease in serum phosphorus was 10% in the teriflunomide group compared to placebo. These effects are considered to be related to increase in renal tubular excretion and not related to changes in glomerular functions.

PHARMACOKINETICS

Absorption

Median time to reach maximum plasma concentrations occurs between 1 to 4 hours post-dose following repeated oral administration of teriflunomide, with high bioavailability (~100%) determined by cross study comparison. Food produced a statistically significant decrease in C_{max} (18%) and an increase in t_{max} (~ 3 hours), that does not have a clinically relevant effect on teriflunomide pharmacokinetics.

Based on individual prediction of pharmacokinetic parameters using the population pharmacokinetic (PopPK) model of teriflunomide in healthy volunteers and MS patients, dose was not a significant covariate of teriflunomide pharmacokinetics.
There is a slow approach to steady-state concentration (i.e. ~100 days [3.5 months] to attain 95% of steady state concentrations, based on a median terminal half-life (t1/2z) of ~19 days calculated from the population pharmacokinetic (PopPK) analysis using data from healthy volunteers and MS patients), and the estimated AUC accumulation ratio is ~ 34-fold for 14 mg teriflunomide.

Distribution

Teriflunomide is extensively bound to plasma protein (>99%), probably albumin and is mainly distributed in plasma, rather than red blood cells. The volume of distribution is low (11 L) after a single intravenous (IV) administration.

Metabolism

Teriflunomide is moderately metabolised and is the only component detected in plasma. The primary biotransformation pathway for teriflunomide is hydrolysis, with oxidation being a minor pathway. Other pathways involve N-acetylation and sulfate conjugation.

Excretion

Teriflunomide is excreted in the gastrointestinal tract mainly through the bile as unchanged drug and possibly by direct secretion. Teriflunomide is a substrate of the efflux transporter Breast Cancer Resistant Protein (BCRP), which could be involved in direct secretion. Over 21 days, 60.1% of the administered dose is excreted via faeces (37.5%) and also via urine (22.6%). After the rapid elimination procedure with cholestyramine, an additional 23.1% was recovered (mostly in faeces). Based on individual prediction of pharmacokinetic parameters using the PopPK model of teriflunomide in healthy volunteers and MS patients, median terminal exponential half-life (t1/2z) was ~ 19 days after repeated doses of 14 mg. After a single IV administration, the total body clearance of teriflunomide is 30.5 mL/h. Biliary recycling is a major contributor to the long elimination half-life of teriflunomide. After a single IV administration, the total body clearance of teriflunomide is 30.5 mL/h. Studies with both haemodialysis and CAPD (chronic ambulatory peritoneal dialysis) indicate that teriflunomide is not dialysable.

Special populations

Gender, Elderly Paediatric patients

Several sources of intrinsic variability were identified in healthy subjects and MS patients based on the population pharmacokinetic analysis: age, body weight, gender, race, and albumin and bilirubin levels. Nevertheless their impact remains limited (£31%).

Hepatic impairment

Mild and moderate hepatic impairment had no impact on the pharmacokinetics of teriflunomide. Therefore no dose adjustment is anticipated in mild to moderate hepatically impaired patients. However, teriflunomide is contraindicated in patients with severe hepatic impairment (see CONTRAINDICATIONS).

Renal impairment

Severe renal impairment had no impact on the pharmacokinetics of teriflunomide. Therefore, no dose adjustment is anticipated in severe renally impaired patients.

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CLINICAL TRIALS

The efficacy of Aubagio was demonstrated in the EFC6049/TEMSO study that evaluated once daily doses of teriflunomide 7 mg and 14 mg. The patient population in this study included those with Relapsing Remitting Multiple Sclerosis and Secondary Progressive Multiple Sclerosis with superimposed relapses.

One thousand eighty-eight patients with RMS were randomised to receive 7 mg (n=366) or 14 mg (n=359) of Aubagio or placebo (n= 363) for 108 weeks duration. All patients had a definite diagnosis (based on MacDonald criteria) of MS exhibiting a relapsing clinical course, with or without progression, and experienced at least 1 relapse over the year preceding the trial or at least 2 relapses over the 2 years preceding the trial. At entry, patients had an Expanded Disability Status Scale (EDSS) score ≤5.5. The mean age of the study population was 37.9 years.
The primary endpoint was the annualised relapse rate (ARR). The annualised relapse rate was significantly lower in patients treated with Aubagio than in patients who received placebo. The key secondary endpoint was the time to disability progression, sustained for 12 weeks. Time to disability progression was statistically significantly reduced in the teriflunomide 14 mg group compared to placebo. A statistically significant difference in disability progression sustained for 24 weeks was not demonstrated. The estimated proportion of patients free of relapses at Week 108 was 45.6% in the placebo group and 56.5% in the teriflunomide 14 mg group. Aubagio effects on magnetic resonance imaging (MRI) variables (burden of disease defined as the total volume of all abnormal brain tissue lesions, and other MRI variables) were assessed. The results indicated that Aubagio 14 mg is more efficacious in disability progression and MRI parameters than Aubagio 7 mg. The results for this study are shown in Table 1 and Figure 1

Table 1 - Clinical and MRI Results of EFC6049/TEMSO Study

	Aubagio 14 mg (N=358*)	Placebo (N=363)	Aubagio 14 mg versus Placebo
Clinical Endpoints			
ARR: adjusted (primary endpoint)	0.369	0.539	RR[a] (95% CI): 0.69 (0.55, 0.85) 0.0005[b]
Probability of disability progression at Week 108	20.2%	27.3%	HR[c] (95% CI): 0.70 (0.51, 0.97) 0.0279[b]
MRI Endpoint			

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	Aubagio 14 mg (N=358*)	**Placebo (N=363)**	**Aubagio 14 mg versus Placebo**
Burden of disease (mL)			
Mean (SD) change from baseline at Week 108	0.723 (7.59)	2.208 (7.00)	
Mean (SD) [LSM (SE)] change in absolute value of cubic root transformed BOD from baseline at Week 108	0.045 (0.30) [0.043 (0.02)]	0.111 (0.31) [0.132 (0.02)]	LSM mean difference (SE) from placebo: -0.089 (0.025) 0.0003[b]
Number of Gd-enhancing T1 lesion per MRI scan at Week 108	0.261	1.331	RR[a] (95% CI): 0.196 (0.120, 0.321) <0.0001[b]
Volume of hypointense T1 lesions (ml)			
Mean (SD) change from baseline at Week 108	0.331 (1.012)	0.533 (1.063)	
LS Mean (SE) change from baseline at Week 108	0.066 (0.009)	0.096 (0.009)	LSM mean difference (SE) from placebo: - 0.030 (0.013) 0.0161[b]

*One patient randomized to teriflunomide 14mg was not treated.
a: Relative risk
b: p value
c: Hazard ratio
ARR – Annualised Relapse Rate
BOD – Burden of disease
HR – Hazard Ratio

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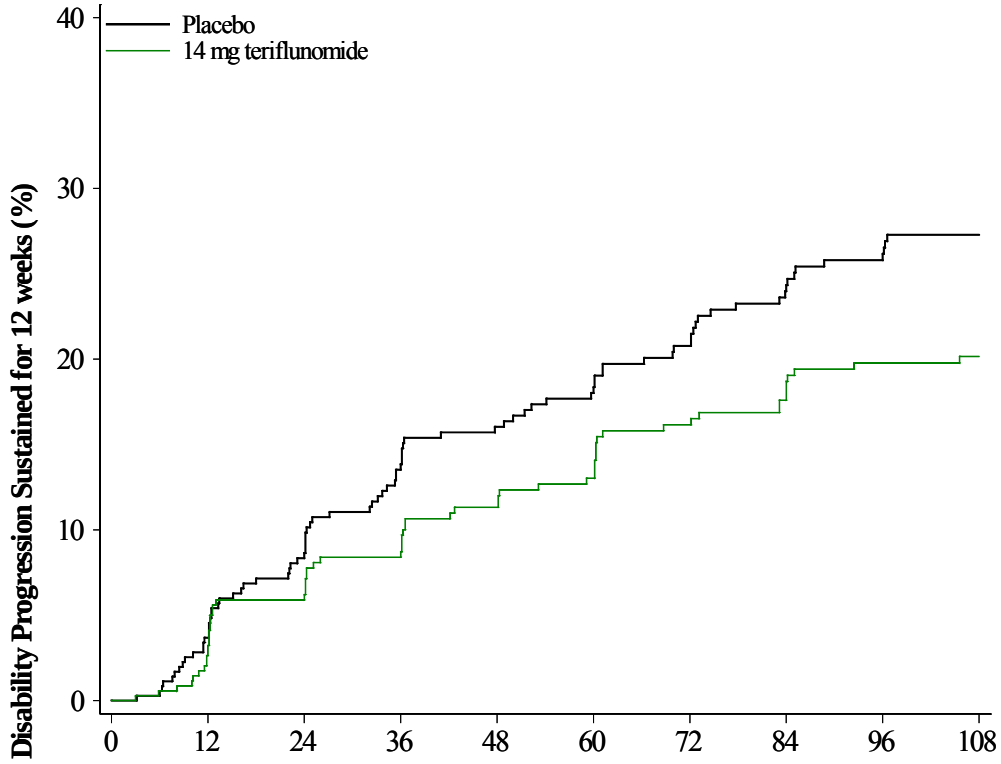
Figure 1 - Kaplan-Meier plot of time to disability progression sustained for 12 weeks - intent-to-treat population



Number at Risk

Placebo	363	336	306	279	258	242	224	211	200	160
14 mg teriflunomide	358	329	302	285	262	251	234	227	217	175

The probability of disability progression at 108 weeks (with 90% CIs) was 0.273 (0.223, 0.323) for placebo and 0.202 (0.156, 0.247) for teriflunomide 14mg.

The Aubagio MRI activity was also shown in a phase 2 study. A total of 179 patients received 7 mg (n=61) or 14 mg (n=57) of Augabio or placebo (n= 61) for 36 weeks duration. Baseline demographics were consistent across treatment groups. The mean number of unique active lesions per brain MRI scan during the 36-week treatment period was lower in patients treated with Aubagio 14 mg (0.98) as compared to placebo (2.69), the difference being statistically significant (p=0.0052).

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INDICATIONS

Aubagio is indicated for the treatment of patients with relapsing forms of Multiple Sclerosis to reduce the frequency of clinical relapses and to delay the progression of physical disability.

CONTRAINDICATIONS

Aubagio must not be given to:

- patients with hypersensitivity to leflunomide, teriflunomide or to any of the excipients in the tablets
- patients with severe immunodeficiency states, e.g. AIDS
- patients with significantly impaired bone marrow function or significant anaemia, leukopoenia or thrombocytopenia
- patients with severe, uncontrolled infections
- patients with severe impairment of liver function
- pregnant women
- women of childbearing potential who are not using reliable contraception during treatment with teriflunomide and for a certain period of time thereafter, as long as the plasma levels of the active metabolite are above 0.02 mg/L, unless undergoing washout treatment (see Use in Pregnancy)
- women who are breast-feeding
- patients with severe hypoproteinaemia
- patients who have or have had Stevens- Johnson syndrome, toxic epidermal necrolysis or erythema multiforme

PRECAUTIONS

Hepatotoxicity

Elevations of liver enzymes have been observed in patients receiving Aubagio. During placebo controlled trials, 3-fold the upper limit of normal (ULN) or greater elevation in liver transaminases (ALT) occurred in 6.1% of patients treated with teriflunomide 14 mg, as compared to 6.2% of patients on placebo. Elevations of 5-fold the ULN (ALT) or greater occurred in 2.6%

of patients on Aubagio and 2.2% of patients on placebo. These elevations occurred mostly within the first year of treatment. In clinical trials, teriflunomide was discontinued if the ALT elevation exceeded 3 times the ULN twice. Serum transaminase levels returned to normal within approximately 2 months after discontinuation of Aubagio.
Very rare cases of severe liver injury, with fatal outcome in isolated cases, have been reported during treatment with leflunomide, the parent compound of teriflunomide. Most of the cases occurred within the first 6 months of treatment. Although confounding factors were present in many cases, a causal relationship to leflunomide and hence teriflunomide cannot be excluded. It is considered essential that monitoring recommendations are strictly adhered to (see Liver function monitoring).

Liver function monitoring

ALT and AST must be checked before the start of Aubagio treatment and monitored at monthly or more frequent intervals for at least the first 6 months and then, if stable, every 6-8 weeks thereafter. For minor elevations in ALT or AST (<2-fold ULN), repeat testing in 2-4 weeks. For moderate elevations in ALT or AST (>2 fold but <3-fold ULN), closely monitor, with LFTs every 2-4 weeks. If ALT or AST elevations of more than 3-fold ULN are present, Aubagio should be discontinued. Cholestyramine or activated charcoal should be administered to more rapidly lower teriflunomide levels, with close monitoring including retreatment with cholestyramine or activated charcoal as indicated.

Blood Pressure

In placebo controlled studies, mean change from baseline for diastolic blood pressure was 1.3 mmHg and for systolic blood pressure was 2.7 mmHg for teriflunomide 14 mg. Blood pressure elevation should be appropriately managed during treatment with Aubagio.

Infections

In placebo controlled studies, no significant increase in serious infections was observed with teriflunomide 14 mg (2.2%) as compared to placebo (2.1%). Serious opportunistic infections occurred in 0.2% in each group.

However, based on the immunomodulatory effect of Aubagio, if a patient develops a serious infection, consider suspending treatment with Aubagio, and reassess the benefits and risks prior to re-initiation of therapy. Due to the prolonged elimination half-life of teriflunomide, accelerated elimination with cholestyramine or charcoal may be considered (See OVERDOSAGE). Instruct patients receiving Aubagio to report symptoms of infections to a physician. Patients with active

acute or chronic infections should not start treatment with Aubagio until the infection(s) is resolved.

Haematologic Effects

A mean decrease affecting white blood cells (WBC) count (<15%, mainly neutrophil and lymphocytes decrease) was observed in placebo controlled trials with Aubagio, although a greater decrease was observed in some patients. The decrease in mean count occurred during the first 6 weeks then stabilized over time while on treatment. The effect on red blood cells (RBC) (<2%) and platelet counts (<10%) was less pronounced. A complete blood cell count (including differential white blood cell count and platelets) should be performed in all patients before the start of Aubagio treatment and monthly for the first 6 months, followed by 6-8 weeks thereafter. In patients with pre-existing anaemia, leukopenia and/or thrombocytopenia as well as in patients with impaired bone marrow function or those at risk of bone marrow suppression, the risk for occurrence of haematological reactions is increased.

Leflunomide Post-marketing Safety Information

The following information has been derived from the Australian prescribing information for Arava® (leflunomide) and may be pertinent to understanding the safety profile of teriflunomide. Leflunomide is the parent compound of teriflunomide (Aubagio). Leflunomide is indicated in the treatment of rheumatoid arthritis. Leflunomide has been evaluated in clinical studies in rheumatoid arthritis and has over 2 million patient-years of cumulative exposure globally in the post marketing setting. The risks associated with use of leflunomide are well characterized in the rheumatoid arthritis population and may provide insight into potential risks of teriflunomide treatment in the MS population. Please refer to the current Australian PI for Arava® (leflunomide) for additional information. The following events have been reported rarely.

- Hepatotoxicity: Reports of severe liver injury, including fatal liver failure
- Haematological Effects: Rare reports of pancytopenia, agranulocytosis and thrombocytopenia in patients receiving leflunomide alone. These events have been reported most frequently in patients who received concomitant treatment with methotrexate or other immunosuppressive agents, or who had recently discontinued these therapies; in some cases, patients had a prior history of a significant hematologic abnormality.
- Risk of Infection: Reports of fatal infections especially Pneumocystis jiroveci pneumonia and aspergillosis have been reported in patients receiving leflunomide. Most of the reports were confounded by concomitant immunosuppressant therapy and/or comorbid illness which, in addition to rheumatoid disease, may predispose patients to infection

- Skin Disorders: Very rare cases of Stevens Johnson syndrome or toxic epidermal necrolysis have been reported in patients treated with leflunomide, the parent compound of Aubagio. As soon as skin and/or mucosal reactions are observed which raise the suspicion of such severe reactions, Aubagio and any other possible associated medication must be discontinued, and cholestyramine or charcoal should be used immediately to reduce the plasma concentration of teriflunomide (see OVERDOSAGE). A complete washout is essential in such cases. In such cases re-exposure to teriflunomide is contra-indicated.

- Respiratory: Interstitial lung disease has been reported during treatment with leflunomide and has been associated with fatal outcomes. The risk of its occurrence is increased in patients with a history of interstitial lung disease.

Immunosuppression

Although there is no clinical experience in the following patient populations, Aubagio is not recommended for patients with severe immunodeficiency, bone marrow dysplasia, or severe uncontrolled infections because of the theoretical potential for immunosuppression. If Aubagio is used in such patients, it should be done with caution and with frequent haematologic monitoring (see Haematological effects). If evidence of bone marrow suppression occurs in a patient taking Aubagio, treatment should be stopped and cholestyramine or charcoal should be used to reduce the plasma concentration of teriflunomide (see OVERDOSAGE)..

In any situation in which the decision is made to switch from Aubagio to another immunomodifying agent with a known potential for haematologic suppression, it would be prudent to monitor for haemotologic toxicity, because there will be overlap of systemic exposure to both compounds. Aubagio washout with cholestyramine or charcoal may decrease this risk but also may induce disease worsening if the patient had been responding to Aubagio treatment. Patients with tuberculin reactivity must be carefully monitored because of the risk of tuberculosis reactivation.

Immunosuppressive or Immunomodulating Therapies

As leflunomide is the parent compound of teriflunomide, co-administration of teriflunomide with leflunomide is not recommended.

Co-administration with antineoplastic or immunosuppressive therapies used for treatment of multiple sclerosis has not been evaluated.

Safety studies in which teriflunomide was concomitantly administered with other immune modulating therapies for up to one year (interferon beta, glatiramer acetate) did not reveal any

specific safety concerns. The long term safety of these combinations in the treatment of multiple sclerosis has not been established.

Hepatic Impairment

Mild and moderate hepatic impairment had no impact on the pharmacokinetics of teriflunomide. No dosage adjustment is necessary for patients with mild or moderate hepatic impairment. Teriflunomide is contraindicated in patients with severe hepatic impairment (see Contraindications).

Renal Impairment

Leflunomide, the parent compound of teriflunomlde was administered as a single oral 100 mg dose to 3 haemodialysis patients and 3 patients on continuous peritoneal dialysis (CAPD). The pharmacokinetics of teriflunomide in CAPD subjects appeared to be similar to healthy volunteers. A more rapid elimination of teriflunomide was observed in haemodialysis subjects which was not due to extraction of drug in the dialysate but instead to displacement of protein binding. Caution should be used when Aubagio is administered to patients with renal impairment.

Vaccination

No clinical data are available on the efficacy and safety of vaccinations under Aubagio treatment. Vaccination with live vaccines is, however, not recommended. A live vaccine should only be given after a period of at least 6 months has elapsed after stopping Aubagio.

Peripheral neuropathy

In placebo-controlled studies, peripheral neuropathy was reported more frequently in patients taking Aubagio than in patients taking placebo. In one 108-week placebo-controlled study in 1086 patients with multiple sclerosis, the incidence of peripheral neuropathy confirmed by nerve conduction studies was 1.9% (6 patients) on 14 mg Aubagio respectively and 0% on placebo. This included polyneuropathy and mononeuropathy (e.g. carpal tunnel syndrome). Treatment was discontinued in one patient with polyneuropathy. There have been reports of peripheral neuropathy reported in patients receiving leflunomide, the parent compound for teriflunomide. If a patient taking Aubagio develops symptoms consistent with peripheral neuropathy, such as bilateral numbness or tingling of hands or feet, consider discontinuing Aubagio therapy and performing an accelerated elimination procedure

Rapid Elimination Procedure

Teriflunomide concentrations measured during an 11-day procedure to accelerate teriflunomide elimination with either 4 g cholestyramine t.i.d, 8 g cholestyramine t.i.d or 50 g activated charcoal b.i.d following cessation of teriflunomide treatment have shown that these regimens were effective in accelerating teriflunomide elimination, leading to more than 98% decrease in teriflunomide plasma concentrations, with cholestyramine being faster than charcoal. In association with this procedure a higher incidence among patients taking teriflunomide 14mg was seen of the AEs nausea (3.3% vs 1.5% placebo), vomiting (2.4% vs 0% placebo), and increased ALT (1.6% vs. 0 placebo). When desired, elimination can be accelerated by any of the following procedures: (See Overdosage - Rapid Elimination Procedure: Cholestyramine and activated charcoal).

Administration of cholestyramine 4 g or 8 g every 8 hours for 11 days or by 50 g oral activated charcoal powder administered every 12 hours for 11 days (days do not need to be consecutive unless there is a need to lower teriflunomide plasma concentration rapidly).

If cholestyramine 8 g three times a day is not well tolerated, cholestyramine 4 g three times a day can be used.

Both cholestyramine and activated charcoal may influence the absorption of oestrogens and progestogens such that reliable contraception with oral contraceptives may not be guaranteed during the washout procedure with cholestyramine and activated charcoal. Use of alternative contraceptive methods is recommended.

Plasma monitoring

After the wash-out procedure has been performed, teriflunomide plasma levels of < 0.02 mg/L must be verified by 2 separate tests at least 14 days apart. Human teriflunomide plasma concentrations less than or equal to 0.02 mg/L are expected to have minimal risk based on available data. Without the drug elimination procedure, it may take up to 2 years to reach teriflunomide concentrations <0.02 mg/L (after stopping treatment with Aubagio), due to individual variation in drug clearance. However, verification of teriflunomide levels <0.02 mg/L by 2 separate tests at an interval of at least 14 days is required

In pregnant women and women currently attempting to become pregnant, plasma concentrations should be verified to be equal or less than 0.02 mcg/mL. If plasma concentrations are higher than 0.02 mcg/mL, additional elimination should be considered.

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Effects on Fertility

Oral administration of teriflunomide 10mg/kg/day (about 6 times the RHD based on mg/m2) to male rats impaired spermatogenesis but had no effect on fertility; the no-effect dose was 3mg/kg/day. Oral treatment of female rats with teriflunomide from two weeks prior to mating through to implantation (gestation day 6) caused almost complete embryofoetal death and isolated malformations in surviving fetuses at doses of 2.6mg/kg/day and above (about twice the RHD based on mg/m2; the no-effect dose was 0.84mg/kg/day. Estimated systemic exposure (plasma AUC) in these studies was less than anticipated clinical exposure.

Use in pregnancy (Category X)

As teriflunomide is teratogenic in rats and rabbits, it may cause foetal harm in humans. Aubagio must not be given to pregnant women, or women of childbearing potential who are not using reliable contraception during treatment with Aubagio and for a certain period of time thereafter as long as the plasma levels of the active metabolite are above 0.02 mg/L, unless undergoing washout treatment (waiting period or abbreviated wash-out period; see below). Pregnancy must be excluded before the start of treatment with Aubagio.

It is recommended that women of childbearing potential only receive Aubagio after it has been confirmed that they are using a reliable form of contraception. In a study in which leflunomide, the parent compound of teriflunomide, was given to healthy female volunteers concomitantly with a triphasic oral contraceptive pill containing 30 µg ethinyloestradiol, there was no reduction in contraceptive activity of the pill, and teriflunomide pharmacokinetics were within predicted ranges.

Patients must be advised that if there is any delay in the onset of menses or any other reason to suspect pregnancy, they must notify their physician immediately to test for pregnancy. If the test is positive, the physician and patient must discuss the risk to the foetus. It is possible that by rapidly lowering the blood level of the active metabolite at the first delay of menses, using the drug elimination procedure described below, the risk to the foetus may be decreased

Human Experience

There is limited human experience from clinical studies with Aubagio. A total of 31 patients became pregnant during clinical studies while using teriflunomide. A total of 7 patients were reported having pregnancy with live birth outcome. All of these patients underwent an accelerated elimination procedure. Maternal exposure to teriflunomide was between 5 weeks and 489 weeks. The foetal exposure was from a few days to 11 weeks prior to the accelerated elimination procedure. All seven patients exposed to teriflunomide gave birth to normal healthy newborns,

without evidence of structural or functional defects. Of the remaining pregnancies, 13 were electively terminated, 8 resulted in miscarriages and three were ongoing. Due to the limited nature of these data no firm conclusions can be drawn regarding the use of teriflunomide in pregnant women. Aubagio is contraindicated in women who are pregnant or currently attempting to become pregnant (see CONTRA-INDICATIONS).

Pregnancy Registry

A pregnancy registry has been established to collect information about the effect of Aubagio use during pregnancy. If physicians or patients become aware of pregnancy during treatment with Aubagio, they are encouraged to enrol the patient in the Aubagio pregnancy registry.

Labour and Delivery

There is no adequate information regarding the effects of Aubagio on labour and delivery in pregnant women.

Use in Lactation

Animal studies indicate that teriflunomide passes into milk and can cause harm to the developing neonate at subclinical maternal exposures. Up to 23% of a maternal dose was ingested by suckling rat pups. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Aubagio, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Use in males

The risk of male-mediated embryo-foetal toxicity through teriflunomide treatment is considered low. The estimated female plasma exposure via the semen of a treated patient is expected to be 100 times lower than the plasma exposure observed at steady state after 14 mg of oral teriflunomide. There were no external malformations in the offspring of male rats administered teriflunomide for at least 10 weeks prior to mating with untreated female rats at oral doses up to 10mg/kg/day (about 6 times the RHD based on mg/m^2).

Paediatric Use

The safety and effectiveness of Aubagio in paediatric patients with MS below the age of 18 years have not yet been established.

Use in the elderly

Clinical studies of Aubagio did not include patients over 65 years old. Aubagio should be used with caution in patients aged over 65 years.

Genotoxicity

Teriflunomide was not mutagenic in bacteria (Salmonella typhimurium and Escherichia coli) or in Chinese hamster lung cells *in vitro* and did not cause chromosomal damage *in vivo* (mouse, rat and Chinese hamster bone marrow cells). A positive effect was found in a chromosomal damage *in vitro* assay in human lymphocytes, but the significance of this is unclear.

4-Trifluoromethylaniline (4-TFMA), a minor metabolite of teriflunomide, was positive in assays for gene mutation (bacteria and Chinese hamster cells) and for chromosome aberration at high *in vitro* concentrations (Chinese hamster cells), but negative in the unscheduled DNA synthesis test and it was not clastogenic *in vivo* in mice (micronucleus test) and Chinese hamsters (chromosome aberration test).

Carcinogenicity

No evidence of carcinogenicity was observed in a 2 year bioassay in rats at oral doses of teriflunomide up to the maximally tolerated dose of 4 and 12 mg/kg/day respectively. Respective systemic exposures in these studies were about 30% and 3-fold the maximum human teriflunomide exposure based on plasma AUC_{0-24}). The risk of malignancy, particularly lymphoproliferative disorders, is increased with the use of some immunosuppressant medications. There is a potential for immunosuppression with Aubagio. Large, long-term studies would be needed to determine whether there is an increased risk of malignancy or lymphoproliferative disorders with Aubagio.

INTERACTIONS WITH OTHER MEDICINES

The primary biotransformation pathway for teriflunomide is hydrolysis, with oxidation being a minor pathway. The extensive protein binding of teriflunomide could lead to displacement of other highly bound drugs.

Potential for Other Drugs to affect Teriflunomide

Potent CYP and transport inducers

Co-administration of repeated doses (600 mg once daily for 22 days) of rifampicin (a CYP2B6, 2C8, 2C9, 2C19, 3A inducer, as well as an inducer of the efflux transporters P-gp and BCRP) and teriflunomide (70 mg single dose) resulted in an approximately 40% decrease in teriflunomide exposure**.** Rifampicin and other known potent CYP and transporter inducers such as carbamazepine, phenobarbital, phenytoin and St John's Wort should be used with caution during the treatment with teriflunomide.

Potential for Teriflunomide to affect other drugs

Repeated administration of teriflunomide was used to assess the effect of teriflunomide on the exposure of other drugs. The regimen used resulted in teriflunomide plasma concentrations which were in the range of the ones observed in patients after repeated doses of 14 mg teriflunomide.

CYP2C8 substrates: repaglinide

There was an increase in mean repaglinide Cmax and AUC (1.7- and 2.4-fold, respectively), following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of CYP2C8 *in vivo*. Therefore, drugs metabolised by CYP2C8, such as repaglinide, paclitaxel, and pioglitazone should be used with caution during the treatment with teriflunomide.

CYP3A substrates: midazolam

There was an increase in mean midazolam Cmax and AUC (1.13- and 1.27-fold, respectively), following repeated doses of teriflunomide, suggesting that teriflunomide is a weak inhibitor of CYP3A *in vivo*.

Oral contraceptive: 0.03mg ethinyloestradiol and 0.15mg levonorgestrel

There was an increase in mean ethinyloestradiol Cmax and AUC_{0-24} (1.58- and 1.54-fold, respectively) and levonorgestrel Cmax and AUC_{0-24} (1.33- and 1.41-fold, respectively) following repeated doses of teriflunomide. While this interaction of teriflunomide is not expected to adversely impact the efficacy of oral contraceptives, consideration should be given to the type or dose of oral contraceptives used in combination with teriflunomide.

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CYP1A2 substrates: caffeine

Repeated doses of teriflunomide decreased mean Cmax and AUC of caffeine (CYP1A2 substrate) by 18% and 55%, respectively, suggesting that teriflunomide may be *in vivo* a weak inducer of CYP1A2. Therefore, drugs metabolised by CYP1A2 (such as duloxetine, ondansetron, theophylline and agomelatine) should be used with caution during treatment with teriflunomide, as it could lead to the reduction of efficacy of these drugs.

CYP2C9 substrates: S-warfarin

Repeated doses of teriflunomide had no effect on the pharmacokinetics of S-warfarin, indicating that teriflunomide is not an inhibitor or an inducer of CYP2C9. However, a 25% decrease in peak international normalized ratio (INR) was observed when teriflunomide was co-administered with warfarin as compared with warfarin alone. Therefore, when warfarin is co-administered with teriflunomide, close INR follow-up and monitoring is recommended.

CYP2B6 substrates: bupropion

Repeated doses of teriflunomide had no effect on the pharmacokinetics of bupropion. Based on *in vivo* data, teriflunomide is not considered as an inhibitor or an inducer of CYP2B6 at the anticipated therapeutic dose.

CYP2C19 substrates: omeprazole

Repeated doses of teriflunomide had no effect on the pharmacokinetics of omeprazole. Based on *in vivo* data, teriflunomide is not considered an inhibitor or an inducer of CYP2C19 at the anticipated therapeutic dose.

CYP2D6 substrates: metoprolol

Repeated doses of teriflunomide had no effect on the pharmacokinetics of metoprolol. Based on *in vitro* and *in vivo* data, teriflunomide is not considered as a CYP2D6 inhibitor at the anticipated therapeutic dose.

NSAIDS

NSAIDS (including COX-2 inhibitors) are known to cause hepatotoxicity, therefore caution is advised when Aubagio is used concomitantly. Studies showed that ibuprofen and diclofenac did not displace teriflunomide. Teriflunomide displaced ibuprofen and diclofenac and the unbound fraction of these drugs was increased by 10 - 50%. In clinical trials, no safety problems were

observed when leflunomide, the parent compoud of teriflunomide and NSAIDs metabolised by CYP2C9 were co-administered.

ADVERSE EFFECTS

The most frequent adverse reactions for Aubagio (incidence ≥10% and a difference with placebo using relative risk >1.0 and lower limit of 95% confidence interval >1.0) were diarrhoea, ALT increased, nausea, and alopecia in the placebo controlled studies. In general, diarrhoea, nausea and alopecia, were mild to moderate, transient and infrequently led to treatment discontinuation.

If desired, teriflunomide can be rapidly cleared from the body by the use of the rapid elimination procedure (see OVERDOSAGE).

Clinical Trial Experience

A total of 844 patients on teriflunomide (7 or 14 mg once daily) constituted the safety population in the pooled analysis of placebo controlled studies in patients with relapsing forms of MS (RMS).

The EFC6049/TEMSO study was a 108-week placebo controlled clinical study in 1086 RMS patients treated with teriflunomide 7 mg (n=368), teriflunomide 14 mg (n=358) or placebo (n=360).

Table 2 - Adverse Reactions in EFC6049/TEMSO Study (occurring in ≥1% of patients, and reported for teriflunomide 14 mg at ≥1% higher rate than for placebo)

PRIMARY SYSTEM ORGAN CLASS Preferred Term n (%)	teriflunomide 14 mg (N=358)	Placebo (N=360)
Infections and Infestations		
Influenza	43 (12.0%)	36 (10.0%)
Upper respiratory tract infection	32 (8.9%)	25 (6.9%)
Bronchitis	29 (8.1%)	22 (6.1%)
Sinusitis	23 (6.4%)	16 (4.4%)
Gastroenteritis	21 (5.9%)	17 (4.7%)
Cystitis	13 (3.6%)	5 (1.4%)
Gastroenteritis viral	13 (3.6%)	5 (1.4%)
Oral herpes	13 (3.6%)	6 (1.7%)

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PRIMARY SYSTEM ORGAN CLASS Preferred Term n (%)	teriflunomide 14 mg (N=358)	Placebo (N=360)
Rhinitis	12 (3.4%)	7 (1.9%)
Ear infection	8 (2.2%)	4 (1.1%)
Lower respiratory tract infection	8 (2.2%)	4 (1.1%)
Tooth infection	7 (2.0%)	2 (0.6%)
Laryngitis	5 (1.4%)	1 (0.3%)
Tinea pedis	5 (1.4%)	1 (0.3%)
Blood and lymphatic system disorders		
Neutropenia	16 (4.5%)	1 (0.3%)
Immune system disorders		
Seasonal allergy	11 (3.1%)	5 (1.4%)
Psychiatric disorders		
Depression	33 (9.2%)	28 (7.8%)
Anxiety	15 (4.2%)	7 (1.9%)
Nervous system disorders		
Paraesthesia	35 (9.8%)	30 (8.3%)
Sciatica	10 (2.8%)	4 (1.1%)
Burning sensation	9 (2.5%)	5 (1.4%)
Carpal tunnel syndrome	9 (2.5%)	1 (0.3%)
Multiple sclerosis	7 (2.0%)	3 (0.8%)
Neuralgia	5 (1.4%)	0
Eye disorders		
Vision blurred	10 (2.8%)	5 (1.4%)
Cardiac disorders		
Tachycardia	6 (1.7%)	2 (0.6%)
Vascular disorders		
Hypertension	13 (3.6%)	6 (1.7%)
Gastrointestinal disorders		
Diarrhoea	64 (17.9%)	32 (8.9%)
Nausea	49 (13.7%)	26 (7.2%)

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PRIMARY SYSTEM ORGAN CLASS Preferred Term n (%)	teriflunomide 14 mg (N=358)	Placebo (N=360)
Abdominal pain upper	20 (5.6%)	15 (4.2%)
Vomiting	18 (5.0%)	14 (3.9%)
Toothache	15 (4.2%)	8 (2.2%)
Inguinal hernia	4 (1.1%)	0
Skin and subcutaneous tissue disorders		
Alopecia[a]	47 (13.1%)	12 (3.3%)
Rash	19 (5.3%)	15 (4.2%)
Acne	10 (2.8%)	5 (1.4%)
Pruritus	10 (2.8%)	6 (1.7%)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	16 (4.5%)	11 (3.1%)
Myalgia	12 (3.4%)	6 (1.7%)
Renal and urinary disorders		
Pollakiuria	8 (2.2%)	2 (0.6%)
Reproductive system and breast disorders		
Menorrhagia	7 (2.0%)	2 (0.6%)
General disorders and administration site conditions		
Pain	7 (2.0%)	2 (0.6%)
Investigations		
Alanine aminotransferase increased	51 (14.2%)	24 (6.7%)
Gamma-glutamyltransferase increased	12 (3.4%)	5 (1.4%)
Aspartate aminotransferase increased	10 (2.8%)	5 (1.4%)
Weight decreased	7 (2.0%)	3 (0.8%)
Neutrophil count decreased	6 (1.7%)	1 (0.3%)
White blood cell count decreased	4 (1.1%)	0
Injury, poisoning and procedural complications		
Post-traumatic pain	8 (2.2%)	2 (0.6%)

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	teriflunomide	
PRIMARY SYSTEM ORGAN CLASS	**14 mg**	**Placebo**
Preferred Term n (%)	**(N=358)**	**(N=360)**

a: most cases reported as hair thinning, decrease hair density, hair loss, associated or not with hair texture change, most often described as diffuse or generalized over the scalp (no complete hair loss reported) with a high probability of occurrence during the first 6 months with spontaneous resolution even on-treatment for some patients or after study medication discontinuation for others.

Clinically relevant adverse reactions in the TEMSO study, including uncommon reactions listed in CIOMS format by System Organ Class is shown in Table 3.

The following CIOMS frequency rating is used, when applicable:

Very common ³ 10 %; Common ³ 1 and <10 % ; Uncommon ³ 0.1 and < 1 %; Rare ³ 0.01 and < 0.1 %; Very rare < 0.01 %, Unknown (cannot be estimated from available data).

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Table 3 - Adverse Reactions in EFC6049/TEMSO Study in CIOMS format

System organ class	Very common (≥ 1/10)	Common (≥ 1/100 to <1/10)	Uncommon (≥ 1/1000 to <1/100)
Infections and Infestations	Influenza	Upper respiratory tract infection,	
		Bronchitis,	
		Sinusitis,	
		Gastroenteritis,	
		Cystitis,	
		Gastroenteritis viral,	
		Oral herpes	
		Rhinitis	
		Ear infection	
		Lower respiratory tract infection	
		Tooth infection	
		Laryngitis	
		Tinea pedis	
Blood and lymphatic system disorders		Neutropenia	Lymphopenia
Immune system disorders		Seasonal allergy	
Metabolism and nutrition disorders			Hyperamylasaemia
Psychiatric disorders		Depression	
		Anxiety	
Nervous system disorders		Paraesthesia	Dysgeusia
		Sciatica	Neuropathy peripheral
		Burning sensation	Polyneuropathy
		Carpal tunnel syndrome	
		Multiple sclerosis	
		Neuralgia	
Eye disorders		Vision blurred	
Cardiac disorders		Tachycardia	

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System organ class	Very common (≥ 1/10)	Common (≥ 1/100 to <1/10)	Uncommon (≥ 1/1000 to <1/100)
Vascular disorders		Hypertension	
Gastrointestinal disorders	Diarrhoea	Abdominal pain upper	
	Nausea	Vomiting	
		Toothache	
		Inguinal hernia	
Skin and subcutaneous tissue disorders	Alopecia	Rash	Pruritus generalised
		Acne	
		Pruritus	
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	
Investigations	Alanine aminotransferase increased	Gamma-glutamyltransferase increased	Blood creatinine increased
		Aspartate aminotransferase increased	
		Weight decreased	
		Neutrophil count decreased	
		White blood cell count decreased	
Injury, poisoning and procedural complications		Post-traumatic pain	

Polyneuropathy

In placebo controlled studies, 0.7% of patients treated with teriflunomide 14 mg displayed symptoms of suspected polyneuropathy (0% in the placebo group).

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DOSAGE AND ADMINISTRATION

The recommended dose of Aubagio is 14mg orally once daily. Aubagio can be taken with or without food.

SPECIAL POPULATIONS

Children

The safety and efficacy of Aubagio in paediatric patients with MS below the age of 18 years has not yet been established.

Elderly

Clinical studies of Aubagio did not include patients over 65 years old. Aubagio should be used with caution in patients aged over 65 years.

Hepatic Impairment

No dosage adjustment is necessary for patients with mild or moderate hepatic impairment. Teriflunomide is contraindicated in patients with severe hepatic impairment (see Precautions).

Renal Impairment

No dosage adjustment is necessary for patients with severe renal impairment (see PRECAUTIONS – Renal impairment).

OVERDOSAGE

There is no experience regarding teriflunomide overdose or intoxication in humans. Teriflunomide 70 mg daily up to 14 days was well tolerated by healthy subjects.

In the event of relevant overdose or toxicity, cholestyramine or activated charcoal is recommended to accelerate elimination (see PRECAUTIONS).

Rapid Elimination Procedure: Cholestyramine and activated charcoal

The elimination of teriflunomide from the circulation can be accelerated by administration of cholestyramine or activated charcoal, presumably by interrupting the reabsorption processes at the

intestinal level. Teriflunomide concentrations measured during an 11-day procedure to accelerate teriflunomide elimination with either 4 g cholestyramine t.i.d, 8 g cholestyramine t.i.d or 50 g activated charcoal b.i.d following cessation of teriflunomide treatment have shown that these regimens were effective in accelerating teriflunomide elimination, leading to more than 98% decrease in teriflunomide plasma concentrations, with cholestyramine being faster than charcoal. In association with this procedure a higher incidence among patients taking teriflunomide 14mg was seen of the AEs nausea (3.3 vs 1.5% placebo), vomiting (2.4% vs 0% placebo), increased ALT (1.6% vs. 0 placebo). The choice between the 3 elimination procedures should depend on the patient's tolerability. If cholestyramine 8 g three times a day is not well tolerated, cholestyramine 4 g three times a day can be used. Alternatively, activated charcoal may also be used (The 11 days do not need to be consecutive unless there is a need to lower teriflunomide plasma concentration rapidly).

For information on the management of overdose, contact the Poison Information Centre on 131126.

PRESENTATION AND STORAGE CONDITIONS

Aubagio is available as pale blue to pastel blue, pentagonal film-coated tablets with "14" imprinted on one side and engraved with a logo on the other.

Aubagio is supplied as:

84 tablets in a carton containing 3 wallets of 2 folded polyamide/aluminium/polyvinylchloride blisters of 14 tablets per blister*.

28 tablets in a carton containing 1 wallet composed of 2 folded polyamide/aluminium/polyvinylchloride blisters of 14 tablets per blister.

14 tablets in a carton containing 1 wallet composed of 1 polyamide/aluminium/polyvinylchloride blister of 14 tablets per blister*.

10 tablets in a carton containing 2 polyamide/aluminium/polyvinylchloride blister of 5 tablets*.

5 tablets in a carton containing 1 polyamide/aluminium/polyvinylchloride blister of 5 tablets*.

Store below 30 degrees Celsius.

* Not marketed

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NAME AND ADDRESS OF SPONSOR

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Macquarie Park NSW 2113
Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE ARTG

14 November 2012

DATE OF MOST RECENT AMENDMENT

12 December 2012