Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Teriflunomide

Proprietary Product Name: Aubagio/ Teriflunomide Winthrop/Teriflunomide Sanofi

Sponsor: Sanofi-Aventis Australia Pty Ltd

May 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission:	New Chemical Entity
Decision:	Approved
Date of Decision:	30 October 2012
Active ingredient:	Teriflunomide
Product Names:	Aubagio/Teriflunomide Withnrop/Teriflunomide Sanofi
Sponsor's Name and Address:	Sanofi-Aventis Australia Pty Ltd Talavera Corporate Centre, Building D 12-24 Talavera Road Macquarie Park NSW 2113
Dose form:	Film coated tablet
Strength:	14 mg
Container:	Blister pack
Pack sizes:	5, 10, 14, 28, 84
Approved Therapeutic use:	Aubagio/Teriflunomide Winthrop/Teriflunomide Sanofi/ 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.

Route of administration:	Oral
Dosage:	14 mg [one tablet] once daily
ARTG Numbers:	192672, 191696, 191700

Product background

Teriflunomide is an immunosuppressant agent proposed for the treatment of patients with multiple sclerosis (MS). The main mechanism underlying the immunosuppressant activity of teriflunomide is reversible inhibition of the mitochondrial dihydroorotate dehydrogenase (DHO-DH) enzyme, which results in inhibition of the *de novo* synthesis of pyrimidine. This limits the availability of pyrimidines for cell turnover and affects the ability of cells to proliferate and differentiate.

Teriflunomide is the active, predominant metabolite of the immunosuppressant, leflunomide, which has been registered since 1998 for the treatment of rheumatoid arthritis. Although leflunomide itself is also pharmacologically active, it is rapidly and almost completely converted *in vivo* to the open-ring form (teriflunomide) and therefore virtually all of the activity of leflunomide is due to teriflunomide.

This AusPARs describes the application by Sanofi-Aventis Australia Pty Ltd (the sponsor) to register film coated tablets (under the product names Aubagio, Teriflunomide Winthrop and Teriflunomide Sanofi) containing 14 mg teriflunomide for the following indication, as stated in the sponsor's letter of application:

> *for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical relapses and to delay the accumulation of physical disability.*

The proposed dose is one 14 mg tablet per day.

Regulatory status

The product received initial registration in the Australian Register of Therapeutic Goods (ARTG) on 14th November 2012. At the time of the current application, teriflunomide was not registered anywhere in the world. Applications for registration were submitted to the USA (August 2011), European Union (EU; February 2012), Switzerland (March 2012) and 5 other countries. The proposed indication in Australia is identical to that planned for submission in the EU. In the USA the submitted indication differs in the use of the term 'clinical exacerbations', versus clinical relapses.

Product Information

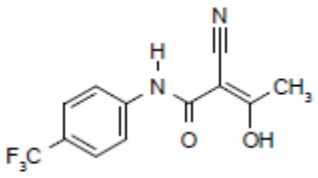
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

Teriflunomide has the following structure:

Figure 1. Structure of teriflunomide



It contains no chiral centres, but can exist in Z and E isomers. In the solid state teriflunomide is in the Z isomeric form (shown above). It is a Class 2 substance in the Biopharmaceutics Classification System, with low aqueous solubility at low pH. Matters relating to particle size requirements and impurity limits have been satisfactorily addressed.

Drug product

The tablets are pale blue to pastel blue pentagonal film coated tablets with "14" imprinted on one side and engraved with a logo on the other, manufactured by a conventional process. The specifications include a dissolution test. The finished product specification for the specified impurity is in line with relevant International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines. Shelf life and storage conditions of 24 months below 30°C have been assigned to the tablet in the proposed blister packs.

Biopharmaceutics

An absolute bioavailability study was not performed because of the high permeability of the drug allowing for an expectation of nearly complete absorption in humans and because > 98% of ^{14}C-labelled drug was recovered from faeces following administration of an oral dose. Three bioavailability studies were submitted (Table 1 below).

Table 1. Bioavailability studies of teriflunomide

Study Number	Comments
BEQ10169	Comparative bioavailability between tablets made with or without silica
BDR6639	Comparative bioavailability between tablets made with unmilled product and tablets made with milled product
ALI6504	Investigation of food effect (7 and 14 mg doses)

Study BEQ10169 showed that the 14 mg tablet proposed for registration is bioequivalent in, terms of the maximum plasma concentration (Cmax) and area under the concentration versus time curve (AUC), to an earlier development formulation containing silica under fasting conditions.

Study BDR6639 compared tablets manufactured from milled active pharmaceutical ingredient (API) to those manufactured from unmilled API under fasting conditions. The two formulations were shown to be bioequivalent.

Study ALI6504 investigated the effect of food; no effect was found in relation to AUC, but Cmax was reduced (from 1.70 µg/mL down to 1.47 µg/mL), and time to reach maximum plasma concentration (Tmax) increased (from 1.5 h up to 6.3 hrs) following administration of the 14 mg tablet in the fed state.

Advisory committee considerations

The pharmaceutical chemistry and quality aspects of the application were considered by the Pharmaceutical Sub-Committee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) at its meeting in March 2012. All questions raised by the TGA were endorsed by the PSC and the submission was not requested to be presented to the PSC for further consideration.

Quality summary and conclusions

Approval of this submission with respect to chemistry and quality control is recommended. With regard to biopharmaceutics, the PI reflects the results of the bioavailability and absorption studies.

III. Nonclinical findings

Introduction

Previously evaluated nonclinical studies established that the activity of leflunomide is accounted for mainly (> 95%) by the open-ring form, teriflunomide. Nevertheless, a full dossier of nonclinical toxicity studies has been performed to support the registration of teriflunomide in its own right. These adequately defined the toxicity profile of teriflunomide in animal species that were demonstrated to be relevant human models in terms of pharmacokinetics (PK) and (based mainly on previously evaluated studies) in terms of primary pharmacological activity.

Nonclinical studies included several toxicity studies of teriflunomide (then called A77 1726) from the previous dossier to support the registration of leflunomide. These, as well as other studies that were not re-submitted but were detailed in the leflunomide TGA nonclinical evaluation report, allowed the profile of teriflunomide to be assessed and compared across a range of early and more recent studies that were conducted according to regulatory standards.

Pharmacology

Mechanistic studies show that teriflunomide has immunosuppressant activity and may be beneficial in disorders particularly with a T cell proliferation component. Efficacy studies in animal models of a disease that resembles MS in humans supported the hypothesis that teriflunomide might be efficacious in humans with MS; whether or not this is the case will rely on human clinical trial data. Animal studies provided limited or no information on the course of the disease with long-term treatment or once treatment is withdrawn.

Studies evaluated previously and those submitted in the teriflunomide dossier suggest that teriflunomide has little potential for off-target pharmacological activity, which is consistent with findings in toxicity studies where the primary effects can be attributed to suppression of rapidly dividing cells. While a diuretic effect was observed in a rat safety

pharmacology study, and teriflunomide was found to inhibit urate transport through the apical urate/anion exchanger, the kidney did not feature as a primary target organ for the effects of teriflunomide.

Pharmacokinetics

The PK profiles of teriflunomide in the animal species used in the pivotal repeat-dose toxicity studies were sufficiently similar to humans to allow them to serve as appropriate models for the assessment of teriflunomide toxicity. At a given oral (PO) dose, exposure to teriflunomide was generally lower in animals than in humans, possibly as a result of faster clearance and/or differences in the extent of enterohepatic re-circulation. In addition, animals are substantially more sensitive to the pharmacological activity (DHO-DH inhibition) of teriflunomide, and therefore exposure greatly in excess of that expected in humans is not feasible because of unacceptable toxicity, including death. Nevertheless the species used in all toxicity studies are valid for assessing the potential toxicity profile of teriflunomide covering the range of doses up to the maximum tolerated dose (MTD). Exposure to the only circulating human metabolite, 4-trifluoro methyline (4-TFMA), was variable in animals; however a specific toxicity study was performed with 4-TFMA exposure well in excess of that anticipated in humans.

Toxicology

The toxicology program for teriflunomide was consistent with contemporary regulatory standards in terms of species used, study durations, route and frequency of dosing. Deviations in some studies (for example, increases in dose-levels as the study progressed; early termination of treatment and/or study groups) did not detract from the validity of the overall program; however, such deviations may have been considered major flaws if there was not a large body of relevant information (that is, for leflunomide) already available.

The primary toxicities associated with teriflunomide treatment can be attributed to its pharmacological effect of inhibiting cellular proliferation. Details of the studies performed and of the histopathological findings are in Table 2, below, along with estimates of exposure to teriflunomide.

Table 2. Overview of repeat dose toxicity and carcinogenicity studies, with kinetic data

Report no. (date); GLP status	Study duration, route; doses teriflunomide (mg/kg/day)	Teriflunomide Cmax (µg/mL) at respective doses	Teriflunomide AUC (µg.h/mL) at respective doses	Main target organs / effects
Mouse (CD-1) Male (M) / Female (F)				
2004-0511 (Apr 2006); GLP; day 85 kinetic data	3 months PO range finding study; 0, 5, 25, 50, 75	90 / 66 234 / 263 239 / 261 (day 1) 290 / 323 (day 1)	1660 / 1040 4520 /4880 4670 / 5090 (day 1) 6140 / 6760 (day 1)	Haematopoietic tissues/organs (bone marrow hypocellularity and spleen necrosis/ atrophy); lymphoid tissues/organs (thymus and lymph node necrosis and atrophy); intestinal tract (degeneration/ regeneration /glandular necrosis/ulcer /inflammation); liver (hepatocyte centrilobular hypertrophy and (at fatal doses) single cell necrosis), reproductive organs (degeneration, atrophy). Deaths at ≥ 50 mg/kg/day. NOEL not established.
CAR0092 (Jun 201); GLP; day 29 kinetic data	2 year PO (carcinogenicity study); 0, 1, 4, 12	9.7 / 9.0 57 / 48 232 / 204	162 / 184 1020 / 828 3600 / 3120	Skin (ulcer), GI tract (atrophic changes), thymus (atrophy), liver (granuloma, inflammatory cell infiltrate), bone marrow (granulopoiesis), heart (bacteria and thrombus), kidney (↑ incidence of chronic progressive nephropathy), generalised amyloidosis. ↑ mortality at 12

Report no. (date); GLP status	Study duration, route; doses teriflunomide (mg/kg/day)	Teriflunomide Cmax (µg/mL) at respective doses	Teriflunomide AUC (µg.h/mL) at respective doses	Main target organs / effects
				mg/kg/day. NOAEL 1 mg/kg/day. No neoplastic findings.
Rat M / F				
017716 (Jun 1999); GLP; day 30 kinetic data	3 months PO in Wistar rats; 0, 0.5, 1, 4	2.4 / 2.8 4.7 / 5.7 17 / 21	35 / 38 71 / 70 217 / 202	Red blood cell parameters (marginal ↓), liver (marginal ↑ in weight) at HD. NOAEL 4 mg/kg/day.
2003-1492 (Sep 2005); GLP; day 181 kinetic data	6 months PO in SD rats; 0, 0.3, 1.5 (↑ to 9 at week 15), 3, 6	1.5 / 1.8 8.6 / 9.4 (day 90) and 40 / 49 20 / 21 33 / 33	26 / 29 102 / 124 (day 90) and 487 / 568 240 / 330 342 / 418	Atrophic changes in haematopoietic tissues/organs, spleen; lymphoid tissues/organs; intestinal tract and reproductive tissues; liver (hepatocyte focal and (mainly at fatal doses) single cell necrosis). Deaths at 9 mg/kg/day. NOEL 0.3 mg/kg/day.
95.0170 (Mar 1995); GLP	Previously evaluated 4 week IV study in Wistar rats; 0, 3.2, 8, 20	N/A	[C24 h (µg/mL) data: 1.5; 1.2; ≤ 1.8]	As above, and additional toxicity associated with *Baccilus piliformis* infection, and one case of CNS haemorrhage (not associated with infection). Deaths at all doses (attributed to hepatic disease). NOEL not established.

Report no. (date); GLP status	Study duration, route; doses teriflunomide (mg/kg/day)	Teriflunomide Cmax (µg/mL) at respective doses	Teriflunomide AUC (µg.h/mL) at respective doses	Main target organs / effects
95.0288 (May 1995); GLP	Second previously evaluated 4 week IV study in Wistar rats; 0, 0.25, 1	N/A	[Mean concentration 1.1-5.1 µg/mL at various time-points over 0.5-24 h]	Deaths in HD rats (changes as described above, including cerebellar haemorrhage; attributed to *Baccilus piliformis* infection). No effects in rats surviving the HD. NOEL 0.25 mg/kg/day.
01304 (Sep 2009); GLP; day 169 kinetic data	2 year PO (carcinogenicity study) in SD rats; 0, 0.5, 1.5, 4	3 / 4 9 / 11 20 / 27	51 / 60 104 / 148 275 / 329	Bone marrow (hypocellularity, decrease in hematopoietic cells), submandibular lymph node (decreased plasmacytosis), spleen (decreased lymphocytes and increased pigment (hemosiderin), liver (↑ focus of cellular alteration, hypertrophy, multinucleated hepatocytes). Mortality ↑ at MD and HD (♂ only). NOEL not established.
Dog (beagle) M / F				
017737 (Jul 1999); GLP; day 88 kinetic data	3 month PO; 0, 0.8, 2.5, 8	6.4 / 6.7 51 / 34 103 / 72 (day 23)	107 / 118 680 / 590 1673 / 1185 (day 23)	Atrophic changes in haematopoietic tissues/organs, spleen; intestinal tract and oral mucosae; and ↑ siderin storage in liver Kupffer cells. Deaths at HD. NOEL 0.8 mg/kg/day.

Report no. (date); GLP status	Study duration, route; doses teriflunomide (mg/kg/day)	Teriflunomide Cmax (µg/mL) at respective doses	Teriflunomide AUC (µg.h/mL) at respective doses	Main target organs / effects
2003-1491 (Sep 2005); GLP; day 364 kinetic data	12 month PO; 0, 0.2, 0.8, 2 (↑ to 4 at week 27)	1.5 / 1.4 9.3 / 10 34 / 36 (day 90) and 69 / 58	27 / 20 159 / 166 639 / 699 (day 90) and 1313 / 1115	Pancreas (focal or multifocal acinar degeneration and individual acinar cell necrosis, fibrosis and mononuclear inflammatory cell infiltrate) and spleen (increase in pigment (consistent with hemosiderin). Deaths at 4 mg/kg/day (no evidence of infection found). NOEL 0.2 mg/kg/day.
95.0108 (Mar 1995); GLP	Previously evaluated 4 week IV study; 0, 0.8, 2.5, 8	(M + F data) 7.5 33 83	(M + F data) 96; 491; 1273	Atrophic changes in GI tissues, reproductive tissues (♂), erythropoietic changes in bone marrow. NOEL 2.5 mg/kg/day.

Abbreviations and symbols: NOEL: no observed effect level; NOAEL: no observed adverse effect level; LD: low dose; MD: mid dose; HD: high dose; IV: intravenous; GI: gastrointestinal; CNS: central nervous system; SD rat: Sprague Dawley rat; C24 h: plasma concentration at 24 h after dosing;↑: increased; ↓: decreased; ♂: male. Note: Human steady state data after PO teriflunomide 14 mg/day are 1070 µg.h/mL for AUC over time zero to 24 h ($AUC_{0\text{-}24\,h}$) and 45.3 µg/mL for Cmax.

Relative exposure

Given that human teriflunomide exposure is 1070 µg.h/mL (AUC) and 45.3 µg/mL (Cmax) at steady state after 14 mg PO dosing, it is clear that exposure to teriflunomide in animals is much lower than, or not greatly in excess of, clinical exposure. However, as already mentioned, unacceptable levels of toxicity precluded the use of higher doses. With two exceptions (below), toxicities were predictable on the basis of teriflunomide's pharmacological activity across the range of doses up to those causing death in experimental animals.

Liver toxicity was not an anticipated effect of leflunomide/teriflunomide, however it has been observed with leflunomide in patients. As with leflunomide, experimental animals appear less sensitive to the hepatotoxic effects of teriflunomide, with frank toxicity (necrosis, focus of clear cell alterations) observed at the highest doses that were also fatal. Although the liver changes may be partly due to adaptive responses, *in vitro* mechanistic studies were nevertheless undertaken, although these did not shed light on possible underlying mechanisms. According to the sponsor, the liver has been a focus of safety studies in clinical trials of teriflunomide. There is no reason to expect that the risks of liver injury will be any less with teriflunomide than with leflunomide at equivalent doses.

Pancreatic toxicity (dogs) is also not an anticipated effect of teriflunomide and was not observed in previous toxicity studies of leflunomide (with the exception of inflammatory and oedematous changes in the pancreas of (moribund) rats in the carcinogenicity study). The nonclinical studies do not provide conclusive information about whether or not patients taking teriflunomide are likely to be at risk of pancreatic disorder. It is noted that this too has been a focus of safety studies in teriflunomide clinical trials.

The human systemic exposure to teriflunomide at the proposed dose of 14 mg/day ($AUC_{0\text{-}24\,h}$ 1070 µg.h/mL, Cmax 45.3 µg/mL) is slightly less than the clinical exposure to teriflunomide[1] at the maintenance dose (20 mg/day) of leflunomide.

4-TFMA toxicity

While levels of 4-TFMA were variable in animals, they were detectable in most studies, mainly at the highest doses used (AUC values up to approximately 200, 300 and 40 ng.h/mL were recorded in dogs, rats and mice, respectively), although rarely at levels as high as the maximum detected in humans (127.2 ng.h/mL, based on a maximum recorded individual concentration of 5.3 ng/mL). Nevertheless the toxicity profile of 4-TFMA itself was assessed adequately in a 3 month study where exposure was greatly in excess of that expected in humans. The major toxicity (to red blood cells) was consistent with effects previously identified for this substance.

Genotoxicity

Teriflunomide was negative in a number of *in vivo* and *in vitro* assays of gene mutation, chromosomal damage and unscheduled deoxyribonucleic acid (DNA) synthesis, but it increased the incidence of chromatid breaks in human lymphocytes. The latter assay is known to be associated with a high rate of false positives. Therefore, this finding is not given great weight in view of the consistently negative findings in all of the other assays.

[1] Teriflunomide mean $AUC_{0\text{-}24h}$ approximately 1200 µg.h/mL (maximum 3000 µg.h/mL), steady state concentration range 50-120 µg/mL (data cited in a TGA nonclinical evaluation report for leflunomide).

4-TFMA was previously identified as genotoxic in *in vitro* but not *in vivo* assays, but the risks to humans due to genotoxic activity are considered low because this metabolite is not routinely detected in humans and concentrations causing genotoxicity *in vitro* were greatly in excess of the highest levels expected in humans. Further, the lack of genotoxicity with 4-TFMA *in vivo* was confirmed in additional assays provided in this submission.

Carcinogenicity

The two year carcinogenicity studies of PO teriflunomide in mice and rats were modified in that all male rats were terminated prematurely (at weeks 92-97) and treatment with teriflunomide was ceased prematurely (at week 96) for high dose (HD) male mice, although they were continued on the study. In both cases, study modifications (which were done after consultation with the FDA) were required because of a higher-than-anticipated mortality in certain groups due to non-neoplastic toxicity of teriflunomide. Nevertheless, both studies remain valid for identifying potential carcinogenic activity since the treatment duration in males was still sufficient to reveal any group differences in pre-neoplastic and neoplastic lesions and all female groups were exposed to treatment for the full duration. Further, the mid and/or low doses in males were associated with drug activity/toxicity that was close to the maximum tolerated dose.

The no-effect dose for toxicity was 1 mg/kg/day in mice and was not established in rats, while no carcinogenicity was seen at the highest doses used (associated with AUC 3 times higher in mice but 4-5 times lower in rats, when compared with the human AUC; see Table 2, above). While exposure was low with regard to human exposure, selected teriflunomide doses were appropriate, ranging from those that caused no or minimal toxicity to those that probably exceeded the maximum tolerated dose.

A higher incidence of common tumours was observed at the HD in male (pituitary gland adenomas) and female (thyroid C cell adenomas) rats; however, the increase cannot unequivocally be attributed to teriflunomide because of high spontaneous incidences of these tumours in rats, lack of dose-relationship, lack of similar findings in the opposite sex, and lack of increased incidence of pre-neoplastic hyperplasia in these tissues. Further, the incidence of these tumours was not increased in (previously evaluated) rodent carcinogenicity studies of leflunomide, and the pituitary and thyroid glands have not been identified as target organs for the activity of these drugs.

Target organs for toxicity associated with teriflunomide in both carcinogenicity studies were consistent with those identified in the repeat dose toxicity studies (erythropoietic, lymphoid, gastrointestinal (GI) and/or dermal tissues). Additional toxicity observed only in teriflunomide-treated mice (generalised amyloidosis, cardiac thrombus and bacteria) were most likely secondary to effects on the immune and haematological systems, respectively. In rats, the incidences of mononuclear cell infiltrates into the epididymis and of liver clear cell focus of cellular alteration were increased in HD males, while HD females showed a higher incidence of hepatocyte hypertrophy and multinucleated hepatocytes. The hepatic findings tend to confirm the liver as a target organ for teriflunomide toxicity.

In previously evaluated carcinogenicity studies, PO administration of leflunomide was associated with the development of respiratory toxicity and bronchoalveolar adenomas and carcinomas in rats and of malignant lymphomas in male mice. Similar findings were not observed in the current studies with teriflunomide doses associated with similar exposure. In the leflunomide nonclinical program, evidence of widespread infection, secondary to drug-associated immune suppression, was seen across several studies, including the carcinogenicity studies. This was less evident or absent in the teriflunomide program, possibly due to superior environmental conditions. Therefore, differences in

leflunomide and teriflunomide carcinogenicity study findings may have been due to differences in the immunological state of the animals.

While these studies do not provide evidence for a direct carcinogenic effect of teriflunomide, the possibility of tumourigenic activity associated with immune suppression must be considered, as with all drugs of this nature.

Reproductive toxicity

The full range of reproductive toxicity studies was conducted with teriflunomide administered PO in a rodent and/or a non-rodent species. The design of the major studies was consistent with contemporary requirements and standards and the dose-range used was adequate to demonstrate the range of activities expected with teriflunomide. These are summarised in Table 3, below, along with actual/estimated exposure levels and animal/human relative exposure.

As with leflunomide, teriflunomide caused embryofetal deaths and teratogenicity when administered to pregnant rats and rabbits at PO doses associated with exposure (AUC) substantially lower than that expected in humans, and in the absence of maternal toxicity. Malformations were qualitatively similar to those observed with leflunomide, comprising mainly abnormalities of the central nervous system (CNS; spinal column), skeleton and associated structures. Teriflunomide inhibits cell proliferation and differentiation by reducing the availability of an essential component of DNA/ribonucleic acid (RNA) synthesis and therefore it is expected that this drug would profoundly affect embryofetal (and neonatal) development. A no-effect dose of 1 mg/kg was established for effects *in utero*.

Table 3. Reproductive toxicity doses, exposures and animal/human exposure ratios

Species	Study	Dose (mg/kg/day)	AUC_{0-24h} (µg·h/mL)	Exposure ratio#
Rat (SD)	Fertility (male)	1	71e	0.07
		3	188e	0.2
		10	542e	0.5
	Fertility (female)	**0.84**	59e	0.06
		2.6	157e	0.15
		8.6	434e	0.4
	Embryofetal development	**1**	110	0.1
		3	298	0.3
		10	635	0.6
Rabbit (NZW)	Embryofetal development	1	59.8	0.06
		3.5	431	0.4

Species	Study	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µg·h/mL)	Exposure ratio#
		12	4810	4.5
Rat (SD)	Pre/postnatal development	0.05	5.5e	0.005
		0.1	11e	0.01
		0.3	33e	0.03
		0.6	66e	0.06
		1	110e	0.1
Human patients	steady state	[14 mg]	1070	–

= animal:human plasma $AUC_{0-24\,h}$. Values with 'e' suffix are extrapolated rather than actual data: for the pre-/post natal studies they are extrapolated from data obtained at the same dose levels in pregnant females; for the male and female fertility study, they are extrapolated from male and non-pregnant female rats given 1 mg/kg/day in the 3 month rat toxicity study (day 30 kinetic data). NOAEL doses are bolded.

Teriflunomide was teratogenic regardless of when a 3 day treatment schedule was commenced over gestation days (GD) 6-17 in rats; however, it was not embryolethal if treatment commenced after the period of most rapid development (that is, after GD 12) in this species. Co-administration of uridine with leflunomide (in effect, the pro-drug for teriflunomide) did not modify the drug's teratogenic activity but it reduced its embryolethal potency. These findings are not re-assuring of any potential benefits of uridine during pregnancy if patients have been taking teriflunomide.

Administration of teriflunomide 10 mg/kg/day PO to male rats for 10 weeks prior to mating had no effect on fertility, however, it reduced sperm, suggesting that sperm is exposed to the drug. Atrophy of reproductive organs was also a feature of repeat dose toxicity studies of teriflunomide and these findings also are consistent with teriflunomide distributing to the sperm and associated structures. The potential transfer of teriflunomide to the embryo *via* sperm must be considered.

In an initial pre/postnatal study, adverse (including lethal) effects on pup development were observed if pups were exposed to teriflunomide *in utero* plus *via* milk during lactation, and a no-effect dose was not established (< 0.3 mg/kg/day). Based on a tissue distribution study in rat pups, the sponsor estimates that suckling pups would receive 23% of a maternal PO dose as a result of exposure *via* milk. A group concurrently dosed with 1 mg/kg/day during gestation only (the 'gestation group') showed no notable findings in this study, consistent with the NOAEL dose in the rat embryofetal development study and indicative of adverse effects with added postnatal exposure. A further pre/postnatal study established the first generation offspring (F_1) NOAEL at 0.1 mg/kg/day.

The ability of teriflunomide to cause embryofetal deaths and malformations and to adversely affect growth development is consistent with effects observed in previously evaluated studies of leflunomide. In the case of the latter drug, a study (not re-submitted for the current application) established both leflunomide and teriflunomide as potential

teratogens, and that teriflunomide is twice as potent as leflunomide in this regard, and that both have activity similar to the cytotoxic agent 5-fluorouracil in this model.

Pregnancy classification

The sponsor has proposed pregnancy Category D for teriflunomide, which is not appropriate given its potent and expected teratogenic activity. Leflunomide is currently classified in pregnancy Category X (*Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy*). There is no justification for placing teriflunomide in a category different to that for leflunomide; therefore teriflunomide should be included in pregnancy Category X. It is noted that the sponsor proposes to establish a pregnancy register for teriflunomide which is appropriate.

Paediatric use

Teriflunomide is not specifically proposed for paediatric use and no studies in juvenile animals were submitted. Teriflunomide was found to adversely affect growth and development in neonatal rats exposed to teriflunomide *via* milk during lactation, which is consistent with its intended mode of action in inhibiting cell differentiation and proliferation. From a nonclinical viewpoint, teriflunomide should not be used in children.

Impurities

The proposed limits are acceptable.

Nonclinical summary

- The nonclinical data included several studies on the efficacy of teriflunomide in animal models of MS but there were few primary pharmacology (mechanistic) studies; this is acceptable given that the mechanism of action was established previously in studies supporting the registration of leflunomide. The toxicology program for teriflunomide was comprehensive, well documented and covered the range of studies expected to support the registration of a new chemical entity proposed for long-term use. Several toxicity studies of teriflunomide (then called A77 1726) from the previous leflunomide dossier were also re-submitted.
- Teriflunomide reversibly inhibits the mitochondrial DHO-DH enzyme, which reduces the de novo synthesis of pyrimidines and ultimately inhibits cell proliferation/differentiation by preventing cell cycle progression. The respective concentration causing 50% inhibition (IC50) values for teriflunomide at DHO-DH are approximately 20, 80 and 1000 nM for rat, mouse and human enzyme. The inhibitory effect on DHO-DH in vitro can be overcome by exogenous uridine.
- Inhibition of lymphocyte proliferation by teriflunomide was demonstrated in several assays, including recent assays in human peripheral blood mononuclear cells where the proliferation of various T lymphocyte subtypes (CD3 expressing populations in combination with CD4, CD8, or CXCR5), CD19+ B lymphocytes (but not activated CD19+/CD80 B cells) and memory cells expressing CD3+, CD4+ and CD45RO (but not T cells activated by tetanus toxin) was inhibited at the tested concentrations of 25 and 100 μM.
- Previous studies showed teriflunomide to have no noteworthy direct anti-inflammatory activity or effect on cytokine release. No relevant systems for secondary pharmacological activity have been identified.

- In animal models of MS, teriflunomide ameliorated disease-associated neurological symptoms and cellular and histopathological changes, and improved neurological conduction. The effect was dose dependent (3-10 mg/kg/day in rats, 20 mg/kg/day in mice) and was independent of the time of administration once disease was established. There was some evidence for prophylactic activity, since teriflunomide prevented disease development if it was administered at the same time as disease induction but before disease onset. In comparator studies, the effect of the highest tested dose of teriflunomide was as (or less) effective than dexamethasone. The duration and design of the animal studies were not sufficient to allow comment on the potential for disease flare once treatment ceased or on whether the therapeutic effect is maintained with prolonged treatment.
- The full range of safety pharmacology studies and a comprehensive battery of receptor interaction studies were conducted with teriflunomide doses/concentrations that were therapeutically active/relevant. Teriflunomide was generally without activity in these. Exceptions were a diuretic effect and a decrease in activity at the highest doses tested in rats.
- The PK of teriflunomide in all animal species investigated were generally similar to those in humans. Teriflunomide is rapidly and well absorbed, has high oral bioavailability and is the major component found in the circulation. It is bound extensively (> 95%) to plasma proteins, has a small volume of distribution, is cleared slowly, undergoes enterohepatic recirculation (confirmed in rats) and is excreted as parent compound and metabolites via the faeces and urine. The PO plasma kinetics in animals were roughly dose proportional and there is potential for accumulation, consistent with the long half-life (t½), which is shorter in animals (range 18-37 h, but up to 168 h, after PO dosing) than humans (median t½, 19.4 days (466 h)).
- The metabolism of teriflunomide in all species investigated involves oxidation, hydrolysis, and glucuronide and sulfate conjugation; while cytochrome P450 (CYP450) enzymes are involved to some extent, no particular isozyme dominates. The only circulating metabolite of teriflunomide detected in humans and animal species, 4-TFMA, generally accounts for < 0.01% of drug-related compounds in all species tested and the major human urinary metabolite (TFMA-oxanilic acid) is also a major metabolite in animal excreta. While several other teriflunomide metabolites have been detected in all species, none accounts for > 3% of drug-associated material in any human biological matrix and they are also minor metabolites in other species.
- The tissue distribution pattern of teriflunomide after PO dosing was investigated in adult albino and pigmented normal rats, rats with MS, and suckling neonatal pups from dams treated with teriflunomide. In all cases, teriflunomide was widely distributed to all tissues; however low levels observed in the CNS were thought to be due to levels in residual blood rather than in neural tissue. There is prolonged retention in pigmented skin, but no real evidence for target organs for accumulation after single or repeated dosing. A study in suckling pups from teriflunomide-treated dams showed that the drug is excreted into milk, absorbed by the neonate and distributed widely to neonatal tissues. Previously evaluated studies confirmed that teriflunomide crosses the placenta in pregnant rats and rabbits.
- In vitro studies with human-derived systems suggest that teriflunomide is a substrate for and inhibitor of the breast cancer resistant protein (BCRP) transporter and has potential to inhibit renal anion transporters. Inhibition of urate transport through the apical urate/anion exchanger was demonstrated, with teriflunomide being more potent than the uricosuric drugs sulfinpyrazone and probenecid in this regard. Teriflunomide was not identified as a P-glycoprotein pump inhibitor or substrate.

- Studies with human-derived CYP450 subtypes showed potential for teriflunomide to inhibit the activity of CYP2C8 and CYP2B6, to induce the activity of CYP3A4, and to induce or inhibit (depending on the concentration) the activity of CYP2C9. Clinical studies assessed potential interactions.
- Acute intraperitoneal (IP) or PO doses causing 50% deaths in a group of animals (lethal dose (LD) LD50) teriflunomide doses in rats or mice were 100-200 mg/kg (10-20 times the highest "efficacious" doses in animal models of MS). Clinical signs and necropsy findings were indicative of GI toxicity, while survivors of near-lethal doses showed no adverse effects after a 3 week recovery period.
- The main repeat dose toxicology studies were in mice (3 month study), rats (3 and 6 months) and dogs (3 and 12 months) given daily PO doses. These species were relevant to humans in terms of PK and all were more sensitive than humans in terms of the primary pharmacological activity of teriflunomide (inhibition of DHO-DH). No studies were done with the proposed tablet formulation, which is acceptable given the lack of novel excipients and the lack of anticipated interactions among these and the active.
- Based on AUC at steady state, exposure to teriflunomide at the highest doses used in animals was in most cases substantially lower than exposure expected in humans. Further, dose-adjustment during the 6 month rat and 12 month dog studies resulted in animals being exposed to the higher drug levels for relatively short periods. Nevertheless, the toxicology program sufficiently defined the toxicology profile of teriflunomide over the range of doses, from those causing no-effect to those causing deaths in a non-rodent and rodent species.
- The major toxicities were associated with inhibition of rapidly dividing cells, consistent with the pharmacological (intended) action of teriflunomide: anaemia, thrombocytopenia and leucocytopenia (with associated cellular and atrophic changes in bone marrow, spleen, thymus and lymphoid tissues); GI tract ulceration and haemorrhage; skin ulceration; and reproductive tissue atrophy (particularly in males) were all observed. The toxicity profile of teriflunomide in these species was qualitatively and quantitatively (based on teriflunomide AUC) equivalent to that observed with leflunomide (or teriflunomide) in previous studies. At the 14 mg/day dose, human exposure to teriflunomide (AUC0-24 h 1070 µg.h/mL, Cmax 45.3 µg/mL) is slightly less than human exposure to teriflunomide at the maintenance dose (20 mg/day) of leflunomide.
- Toxicities not clearly associated with the pharmacological activity of teriflunomide comprised hepatocellular necrosis at high (usually fatal) doses in rodents, and pancreatic changes (focal or multifocal acinar degeneration and individual acinar cell necrosis, fibrosis and mononuclear inflammatory cell infiltrate) in dogs.
- Special studies on possible mechanisms underlying teriflunomide (and leflunomide) associated liver toxicity (which has been observed in humans) were not definitive, but showed some evidence that teriflunomide might interfere with mitochondrial respiration, increase the generation of superoxide anions, reactive oxygen species, free radicals and/or electrophiles in liver cells, induce apoptosis (weakly), and cause dysregulation in genes associated with inflammation and mitochondrial growth. The biological significance of these actions (especially whether they underpin teriflunomide-induced liver toxicity in patients) is not clear. Pancreatic changes in dogs were associated with lower trypsin-like immunoreactivity but no effects on lipase or amylase levels. There were no other nonclinical investigations of the effect on

the pancreas. According to the sponsor, both the liver and the pancreas were the subject of special monitoring in clinical trials of teriflunomide.

- Standard carcinogenicity studies of teriflunomide were performed in rats and mice. Exposure (AUC) to teriflunomide at the highest doses was well below (rats) or 3 times (mice) that expected in human subjects, however MTDs were used in both studies. Dosing was terminated prematurely in male rats and mice due to teriflunomide-associated toxicities; however these studies remain valid for assessing the carcinogenic potential of teriflunomide. Teriflunomide showed no carcinogenic activity in either study. As with other immune modulators, a potential carcinogenic risk due to immune suppression cannot be ruled out.
- Teriflunomide was negative in assays of gene mutation and in vivo chromosomal damage, and positive in human lymphocyte chromosomal aberration assays in vitro, but the overall profile was negative. 4-TFMA was mutagenic in bacteria and in Chinese hamster V79 cells, and showed clastogenic activity in Chinese hamster V79 cells, but was negative in in vivo assays of chromosomal damage and an unscheduled DNA synthesis assay in rat liver.
- No effect on fertility was observed when male rats were treated with teriflunomide 10 mg/kg/day for 10 weeks prior to mating, despite a decrease in sperm count. Treatment of female rats with teriflunomide from two weeks prior to mating to early gestation caused almost complete embryofetal death and malformations in surviving fetuses. In rats, the embryolethal potency of teriflunomide was reduced by concomitant administration of uridine or by administering teriflunomide after the period of most rapid development, but these modifications did not alter the teratogenic activity. The embryolethal and teratogenic activity was confirmed in rabbits. Exposure (AUC) at the no-effect dose in both species (1 mg/kg/day) was substantially lower than that expected in humans. Treatment of rats with teriflunomide during late gestation and lactation was associated with increased neonatal mortality, mainly as a result of skeletal malformations.
- Leflunomide or teriflunomide showed no activity in tests of parenteral irritation/local toxicity, active/passive cutaneous anaphylaxis, or dermal sensitisation, and that teriflunomide showed no evidence for cutaneous or ocular (in vitro) irritation or phototoxicity.
- The effect of teriflunomide on immune responses to antigens was assessed in a one month repeat dose toxicity in rats where animals were challenged with Keyhole Limpet Hemocyanin 2 weeks after teriflunomide treatment commenced and again 2 weeks after continued teriflunomide treatment. Teriflunomide-treated rats showed suppressed immune responses (lower T and B lymphocytes and lower T-cell dependent antibody responses), particularly after the first challenge. A similar effect was observed with cyclophosphamide.
- In repeat dose toxicity studies of 4-TFMA, the metabolite was found to have a toxicity profile similar to that of the parent drug, but to also cause prominent red blood cell toxicity. This metabolite may have contributed to the severe anaemia and associated haematopoietic tissue toxicity observed in teriflunomide-treated animals. While 4-TFMA is not consistently detected in humans levels up to 5.3 ng/mL have been detected: exposure to 4-TFMA in the 3 month study was > 200 times greater than the highest expected human exposure. Therefore the potential toxicity of this metabolite is considered to have been assessed.
- Limits for impurities above those accepted without qualification were adequately justified on toxicological grounds.

Conclusions and recommendation

Teriflunomide, the ring-opened form of leflunomide, is an immunomodulatory agent that inhibits DHO-DH, thereby blocking activation/proliferation of stimulated lymphocytes and potentially reducing activated lymphocytes in the CNS. Efficacy data in animal models of MS support potential efficacy in patients with MS, although the exact mechanism of action in this disorder is not fully understood.

Teriflunomide was extensively investigated in animal studies of safety pharmacology, PK, toxicity, carcinogenicity, genotoxicity and reproductive toxicity. The toxicological profile of teriflunomide across the range of studies is qualitatively and (based on AUC for teriflunomide) quantitatively similar to that of its parent compound leflunomide, with the main target tissues/organs being those with rapidly dividing cells (haematopoietic, GI, skin and reproductive in particular). Suppressed immune responses to antigens were shown in limited studies. Considering its pharmacological activity and the known toxicities of leflunomide, teriflunomide studies did not reveal toxicities that were novel, unexpected or previously unidentified, with the possible exception of the pancreas. Risks associated with the use of leflunomide will almost certainly also apply to the use of teriflunomide.

Like leflunomide, teriflunomide is teratogenic and should be included in Pregnancy Category X.

There were no objections on nonclinical grounds to the registration of teriflunomide as proposed. Several revisions were recommended to nonclinical aspects of the proposed PI; details of these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Proposed indication

The sponsor's original draft PI contained the following proposed indication: *[Product[2]] is indicated for the treatment of Relapsing Remitting Multiple Sclerosis and Secondary Progressive Multiple Sclerosis with superimposed relapses to reduce the frequency of clinical relapses and to delay the accumulation of physical disability*. The sponsor later retracted this indication as an error and confirmed the proposed indication as:

> *[Product] is indicated for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical relapses and to delay the accumulation of physical disability.*

The sponsor commented that the proposed indication was discussed with the Delegate at a pre-submission meeting with the TGA, and it continues to reflect the patient population in the pivotal trial. The TGA had advised that an indication for 'relapsing forms of MS' may not be supportable, as only a minority of patients had a form different from relapsing-remitting MS in the pivotal study population; guidance from neurologists was likely to be

[2] 'Product' refers to any of the proposed trade names: Aubagio, Teriflunomide Withrop, or Teriflunomide Sanofi.

sought on this aspect. The sponsor indicated they would await the outcome of any advice sought by the TGA from neurologists, prior to any further amendments to the indication.

In accordance with TGA processes, the evaluator proceeded with the evaluation on the basis of the following indication, as stated in the sponsor's application documents:

> *[Product] is indicated for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical relapses and to delay the accumulation of physical disability.*

Background

Multiple sclerosis is an immune-mediated disease involving both the cellular and humoral arms of the immune system. The generally accepted view of human MS immune pathogenesis implicates nonanergic, myelin-specific, autoreactive T cells activated in the peripheral immune system *via* interplay between environmental triggers and genetic susceptibility. After activation, T lymphocyte cells acquire the potential to cross the blood brain barrier, resulting in CNS lesions which can be assessed by various magnetic resonance imaging (MRI) techniques.

The European Medicines Agency (EMA) Committee for Medicinal Products for Human use (CHMP) *Guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis* (CPMP/EWP/561/98 Rev. 1,16 November 2006), [3] states the following:

As many as 80-85% of all patients present with a form of disease known as relapsing-remitting MS (RRMS), which is characterised by unpredictable, acute episodes of neurological dysfunction, named clinical attacks or relapses, followed by variable recovery and periods of clinical stability. Within ten years, more than 50% of patients who presented with a RR form eventually develop sustained deterioration with or without relapses superimposed; this form is called the secondary progressive variety of MS (SPMS).

The term relapsing MS (RMS) applies to those patients either with a RRMS form or a SPMS form that are suffering relapses. Patients with RMS, in spite of suffering from different MS forms, constitute a common target for current treatments. Around 15% of patients develop a sustained deterioration of their neurological function from the beginning: this form is called primary progressive MS (PPMS). Some patients who begin with a progressive deterioration may experience relapses with time and this form is called progressive relapsing MS (PRMS).

Besides these main types of disease, the benign variety of MS refers to a RRMS form with few relapses and no significant disability after several years of evolution. Conversely, the term malignant MS applies to a very aggressive variety leading to severe disability or death in a few years after the onset of the disease. Finally, the term clinically isolated syndrome (CIS) applies to those patients who have suffered a single clinical event but do not comply with the diagnostic criteria for definite MS.

Rationale

Teriflunomide is an immunomodulator with both anti-proliferative and anti-inflammatory activity by potent (IC_{50} 1.25 μM), noncompetitive, selective and reversible inhibition of the mitochondrial enzyme DHO-DH. That leads to a blockade of the *de novo* pyrimidine synthesis and a subsequent cytostatic effect on proliferating T and B lymphocytes in the

[3] This Guideline was adopted by TGA on 10 January 2002).

periphery, resulting in diminished numbers of activated lymphocytes available to enter the CNS. Slowly dividing or resting cells which rely on salvage pathways for pyrimidine supply are unaffected by teriflunomide.

Teriflunomide has been developed as disease modifying therapy with the following objectives:

- To demonstrate that teriflunomide as monotherapy reduces the frequency of clinical exacerbations and delays the accumulation of physical disability in patients with RMS;
- To demonstrate that teriflunomide as monotherapy reduces conversion of patients presenting with their first clinical episode consistent with MS (CIS) to clinically definite MS;
- To demonstrate that teriflunomide as adjunct therapy to interferon beta (IFN-β) or glatiramer acetate (GA) reduces the frequency of clinical exacerbations and delays the accumulation of physical disability in patients with RMS.

The present submission corresponds to the first objective. Clinical studies for the second and third objectives are ongoing.

Scope of the clinical dossier

The submission included only one efficacy study of monotherapy for ≥ 104 weeks.[4]

The submission contained the following clinical information:

- 20 clinical pharmacology studies, including 12 that provided PK data and 9 that provided pharmacodynamic (PD) data;
- 5 population PK (PopPK) analyses;
- 1 pivotal efficacy/safety study;
- No dose-finding studies;
- 6 other efficacy/safety studies;
- 4 safety studies;
- 2 'other' studies (such as pooled analyses, meta-analyses, Periodic Safety Update Reports (PSURs), Integrated Summary of Efficacy, and Integrated Summary of Safety);
- literature references.

Guidance

The *Guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis* (CPMP/EWP/561/98 Rev. 1,16 November 2006), states, under Section 2.1, Different goals of treatments:

> "Treatments of MS may have different goals that will lead to different clinical development plans and clinical trial designs:
>
> A. Treatment of acute relapses to shorten their duration and/or severity of symptoms and/or preventing their sequelae.
>
> B. Modification of the natural history of the disease. This includes:

[4] The Guideline on *Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis* (CPMP/EWP/561/98 Rev 1, November 2006), section 6.5, *Confirmatory trials*, states that *'Two years is considered the minimum duration to demonstrate efficacy'*.

- Preventing or delaying the accumulation of disability. This may refer to the sustained accumulation of disability related with relapses or to the progression of disability either in the progressive phase of the disease (SPMS) or in PPMS. Those three situations demand a separate approach.
- Preventing or modifying relapses. It is not clear to what extent the effect on relapses is related to the prevention or delay in the long-term accumulation of disability, which is considered a more clinically relevant effect

C. Improvement of an apparently stable residual disability"

The clinical data set is based on that submitted in the USA, with the exception that the Australian dossier does not include an interim analysis of the ongoing clinical Study EFC10531/TOWER. Thus, EU Guidelines have not necessarily been referred to and followed.

Paediatric data

The submission did not include studies in paediatric patients. Teriflunomide is not proposed for use in children.

Good clinical practice

The studies used as a basis for clinical data presented in this dossier were conducted in compliance with Good Clinical Practice (GCP), as required by the ICH E6(R1) *Good Clinical Practice: Consolidated Guidance*. The studies also meet with the requirements of the Declaration of Helsinki.

Pharmacokinetics

Studies providing pharmacokinetic data

Pharmacokinetic data were provided in 17 studies and population analyses. In addition, *in vitro* human biomaterials studies for teriflunomide evaluated potential interactions with p-glycoprotein (P-gp) and breast cancer resistant protein (BCRP); transport in hepatocytes; protein binding; hepatic metabolism; effect on uric acid renal transport; and the potential for non-metabolic-based drug-drug interactions or metabolic based drug-drug interactions.

In all clinical studies, cholestyramine or activated charcoal was administered to subjects and patients to accelerate the elimination of teriflunomide at the end of the studies, presumably by interrupting the re-absorption processes at the intestinal level. In one repeated dose study in healthy subjects, a comparison between cholestyramine (8 g or 4 g three times daily) and charcoal (50 g twice daily) was performed with regards to safety and efficiency to rapidly eliminate teriflunomide.

The doses selected in the first Phase I and Phase II studies were based on doses active in animal experimental allergic encephalomyelitis models and PK data obtained with the parent compound leflunomide, which provided the initial source of information.

Evaluator's overall summary and conclusions on pharmacokinetics

The general PK characteristics of teriflunomide were the long half-life (approximately 19 days), and evidence of enterohepatic recycling based on the reduction in half-life to about one day following administration of either charcoal or cholestyramine.

Absolute bioavailability was not determined in a single study, but rather by cross study comparisons because of the prolonged half-life (terminal half-life associated with the terminal slope ($t_{½z}$) was > 10 days in most studies).

None of the repeated dose studies in healthy subjects were long enough to assess steady state achievement. Based on post hoc, individual-predicted PK parameters from the PopPK model, there was a slow approach to steady-state concentration (approximately 90-100 days, or 3 to 3.5 months, to attain 95% of steady state concentrations, based on a median $t_{½z}$ of approximately 18 to 20 days). The estimated mean AUC accumulation ratio was 30.3 for 7 mg and 33.6 for 14 mg.

The continued excretion of unchanged drug in faeces after 72 h suggests there is a complex route of excretion. Animal (rat) data propose both biliary and direct GI secretion, which lead to enterohepatic recycling from subsequent reabsorption.

Rifampin (a CYP2B6, 2C8, 2C9, 2C19, and 3A inducer, as well as an inducer of P-gp, and BCRP), administered at a dose of 600 mg once daily for 22 days, led to 39% decrease in mean plasma AUC and $t_{½z}$, but not Cmax of teriflunomide after a single 70 mg dose of teriflunomide. According to the sponsor's summary information, a similar effect was observed in patients in Study EFC6049/TEMSO but only when the potent CYP and transporter inducers were considered: carbamazepine, phenobarbitone, phenytoin and St John's Wort. At Week 36, mean (standard deviation; SD) teriflunomide trough plasma concentrations were 19.3 (11.1) µg/mL at 7 mg and 45.0 (30.7) µg/mL at 14 mg for patients with MS overall, and were 12.7 (4.29) µg/mL at 7 mg and 35.8 (19.4) µg/mL at 14 mg for patients with MS given potent inducers.

In relation to the total body clearance of 30.5 mL/h, this was calculated after a constant infusion of 10 mg for 2 h by using an exploratory model adjusted to the concentration-time data. The concentration-time course was described by a sum of two exponential functions for each subject. This sum of exponentials was considered as an open compartmental model, where the compartments are linked mamillarily and where elimination takes place from the central (monitored) compartment.

There were no studies submitted in paediatric patients.

The impact of the intrinsic variability on exposure parameters for 14 mg was: age (+5%), body weight (+26%), gender (female, +16%), race (numbers too small), albumin (no effect), and bilirubin (+31%), reported using the PopPK model study.

In relation to hepatic impairment, numbers were small and variability high. Means (see Table 4) showed some effect on AUC for those with moderate impairment. This is supported by bilirubin levels seen in the PopPK study but not by the lack of effect on alanine aminotransferase (ALT) and aspartate aminotrasferase (AST) levels. These results suggest no dose adjustment is necessary for those with mild to moderate hepatic impairment.

Table 4. Treatment ratio estimates for teriflunomide with 90% confidence interval (CI) - hepatic impairment (HI)

Parameter	Mild HI/Healthy (N=8)		Moderate HI/Healthy (N=8)		Moderate HI/Mild HI (N=8)	
	Estimate	90%CI	Estimate	90%CI	Estimate	90%CI
C_{max}	0.99	(0.88-1.12)	0.95	(0.84-1.07)	0.96	(0.85-1.08)
AUC_{last}	0.97	(0.65-1.44)	0.82	(0.55-1.22)	0.85	(0.57-1.25)
AUC	0.97	(0.64-1.46)	0.82	(0.55-1.23)	0.85	(0.56-1.27)

Note: values are rounded to 3 significant figures or less. N=number of subjects.

In a study of renal impairment, again numbers were small and CIs wide (Table 5), with some effect on Cmax but not AUC, suggesting no dose adjustment is necessary.

Table 5. Treatment ratio estimates with 90% CI for teriflunomide (comparison: severe renal impairment; RI)

Parameter	Severe RI/Healthy (N=8)	
	Estimate	90% CI
C_{max}	1.16	(0.97, 1.39)
AUC_{last}	1.02	(0.63, 1.66)
AUC	1.03	(0.61, 1.74)

Note: values are rounded to 3 significant figures or less. RI: N = 8, versus Healthy: N = 8 (Study POP11432).

The evaluator concluded that the studies generally supported PK and *Drug Interaction* statements in the proposed teriflunomide PI (details of these are beyond the scope of this AusPAR).

Pharmacodynamics

Studies providing pharmacodynamic data

A summary of submitted PD studies is shown in Table 6.

Table 6. Submitted pharmacodynamic studies

Study Centres	Objective(s); Study design	Treatment	Subjects Enrolled/completed Male/Female
TES10852 single centre France March 2010 - February 2011	Assess effect of repeated doses of teriflunomide on QTcF interval[5], compared to placebo and using moxifloxacin (400 mg, single dose) as a positive control Randomised, double-blind, double-dummy, repeated dose, placebo-controlled study, stratified by gender, conducted in 3 parallel groups	Teriflunomide tablets: 70 mg once daily for first 4 Days, then 14 mg once daily for 8 Days, Placebo: matched to teriflunomide tablets once daily for 14 Days Moxifloxacin capsules: 400 mg on Day 12 All treatments preceded by a single-blind placebo run-in day Placebo: matched to moxifloxacin capsules once daily for 11 Days (moxifloxacin group) or 12 Days (teriflunomide and placebo groups)	192/179 (87M/95F) healthy subjects Teriflunomide: 64 Placebo: 56 Moxifloxacin: 62 41.6 ± 16.1 (18 – 65) years
INT6040 1 centre UK February – July 2007	Assess effect of repeated daily oral doses of teriflunomide on PD and PK profile of warfarin after a single oral dose of 25 mg warfarin; assess safety of teriflunomide co administered with warfarin compared to warfarin alone Open, nonrandomised, single sequence, 2-treatment, 2-period study	Teriflunomide 14 mg tablets Loading dose of 70 mg once daily for first 3 Days of Period 2, followed by 14 mg once daily for 8 consecutive days Warfarin 5 mg tablets Single dose of 25 mg (5 tablets) on Period 1 Day l and on Period 2 Day 5	14/12 14M 31.0 ± 9.0 (19-45) years Period 1: 14 (warfarin); Period 2: 12

[5] QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. QT_c: The QT interval is dependent on the heart rate. To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval, QTc, is often calculated. QTcF is the QTc calculated using Fridericia's formula.

Study Centres	Objective(s); Study design	Treatment	Subjects Enrolled/completed Male/Female
		Cholestyramine for 11 days (Day 12 to Day 22) Teriflunomide: 11 Days Warfarin: 2 Days	(warfarin+ teriflunomide) Healthy
POH0295 France Undated	PK/PD analysis of data from Studies EFC6049/TEMSO and 2001	The objective was to explore the relationships between the selected safety and efficacy parameters and mean teriflunomide plasma concentrations in patients with relapsing forms of MS, after 7 or 14 mg of once daily teriflunomide. The selected safety variables were: ALT; neutrophils; lymphocytes; white blood cells; lipase; amylase; supine systolic and diastolic blood pressure; alopecia; creatinine clearance; phosphate; and uric acid. The selected efficacy variables were: annual relapse rate; time to disability progression sustained for 12 weeks; total number of gadolinium-enhanced T1 lesions / number of scans over the treatment period; total number of unique active lesions / number of scans over the treatment period; number of patients free of active lesions; and burden of disease at Week 108.	

Evaluator's overall conclusions on pharmacodynamics

With the usually slow clinical progression of MS, onset of action would be difficult to determine *in vivo*, however *in vitro* studies have only shown that proliferation is prevented over 5-7 days with teriflunomide. The PD studies have shown a potential mechanism of action for teriflunomide in reduction of T cell proliferation. It is not clear if this is an effective surrogate for the desired clinical effect of delaying accumulation of physical disability in patients with MS.

Efficacy

Dosage selection for the pivotal study

In a PK study (Study 1001), relative to leflunomide, teriflunomide Cmax was 63% (90% CI 58%-69%) and $AUC_{0\text{-}72\,h}$ was 73% (90% CI 69%-77%). Based on 10 mg and 20 mg leflunomide being effective and safe in patients with rheumatoid arthritis, 7 mg/day and 14 mg/day teriflunomide doses were chosen for Study 2001.

Following the results of Study 2001, the doses of 7 mg and 14 mg used were both selected for Phase III trials, with the exception that the use of an initial loading dose was omitted in anticipation of decreasing the frequency of adverse events (AEs) in the early treatment period.

The treatment of patients with relapsing forms of multiple sclerosis

A summary of submitted efficacy studies of teriflunomide in the proposed indication is shown in Table 7.

Table 7. Submitted efficacy studies of teriflunomide in the proposed indication

Study	Main objective of the study	Comparator	Treatment duration	Number randomised	Status
Monotherapy					
EFC6049/TEMSO	Evaluate the efficacy and safety of teriflunomide 7 and 14 mg in reducing the frequency of relapses in patients with RMS	Placebo controlled	108 weeks	1088	Completed
LTS6050 (extension of EFC6049)	Assess the long term safety and efficacy of teriflunomide in patients who had completed Study EFC6049	Uncontrolled	Open-ended	742	Ongoing, Interim Analysis
2001	Assess the effect on MRI activity, clinical efficacy, and safety of teriflunomide 7 and 14 mg	Placebo controlled	36 weeks	179	Completed
LTS6048 (extension of 2001)	Assess the long term safety and efficacy of teriflunomide in patients who had completed Study 2001	Uncontrolled	Open-ended	147	Interim Analysis
Not evaluated for efficacy – Monotherapy					
EFC10531/TOWER	Evaluate the efficacy and safety of teriflunomide 7 and 14 mg in reducing the frequency of relapses in patients with RMS	Placebo controlled	Fixed end for all patients, 48 weeks for last patient randomised	1096[a]	Ongoing, Interim analysis[b]

Study	Main objective of the study	Comparator	Treatment duration	Number randomised	Status
Not evaluated (not covered by indications in present submission) - Adjunctive therapy					
PDY6045	Adjunctive safety and efficacy study of teriflunomide 7 and 14 mg and a stable dose of IFN-β versus placebo and IFN-β	Placebo controlled	24 weeks	118	Completed
PDY6046	Adjunctive safety and efficacy study of teriflunomide 7 and 14 mg and a stable dose of GA compared to placebo and GA	Placebo controlled	24 weeks	123	Completed
LTS6047 (extension of PDY6045 and PDY6046)	Double-blind, long term safety extension study enrolling patients who had completed Studies PDY6045 and 6046	Placebo controlled	24 additional weeks	182	Completed

[a] Number of patients randomised by the end of November 2010. Study randomisation completed 17 February 2010 with a total of 1169 patients. [b] Submission of this data was discussed at a presubmission meeting between the sponsor and the TGA. It was agreed the sponsor would submit the complete study report as a condition of registration, not an interim analysis.

In accordance with the relevant Guideline,[6] the submission was evaluated as two separate indications:

for the treatment of patients with relapsing forms of MS:

a. To reduce the frequency of clinical relapses

b. To delay the accumulation of physical disability

The *EU Guideline on Points to Consider on Application with 1. Meta-analyses; 2. One Pivotal Study* (CPMP/EWP/2330/99, 31 May 2001) advises:

"In cases where the confirmatory evidence is provided by one pivotal study only, this study will have to be exceptionally compelling, and in the regulatory evaluation special attention will be paid to:

- The internal validity. There should be no indications of a potential bias.
- The external validity. The study population should be suitable for extrapolation to the population to be treated.
- Clinical relevance. The estimated size of treatment benefit must be large enough to be clinically valuable.
- The degree of statistical significance. Statistical evidence considerably stronger than $p < 0.05$ is usually required, accompanied by precise estimates of treatment effects, i.e. narrow confidence intervals. The required degree of significance will depend on factors such as the therapeutic indication, the primary endpoint, the amount of supportive data and whether the alternative analyses demonstrating consistency are pre-specified. When the aim is to demonstrate non-inferiority, one study is more likely to be accepted if the lower 95% confidence bound is well away from the non-inferiority margin.
- Data quality.
- Internal consistency. Similar effects demonstrated in different pre-specified sub-populations. All-important endpoints showing similar findings.
- Centre effects. None of the study centres should dominate the overall result, neither in terms of number of subjects nor in terms of magnitude of effect.
- The plausibility of the hypothesis tested."

Evaluator's conclusions on clinical efficacy for the proposed indication

Monotherapy - for the treatment of patients with relapsing forms of multiple sclerosis

1. The sponsor argues that the basis of the population for the indication, that is, 'patients with relapsing forms of multiple sclerosis', is that of the pivotal trial (Study EFC6049/TEMSO).

Evaluator comment: In pivotal Study 6049/TEMSO, only 12 patients out of 363 (3.3%) receiving placebo had PRMS; likewise, only 14 patients out of 359 (3.9%) receiving teriflunomide 14 mg had PRMS. In the extension Study 6050, only 10 out of 361 (2.8%) receiving teriflunomide 14 mg had PRMS. There were no patients with other forms of MS with relapses, for example CIS.

The sponsor's *Clinical Overview* states that teriflunomide has been developed for RMS[7] and CIS is a separate objective.[8]

[6] *Guideline on clinical investigation of Medicinal Products for the Treatment of Multiple Sclerosis*. (CPMP/EWP/561/98 Rev 1, 16 November 2006). Section 2.1, *Different goals of treatments*.

Conclusion: The single pivotal trial does not have a population to justify all the population described as 'patients with relapsing forms of multiple sclerosis'.

2. The sponsor believes that the proposed indication reflects the patient population in the pivotal 6049/TEMSO study as dictated by the inclusion criteria.

   The sponsor continues: '*Additionally, the protocol was designed such that patients with any form of relapsing MS could be included in the study*.'

The inclusion criteria for the study are as follows:

- Patients with relapsing forms of MS meeting McDonald's criteria[9] for MS diagnosis at time of screening visit, and Kurtzke Expanded Disability Status Scale (EDSS[10]) score ≤ 5.5 at screening visit.
- At least one recorded relapse in the 12 months preceding randomisation, or at least 2 relapses in the 24 months preceding the randomisation visit.

Evaluator comment: While this is true of the original protocol, this was amended shortly into the trial by protocol amendment 2 to read (with emphasis by the evaluator): *'Exhibiting a relapsing clinical course, with or without progression* ***(relapsing remitting, secondary progressive, or progressive relapsing)'****.*

Conclusion: The inclusion criteria in Study 6049/TEMSO are not sufficient to meet the proposed indication population.

3. The sponsor is most definite that the indication applied for is:

   [Product] is indicated for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical relapses and to delay the accumulation of physical disability.

Overall conclusion: The evaluator finds that efficacy in the proposed population, that is, *'patients with relapsing forms of multiple sclerosis'*, has not been shown.

Monotherapy - To reduce the frequency of clinical relapses

Pivotal Study 6049/TEMSO

In the pivotal Study 6049/TEMSO, efficacy of teriflunomide was shown in the principle variable the Annualised Relapse Rate (ARR), with no overlap of CIs versus placebo and a

[7] *Guideline on clinical investigation of Medicinal Products for the Treatment of Multiple Sclerosis*. (CPMP/EWP/561/98 Rev 1, 16 November 2006). Section 1, *Introduction*: The term relapsing MS (RMS) applies to those patients either with a RRMS form or a SPMS form that are suffering relapses; Section 2.3.1: Relapsing multiple sclerosis: The term relapsing MS includes 1) patients with RRMS, 2) patients with SPMS and superimposed relapses and 3) patients with a single demyelinating clinical event who show lesion dissemination on subsequent MRI scans according to McDonald's criteria.

[8] According to the sponsor, teriflunomide has been developed as disease modifying therapy with the following objectives: • To demonstrate that teriflunomide as monotherapy reduces the frequency of clinical exacerbations and delays the accumulation of physical disability in patients with relapsing MS; • To demonstrate that teriflunomide as monotherapy reduces conversion of patients presenting with their first clinical episode consistent with MS (CIS) to clinically definite MS

[9] Diagnostic criteria for multiple sclerosis integrating magnetic resonance image assessment with clinical and other paraclinical methods. These criteria were introduced by an International Panel on the Diagnosis of Multiple Sclerosis, in association with the National Multiple Sclerosis Society of America, and are known as McDonald's criteria after their lead author. Since their introduction in 2001, they have undergone revision twice, in 2005 and 2010, respectively.

[10] The EDSS is a method of quantifying disability in MS and monitoring changes in the level of disability over time. The scale ranges from 0 (normal neurological examination) to 10 (death due to MS) in 0.5 unit increments that represent higher levels of disability. Scoring is based on an examination by a neurologist. For example, subjects with a score of 6 need intermittent or unilateral constant assistance (cane, crutch or brace) to walk 100 meters with or without resting.

reasonable reduction in relative risk.[11] This held for the intent-to-treat (ITT) population, the per-protocol (PP) population, and when adjustment was made using data from the follow-up period. Most of the subgroups analysed showed similar effect of teriflunomide on ARR. Most of the other efficacy parameters assessed for this indication were similar.

In conclusion, adequate efficacy has been demonstrated in the population of the study in reducing the frequency of relapse to satisfy the requirements of a single pivotal study.

The long term extension of this study (Study 6050) interim analysis was provided. This showed no statistical difference in ARR or in the proportion of patients without confirmed relapse between patients already on teriflunomide and those on placebo during the preceding 2 years of Study 6049, suggesting an ongoing inhibitory effect rather than a deferment. However, when the ARR is compared between the studies, it is much lower in the extension study[12] (for example, 0.369 versus 0.206 for the teriflunomide 14 mg group). Explanation might lie in the ≥ 30% of participants in the Study 6049 groups who discontinued and/or failed to continue on to the extension Study (6050) (see Table 8, below).

Some 54 patients completed Study 6049 but did not enter Study 6050 (22 in the placebo group, 22 in the 7 mg group, and 10 in the 14 mg group), for reasons not given.

Overall, 174/363 (48%) subjects of the initial Study 6049 placebo group, 193/365 (53%) of the initial 7 mg teriflunomide group, and 196/358 (55%) of the 14 mg group continued in the 6050 Study after the interim analysis.

Table 8. Overall discontinuations - Studies EFC6049/TEMSO, 6050

Reason for study treatment discontinuation	Placebo (N = 363)	Teriflunomide	
		7 mg (N = 366)	14 mg (N = 359 [a])
Adverse event	52	58	53
Lack of efficacy	34	25	23
Protocol violation	4	2	5
Lost to follow-up	4	0	3
Death	0	1	1
Progressive disease	16	6	3
Subject did not wish to continue	56	54	55
Other	1	4	7

[11] The adjusted ARR was 0.539 (95% CI: 0.466 to 0.623%) in the placebo group, 0.370 (95% CI: 0.318 to 0.432%) in the teriflunomide7 mg group, and 0.369 (95% CI: 0.308 to 0.441%) in the teriflunomide 14 mg group. These results corresponded to a relative risk reduction of 31.2% (p = 0.0002) in the teriflunomide7 mg group and 31.5% (p = 0.0005) in the teriflunomide 14 mg group, compared to placebo.
[12] The adjusted ARR was 0.251 (95% CI: 0.188 to 0.334%) in the placebo/7 mg group, 0.182 (95% CI: 0.130 to 0.254%) in the placebo/14 mg group, 0.234 (95% CI: 0.186 to 0.295%) in the teriflunomide 7 mg group, and 0.206 (95% CI: 0.163 to 0.261%) in the teriflunomide 14 mg group.

Reason for study treatment discontinuation	Placebo (N = 363)	Teriflunomide	
		7 mg (N = 366)	14 mg (N = 359 [a])
Completed 6049 but did not enter 6050	22	22	10
TOTAL	189	172	160

a: Two participants in Study 6050 were randomised but not treated. Placebo - 7 or 14 mg tablet.

Study 2001

Study 2001 was a Phase II study of short duration (36 weeks) that had MRI results for the primary, and many secondary variables. This accords with the description of *Exploratory trials* in the CPMP *Guideline on clinical investigation of Medicinal Products for the Treatment of Multiple Sclerosis*.[13] Relapse parameters were secondary variables, and there was no statistical difference in total numbers without relapse between placebo and teriflunomide groups. The study had small numbers and short duration for what was a secondary variable and does not provide supporting evidence of efficacy. A summary of participants who discontinued and/or failed to continue on to the extension Study (6048) is shown in Table 9.

Table 9. Overall discontinuations - studies 2001, 6048

Reason for study treatment discontinuation	Placebo (N = 61)	Teriflunomide	
		7 mg (N = 61)	14 mg (N = 57)
No longer meets criteria to remain in study	1	0	0
Adverse event	13	13	17
Lack of efficacy	5	1	4
Subject did not wish to continue	3	10	7
Lost to follow-up	1	1	1
Administrative reasons	2	0	0
Protocol violation	0	1	0
Death	1	1	0
Relapse	0	1	0

[13] Section 6.4 *Exploratory trials:* In exploratory trials in RMS, the use of MRI derived parameters, as the main endpoint, is acceptable. Usually, studies will have a parallel double blind design and duration of 6 month may be adequate. Relapses and other clinically meaningful outcomes should also be evaluated.

Reason for study treatment discontinuation	Placebo (N = 61)	Teriflunomide	
		7 mg (N = 61)	14 mg (N = 57)
Discretion of the investigator	3	2	0
Other	4	3	1
Completed 2001but did not enter 6048	2	6	5
TOTAL	35	39	35

Overall, 26/61 (43%) subjects of the initial Study 2001 placebo group, 22/61 (36%) of the initial 7 mg teriflunomide group and 22/61 (36%) of the 14 mg group continued in the 6048 Study after the interim analysis. The numbers were thus small, with the ARR being 0.252 for placebo/7 mg, 0.316 for 7 mg teriflunomide, 0.212 for placebo/14 mg and 0.200 for the 14 mg teriflunomide group.

Conclusion

In the population of the pivotal study, adequate efficacy in reducing the frequency of relapse has been demonstrated to satisfy the requirements of a single pivotal study. Study 2001, a Phase II study with similar design, did not show a statistically significant difference in relapse rate.

Monotherapy - to delay the accumulation of physical disability

In the pivotal Study 6049/TEMSO, the key secondary efficacy variable was 'time to disability progression'. The numbers of patients with disability progression sustained for 12 weeks were relatively low: placebo 86 (23.7%), teriflunomide 7 mg 68 (18.6%), teriflunomide 14 mg 62 (17.3%); significant difference versus placebo was only shown for the 14 mg teriflunomide (p = 0.0279; from a log-rank test with stratification of EDSS strata at baseline and region). The hazard ratio for the risk of disability progression with 14 mg teriflunomide was 70.2% versus placebo (ITT); the 95% CI approached but did not include 1 (0.506, 0.973).

The Kaplan-Meier method estimated the probability of disability progression at Week 108 as: placebo 27.3% (95% CI 0.223, 0.323) and for teriflunomide 14 mg 20.2% (0.156, 0.247), that is, there was limited overlap of CIs.

Statistical difference could not be shown for time to disability progression sustained for 24 weeks - the numbers were less than for 12 week sustained disability.

The evaluator understood the Statistical Analysis Plan (SAP) called for 'a step down testing procedure' to be applied to the secondary endpoints, of which the first was 'Change from baseline in total score of Fatigue Impact Scale (FIS) at Week 108'. In the mixed-effect model with repeated measures (MMRM) analysis, no statistically significant treatment difference (least squares mean values) was observed in the FIS score at Week 108 (p = 0.3861 for the teriflunomide 7 mg group compared with the placebo group, and p = 0.8271 for the teriflunomide 14 mg group compared with the placebo group). Despite the lack of significance in the result, the subsequently listed MRI variables were analysed.

In response to a request from the TGA for information, the sponsor clarified that the step down procedure applied from 12 Week sustained disability progression for teriflunomide

7 mg versus placebo to FIS, so the analysis of the latter as well as the MRI variables should be considered nominal.

Conclusion

In the presence of a single pivotal study, there is only a limited signal for efficacy in the key secondary efficacy variable, after which, the step down analysis was to halt. Thus, while the other secondary efficacy variables varied from no difference for the FIS, to strong nominal p-values for many of the MRI variables, the latter carried no statistical weight according to the SAP. Further, *'so far, the correlation between MRI and clinical outcomes has not proved to be strong enough as to accept it as a validated surrogate endpoint in pivotal studies.'*[14]

The extension Study 6050 Kaplan Meier analysis showed an increased probability of disease progression in those subjects initially on placebo but beyond 3 years the numbers participating were small. In other assessments of time to disability progression, the 95% CIs overlapped or the p-values were not significant when comparing those always on teriflunomide and those starting after 2 years of placebo.

Study 2001 was exploratory and did little to support the pivotal study results of a limited signal for efficacy in the key secondary efficacy variable, while analyses of the other secondary efficacy variables were not valid according to the SAP.

Safety

Studies providing evaluable safety data

Table 10, below provides a summary of exposure to teriflunomide in clinical studies.

[14] *Guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis* (CPMP/EWP/561/98 Rev 1, 16 November 2006); p 9.

Table 10. Teriflunomide exposure in clinical studies

Study	Investigational Product	All	≥ 3 months	≥ 6 months	≥ 1 year	≥ 2 years
Monotherapy completed and ongoing studies in relapsing MS						
EFC6049/TEMSO + 2001	Teriflunomide 7 mg	429	405	384	303	277
	Teriflunomide 14 mg	415	386	363	289	263
LTS6050 + LTS6048	Placebo to Teriflunomide 7 mg	158	150	141	124	81
	Placebo to Teriflunomide 14 mg	133	128	122	109	70
Adjunct completed Phase 2 studies						
PDY6045+LTS6047	Teriflunomide 7 mg on top of IFN-β	37	36	32	22	--
	Teriflunomide 14 mg on top of IFN-β	38	37	31	23	--
PDY6046+LTS6047	Teriflunomide 7 mg on top of GA	42	37	32	30	--
	Teriflunomide 14 mg on top of GA	41	38	29	27	--
		1293	**1217**	**1134**	**927**	**691**
Other ongoing studies[b]						
EFC6260 (TOPIC)[a]	Blinded	270	227	202	136	57
EFC10891 (TENERE)[a]	Blinded	219	200	164	64	0
		489	**427**	**366**	**200**	**57**
EFC10531 (TOWER)[a]	Teriflunomide 7 mg	365	338	279	155	15
	Teriflunomide 14 mg	365	338	279	155	15
		730	**676**	**558**	**310**	**30**

[a] Approximate number of patients since the study is still blinded

[b] In addition, EFC6058/TERACLES, started in February 2011, is only included in the update for serious treatment-emergent adverse events

Analysis across all studies was not undertaken; instead the data was grouped into:

- Phase II/III monotherapy studies
  - Pool 1: Placebo-controlled, completed Studies 2001 and EFC6049
  - Pool 2: Active treatment patients receiving teriflunomide during the main studies (2001 and 6049/TEMSO), plus any patient who received teriflunomide during the extensions LTS6048 and LTS6050
- Adjunct studies: Patients receiving teriflunomide as adjunctive therapy to IFN-β (Study PDY6045+extension LTS6047) or GA (Study PDY6046+extension LTS6047). These were reported separately and, as combination therapy has not been sought, these data were not included in the main CER.
- Clinical pharmacology studies
  - Pooled clinical pharmacology single-dose studies
  - Pooled clinical pharmacology repeated-dose studies
- Ongoing studies at dossier cut-off
  - Ongoing monotherapy studies active-controlled study in patients with RMS (EFC10891/TENERE) and placebo-controlled study in patients with CIS, early MS (EFC6260/TOPIC)
  - Ongoing adjunct therapy study: placebo-controlled study in patients with RMS receiving teriflunomide as adjunctive therapy to IFN-β (EFC6058/TERACLES).

Cumulative exposure in the monotherapy trials was over 3738 patient years up to the data lock, with a median treatment exposure in placebo controlled trials of 755 days and a maximum exposure of up to 10 years.

Evaluator's summary and overall conclusion on clinical safety

- The lack of a listing of Adverse Reactions (AR) was considered a considerable gap in the sponsor's *Summary of Clinical Safety*.
- It may be that patients with differing pathology (MS versus rheumatoid or psoriatic arthritis) will have a differing AR profile, as well as there being a differing profile between teriflunomide and leflunomide.
- The pattern of ARs reported in the leflunomide (Arava) PI appears to be reflected in the treatment emergent AEs (TEAEs) of teriflunomide (with the exception of diarrhoea, nausea and vomiting) but no summary of investigator's opinion of causality was submitted.
- The number of patients treated with monotherapy was adequate.[15]

The greatest concerns with AEs of leflunomide, and hence teriflunomide, are that they are unlikely to be picked up in trials as they are rare reactions,[16] involving skin, hepatic and haematopoetic systems. Rare reactions listed in the leflunomide (Arava) PI include: eosinophilia, leucopoenia pancytopenia, hepatitis, jaundice/cholestatis, severe infections, and interstitial lung disease (including interstitial pneumonitis); very rare reactions include severe anaphylactoid reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, agranulocytosis, severe liver injury such as hepatic failure and acute hepatic necrosis, pancreatitis, and peripheral neuropathy.[17]

- Of these rare reactions, the Australian Drug Evaluation Committee (ADEC, the predecessor of ACPM) specifically advised that a warning that leflunomide treatment may be associated with pancytopenia and Stevens-Johnson syndrome or toxic epidermal necrolysis be inserted in the Arava PI.

  The teriflunomide proposed PI carries no warning on Stevens-Johnson syndrome or toxic epidermal necrolysis. There was an increase in skin AEs and this is shown in the proposed PI.

- Pancytopenia is not specifically mentioned in the proposed PI; there is a reasonable warning, however the recommendations on monitoring are not specific as for the leflunomide PI. It is recommended that the warning in the PI be the same.

  A mean decrease in white blood cell count was observed (mainly neutrophil and lymphocyte count decrease) that showed a small dose response. The mean decrease occurred during the first 6 weeks, followed by stabilisation over time on-treatment, with a magnitude not exceeding 15%.

The most frequently reported individual TEAEs with a higher incidence in the teriflunomide treatment groups as compared to placebo were: alopecia or hair thinning, diarrhoea, nausea, and increased ALT (liver transaminase).

[15] It is anticipated that the total number of individuals treated with the investigational drug, including short-term exposure, will be about 1500. *The Extent of Population Exposure to Assess Clinical Safety for Medicines Intended for Long-Term Treatment of Non-Life-Threatening Conditions.* CPMP/ICH/375/95

[16] The safety evaluation during clinical product development is not expected to characterise rare adverse events, for example, those occurring in less than 1 in 1000 patients *The Extent of Population Exposure to Assess Clinical Safety for Medicines Intended for Long-Term Treatment of Non-Life-Threatening Conditions.* CPMP/ICH/375/95

[17] Leflunomide PI. For some of these a casual relationship with leflunomide treatment could not be established, but cannot be excluded.

- The US product information for leflunomide carries a boxed warning in relation to hepatotoxicity, and, like the Australian Arava PI, also carries specific recommendations on monitoring. The incidence of >3-fold upper limit of normal (ULN) ALT elevations for Arava monotherapy in Study US301, MN301 and MN302 was 1.5% to 4.4%.[18] There was an incidence of 6.1% for subjects receiving teriflunomide 14 mg (versus 6.2% placebo). The proposed PI recommendation on monitoring is non-specific. In the absence of a summary of causality it is recommended that this warning be strengthened to match that in the leflunomide PI.

  Mild increases in transaminase (ALT) ≤ 3 times ULN were more frequently seen in teriflunomide treated groups as compared to placebo. Transaminase increases occurred usually within the first 6 months of treatment and often recovered with continued treatment.

- Events of nausea and diarrhoea appeared early after initiation of treatment. They were rarely considered as serious and led to treatment discontinuation in only a few patients. However, they appear specific to teriflunomide in this patient group and, since they could be a problem in the more disabled, there is a specific warning in the proposed PI.

- Alopecia carries adequate information in the proposed PI.

Other events occurring with higher frequency in the teriflunomide 7 mg or14 mg groups as compared to placebo were: viral infections, menstruation with increased bleeding, tinea infections and erythema.

- Menorrhagia is not specifically discussed in the proposed PI. Given the interactions with oral contraceptives, it is recommended that PI warnings be strengthened to include both the increased incidence of menorrhagia seen in clinical studies and the concerns about animal teratogenicity.

- Infections were the most frequently reported TEAEs in the placebo-controlled Pool 1 data set, with a slightly higher incidence in the teriflunomide treated groups compared to placebo. The evaluator believes these are adequately presented in the proposed PI.

- Cutaneous reactions, such as urticaria, erythema, pruritus and pruritic rash were observed with low incidences across treatment groups but more frequently in the teriflunomide treatment groups compared to placebo. The evaluator believes these are adequately presented in the proposed PI

Of the common reactions listed in the leflunomide (Arava) PI:

- Increase in blood pressure was common, especially in those with pre-existing hypertension. It is recommended that the teriflunomide PI warning be strengthened accordingly. Blood pressure elevations were more frequent with teriflunomide as compared to placebo with the risk for experiencing hypertension higher in patients with pre-existing hypertension at baseline.

- Weight loss was more frequently observed in the teriflunomide treated groups than in the placebo groups. The maximum median weight loss occurred at Week 48, was below 2 kg for both teriflunomide treatment groups but stabilised thereafter. It is recommended that comment be made under *Adverse Effects*, *Clinical Trial Experience*.

A decrease in mean plasma levels of uric acid was seen with teriflunomide. The uricosuric effect was considered to be most probably due to an increase in renal tubular uric acid elimination. This is adequately discussed under *Pharmacodynamics* in the proposed PI.

[18] From the leflunomide (Arava) PI

Similarly, an approximately 10% mean decrease in phosphorus plasma levels was observed which was also considered to be due to increased renal tubular elimination. This may be considered a potential risk factor for osteoporosis with long-term treatment. However, no signal in the long term Pool 2 data was detected. Again, this is adequately discussed under *Pharmacodynamics* in the proposed PI.

In vivo, teriflunomide was a moderate inhibitor of CYP2C8, a weak inhibitor of CYP3A, but not of CYP2B6, CYP2C9, CYP2C19 and CYP2D6. Teriflunomide also seemed to be a weak inducer of CYP1A2 *in vivo*. No major drug interactions are expected, however, drugs metabolised by CYP2C8 should be used with caution during the treatment with teriflunomide. Apart from the above comments on oral contraceptives, drug interactions were adequately discussed in the PI.

The study on the effects on the QT interval was adequate for safety.

List of questions

Efficacy

The final SAP report states under *Other secondary endpoints*:

> "If all hypothesis tests described above are significant at 5% level, a step down testing procedure will be applied to the following secondary endpoints in the order specified below within each dose at 2.5% significance level, that is, within a dose each hypothesis will be formally tested only if the preceding one is significant at the 2.5% level:
>
> – Change from baseline in total score of fatigue impact scale at week 108
>
> – Total number of gadolinium enhancing (Gd-enhancing) T1-lesions per MRI scan over the treatment period
>
> – Change from baseline in MRI burden of disease at week 108"

For *Fatigue Impact Scale* in the MMRM analysis: no statistically significant treatment difference (least squares mean values) was observed in the FIS score at Week 108 ($p = 0.3861$ for the teriflunomide 7 mg group compared with the placebo group and $p = 0.8271$ for the teriflunomide 14 mg group compared with the placebo group).

Question 1: Given the result for the Fatigue Impact Scale why were the other secondary endpoints tested?

The final SAP report states, under *Total volume of gadolinium-enhancing T1-lesions per MRI scan over the treatment period*:

> "Due to the non-normality of the distribution, total volume of Gd-enhancing T1-lesions per MRI scan will be analysed using rank analysis of covariance.
>
> To perform this rank analysis of covariance, baseline Gd-enhancing T1-lesions and endpoint (volume of lesions per MRI scan) will be respectively ranked (*via* NPLUS1 denominator n+1) for all patients who had both baseline and at least one on-treatment scan. No imputation is needed since patients with post baseline measurements all have the response value."

Question 2: What was the result of this analysis? Analysis results were submitted only for Patient level volume of Gd-enhancing T1-lesions per MRI scan, change from baseline at Week 108.

The evaluator also requested revisions to the PI and CMI; details of these are beyond the scope of this AusPAR.

First round clinical summary and conclusions

Benefit risk assessment

First round assessment of benefits

The benefits of teriflunomide were not demonstrated in the proposed usage, as efficacy in the proposed population of 'patients with relapsing forms of MS' were not shown. The proposed population is inclusive of all patients with MS with relapses and, despite the sponsor's assertion to the contrary, the population of the pivotal study was restricted by protocol amendment.[19] The population in Study 6049 was further restricted in that only 12 patients out of 363 (3.3%) receiving placebo had PRMS; likewise, only 14 patients out of 359 (3.9%) receiving teriflunomide 14 mg had PRMS.

First round assessment of risks

The risks of teriflunomide in the proposed usage are:

- Broadly similar to those of leflunomide, with the exception of the risk of diarrhoea and vomiting, and effects on uric acid and phosphorus.

There does not appear to be an increased risk of rarer events compared with leflunomide; however, ongoing monitoring of patients for hepatic, pancreatic and haematologic function as well as blood pressure is recommended.

First round assessment of benefit-risk balance

The benefit-risk balance of teriflunomide is unfavourable for monotherapy *for the treatment of patients with relapsing forms of MS to reduce the frequency of clinical relapses and to delay the accumulation of physical disability* given that the evaluator finds that efficacy in the proposed population was not shown.

First round recommendation

It is recommended that teriflunomide not be registered as monotherapy *for the treatment of patients with relapsing forms of MS to reduce the frequency of clinical relapses and to delay the accumulation of physical disability*.

It is recommended that the sponsor be asked to consider a more restricted population for the indications. This would require a limited amount of further evaluation of efficacy data.

Sponsor's response to the list of questions

The clinical evaluator's summary of the sponsor's responses to the clinical questions raised following the first round clinical evaluation (see *List of Questions,* above) is shown below under *Second Round Clinical Evaluation Report*.

Second round clinical summary and conclusions

Evaluation of data submitted in response to questions

Regarding question 1, the sponsor has clarified that the step down procedure applied to disability progression after ARR:

> "Statistical significance was not achieved for the key secondary efficacy endpoint of 12 week sustained disability progression for teriflunomide 7 mg versus placebo

[19] Protocol amendment 2 reads: *Exhibiting a relapsing clinical course, with or without progression (relapsing remitting, secondary progressive, or progressive relapsing).*

(p= 0.0835), the last step of this procedure, and so no formal, conclusive statistical testing could be performed for other secondary or tertiary endpoints including those covered by the other secondary endpoint step down testing procedure. The p-values for the secondary and tertiary efficacy endpoints were nominal p-values only."

Regarding question 2, the sponsor provided the location of the data requested and clarified that the p-value presented was for Total volume and not Patient level volume:

"The cumulative volume of Gd-enhancing T1-lesions per MRI scan was 0.089 in placebo group, 0.06 in the teriflunomide 7 mg group, and 0.023 in the teriflunomide 14 mg group. The rank analysis of covariance (ANCOVA) as specified in the SAP was performed to test the treatment differences and the nominal p-value derived from the analysis ($p < 0.0001$ for both doses versus placebo)"

The above were satisfactory.

Second round benefit-risk assessment

Second round assessment of benefit

After consideration of the responses to clinical questions, the benefits of teriflunomide in the proposed usage are unchanged from those identified originally (see *First round assessment of benefit*, above).

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of teriflunomide are unchanged from those identified originally (see *First round assessment of risks*, above).

Second round assessment of benefit-risk balance

The benefit-risk balance of teriflunomide is unfavourable for monotherapy for the treatment of patients with relapsing forms of MS to reduce the frequency of clinical relapses and to delay the accumulation of physical disability, given that the evaluator finds that efficacy in the proposed population was not shown.

Second round recommendation

It is recommended that teriflunomide not be registered as monotherapy *for the treatment of patients with relapsing forms of MS to reduce the frequency of clinical relapses and to delay the accumulation of physical disability*.

It is recommended that the sponsor be asked to consider a more restricted population for the indications. This would require a limited amount of further evaluation of efficacy data.

Addendum to the clinical evaluation report

At the request of the Delegate, the clinical evaluator reviewed the data to determine if efficacy had been shown for any group with MS. The evaluator's conclusions were as follows:

Evaluator's conclusions on populations for which clinical efficacy was shown:

1. Efficacy for the proposed population for the proposed indications was not shown. The inclusion criteria for the pivotal Study 6049 and the actual population enrolled were restricted to patients with RRMS, SPMS, and PRMS, and, while the inclusion criteria in Study 2001 matched that of the proposed indication, the population enrolled included only patients with RRMS and SPMS.

2. In the pivotal Study 6049, efficacy was shown for teriflunomide 14 mg in the study population for reducing the frequency of clinical relapses but not delaying the accumulation of physical disability. However, subgroup analysis showed that teriflunomide 14 mg was effective, versus placebo, in reducing the frequency of clinical relapses only in patients with RRMS; it was not effective in patients with SPMS and PRMS.
3. Subgroup analysis in Study 6049 failed to show efficacy for teriflunomide 14 mg in patients with SPMS and PRMS for delaying the accumulation of physical disability (as measured by the time to disability progression), with CIs for the hazard ratio versus placebo including 1. The same was true of the RRMS subgroup analysis.
4. Phase II exploratory Study 2001, although showing a trend, at 36 Weeks failed to show significant efficacy in reducing the frequency of clinical relapses in the population of patients with RRMS and SPMS. The study did show efficacy in delaying the accumulation of physical disability, as measured by progression in neurological functional impairment; however, the numbers in the study were small.

Overall conclusion

The evaluator concluded that:

1. The efficacy of teriflunomide 14 mg as monotherapy has been shown, to the level required by a single pivotal study, for the treatment of patients with RRMS to reduce the frequency of clinical relapses.
2. The efficacy of teriflunomide 14 mg as monotherapy has not been sufficiently shown, to the level required by a single pivotal study, for the treatment of any patient population with MS to delay the accumulation of physical disability.

The Guideline[20] has two statements relevant to these observations, under section 2.3.1 *Relapsing multiple sclerosis*:

> "Prevention and/or modification of relapse features as well as prevention or delay of the accumulation of disability as sequelae of acute relapses are meaningful goals in the treatment of RMS."
>
> "It is therefore accepted that the indication in relapsing MS will mainly rely on the effects shown in patients with relapsing remitting MS and that an effect on relapses in relapsing remitting MS may be extrapolated to an effect on relapses in secondary progressive MS."

Accordingly, the evaluator considered that the available data support the indication of:

> *Monotherapy for the treatment of patients with relapsing remitting multiple sclerosis and secondary progressive multiple sclerosis to reduce the frequency of clinical relapses*[21]

Further benefit-risk assessment

Further assessment of benefits

The benefits of teriflunomide in the treatment of patients with RRMS and SPMS are:

[20] Guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis (CPMP/EWP/561/98 Rev 1, 16 November 2006).
[21] This was the population referred to in the indications section of the PI provided originally to the TGA, but it was later retracted as an error.

- Monotherapy - *To reduce the frequency of clinical relapse*: the evaluator believes this has been adequately demonstrated.

Benefit of teriflunomide in any population was not shown for:

- Monotherapy - *To delay the accumulation of physical disability*: In the pivotal Study 6049, the evaluator believes that the level of significance required of a single pivotal study for efficacy, when assessed in the key (secondary) efficacy variable, together with the results of the supporting variables, was not met as required by the Guideline CPMP/EWP/2330/98 *Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study*.

Further assessment of risks

There was no addition to be made to this First round assessment of risks (see above):

The risks of teriflunomide in the treatment of patients with RRMS and SPMS are:

- Apparently broadly similar to those of leflunomide, with the exception of the risk of diarrhoea and vomiting and effects on uric acid and phosphorus.

There does not appear to be an increased risk of rarer events compared with leflunomide; however ongoing monitoring of patients for hepatic, pancreatic and haematologic function as well as blood pressure is recommended.

Further assessment of benefit-risk balance

The benefit-risk balance of teriflunomide is favourable for *Monotherapy in the treatment of patients with Relapsing Remitting Multiple Sclerosis and Secondary Progressive Multiple Sclerosis To Reduce the Frequency of Clinical Relapse*: the evaluator believes this has been adequately demonstrated, and the risks are similar to those seen in rheumatoid arthritis with leflunomide.

However, the evaluator believes the benefit-risk balance of teriflunomide for *Monotherapy - To Delay the Accumulation of Physical Disability* is unfavourable in any of the populations considered.

Final clinical recommendation regarding authorisation

It is recommended that teriflunomide be registered as follows:

> *[Product] is indicated as monotherapy for the treatment of patients with relapsing remitting multiple sclerosis and secondary progressive multiple sclerosis to reduce the frequency of clinical relapses.*

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP), Version 1.0, [Data lock point 24 Feb 2011] with Australian Specific Annex (ASA) Version 1.0 dated November 2011 and updated ASA Version 1.1 dated May 2012, which was reviewed by the TGA's Office of Product Review (OPR).

Safety Specification

The summary of the Ongoing Safety Concerns, as specified by the sponsor, is shown below:

Table 11. Summary of the Ongoing Safety Concerns

Important identified risks	Liver transaminase elevation Blood pressure increase
Important potential risks	Potential risk to the fetus in pregnant women White blood cell decrease leading to significant clinical complications, including infections Serious opportunistic infections Platelet count decrease leading to significant clinical complications, including haemorrhages Adverse cardiovascular events potentially associated with blood pressure elevation Interstitial lung disease (based on effects observed with leflunomide) Hypersensitivity reactions, including severe skin reactions Malignancies Peripheral neuropathy Osteoporosis associated with hypophosphatemia Off-label use in adults Interaction with CYP2C8 substrates Interaction with CYP1A2 substrates Interaction with warfarin Interaction with oral contraceptives
Important missing information	Use in pregnant and lactating women Use in Non-Caucasian patients Use in patients with severe hepatic impairment Use in combination with transporter substrates (OATP1B1, BCRP and OAT3) Use in children and adolescents Use in elderly patients Use in combination with MS treatments (other than IFN and GA) Concomitant use of vaccine

The reviewer considered the above summary of the Ongoing Safety Concerns is acceptable.

Pharmacovigilance plan

Routine pharmacovigilance activities are proposed to monitor all ongoing safety concerns. In addition, the sponsor proposes the following additional pharmacovigilance activities:

Table 12. Proposed pharmacovigilance activities

Additional pharmacovigilance activity	Assigned safety concerns	Conducted in Australia?
Long term safety study	**Important identified risks** Liver transaminase elevation Blood pressure increase **Important potential risks** White blood cell decrease leading to significant clinical complications, including infections Serious opportunistic infection Platelet count decrease leading to significant clinical complications, including haemorrhages and thromboembolic events Adverse cardiovascular events potentially associated with blood pressure elevation Interstitial lung disease (based on effects observed with leflunomide) Malignancy Peripheral neuropathy	No (European countries only)
Pregnancy registry	**Important potential risks** Potential risk to the foetus in pregnant women	Inclusion of Australian patients
Targeted questionnaires	**Important identified risks** Liver transaminase elevation **Important potential risks** Potential risk to the foetus in pregnant women Interstitial lung disease (based on effects observed with leflunomide) Peripheral neuropathy **Important missing information** Use in pregnant and lactating women	Yes

These were considered acceptable.

Risk minimisation activities

The sponsor states in their evaluation of the need for risk minimisation activities:

> "The product labelling and the patient information leaflet (PIL) are the routine communication tools for risk. However, for the important identified risks and several of the potential risks, additional risk minimisation activities are also proposed to further enhance this positive benefit-risk profile and to ensure that teriflunomide is used in line with the current prescribing information."

The sponsor describes in the updated ASA:

> "Additional risk minimisation activities include communication tools designed to inform, educate and mitigate identified and potential risks. The tools include a Prescriber/Healthcare Professional Checklist, which is the equivalent of the Discussion Guide described in the Core RMP, and a Patient Education Card and a Referral Letter Template for specialists to communicate ongoing monitoring requirements for patients referred to General Practitioners."

The sponsor's conclusions regarding the need for risk minimisation activities are considered acceptable.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application:

It is recommended that the Delegate:

- Implement RMP Version 1.0, dated 24 Feb 2012 with ASA Version 1.1 dated May 2012, including the sponsor's response to the TGA's request for information/documents and any future updates, as a condition of registration.
- May consider aligning the proposed PI with the PI of Arava (leflunomide), particularly with regards to liver function monitoring and use in patients with pre-existing acute or chronic liver disease or those with ALT > 2times ULN.
- Note that if teriflunomide is not granted registration in the EU, then the planned study to assess long-term safety in routine clinical practice and to determine incidence of AEs of special interest is unlikely to be done.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Background

Teriflunomide is the active, predominant metabolite of leflunomide, an immunomodifier approved for use in the treatment of active rheumatoid arthritis and active psoriatic arthritis.

Multiple sclerosis is characterised by the development of inflammatory plaques in the central nervous system including the brain, spinal cord and optic nerves. The primary process is inflammatory damage to the myelin of the CNS, which may be reversible but axonal damage may also occur and leads to increasing permanent disability. Multiple sclerosis also has a degenerative component and is associated with progressive brain atrophy.

The TGA has adopted the November 2006 version of the EU *Guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis* (CPMP/EWP/561/98 Rev. 1, 16 November 2006). That Guideline states that the term

'relapsing MS' includes: 1) patients with RRMS, 2) patients with SPMS and superimposed relapses, and 3) patients with a single demyelinating clinical event who show lesion dissemination on subsequent MRI scans according to McDonald's criteria (2005 revision). Relapses are considered the clinical expression of acute inflammatory focal lesions, whereas progression is considered to reflect the occurrence of demyelination, axonal loss and gliosis. Relapsing remitting MS and SPMS are probably different stages of the same disease, while PPMS may imply different processes.

McDonald's criteria are diagnostic criteria for MS. Following adoption of the above Guideline, the McDonald criteria were revised. The current McDonald criteria allow for a single symptomatic episode with MRI evidence of past demyelination. The criteria as amended in 2010/2011 are shown in Table 13.

Table 13. McDonald's criteria for diagnosis of Multiple Sclerosis (2010)

Clinical Presentation	Additional Data Needed for MS Diagnosis
≥2 attacks[a]; objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack[b]	None[c]
≥2 attacks[a]; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or Await a further clinical attack[a] implicating a different CNS site
1 attack[a]; objective clinical evidence of ≥2 lesions	Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack[a]
1 attack[a]; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For DIS: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or Await a second clinical attack[a] implicating a different CNS site; and For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack[a]
Insidious neurological progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria[d]: 1. Evidence for DIS in the brain based on ≥1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions 2. Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

If the Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is "MS"; if suspicious but the Criteria are not completely met, the diagnosis is "possible MS"; if another diagnosis arises during the evaluation that better explains the clinical presentation, then the diagnosis is "not MS."

[a]An attack (relapse; exacerbation) is defined as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection. It should be documented by contemporaneous neurological examination, but some historical events with symptoms and evolution characteristic for MS, but for which no objective neurological findings are documented, can provide reasonable evidence of a prior demyelinating event. Reports of paroxysmal symptoms (historical or current) should, however, consist of multiple episodes occurring over not less than 24 hours. Before a definite diagnosis of MS can be made, at least 1 attack must be corroborated by findings on neurological examination, visual evoked potential response in patients reporting prior visual disturbance, or MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms.

[b]Clinical diagnosis based on objective clinical findings for 2 attacks is most secure. Reasonable historical evidence for 1 past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristics for a prior inflammatory demyelinating event; at least 1 attack, however, must be supported by objective findings.

[c]No additional tests are required. However, it is desirable that any diagnosis of MS be made with access to imaging based on these Criteria. If imaging or other tests (for instance, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS, and alternative diagnoses must be considered. There must be no better explanation for the clinical presentation, and objective evidence must be present to support a diagnosis of MS.

[d]Gadolinium-enhancing lesions are not required; symptomatic lesions are excluded from consideration in subjects with brainstem or spinal cord syndromes.

MS = multiple sclerosis; CNS = central nervous system; MRI = magnetic resonance imaging; DIS = dissemination in space; DIT = dissemination in time; PPMS = primary progressive multiple sclerosis; CSF = cerebrospinal fluid; IgG = immunoglobulin G.

An important point to consider in the Guideline with respect to RMS is that, although the effect on relapse rate may be investigated in patients with any form of relapsing MS, it is advised to assess the effect on disability only in patients with RRMS. It is therefore accepted that the indication in RMS will mainly rely on the effects shown in patients with RRMS and that an effect on relapses in RRMS may be extrapolated to an effect on relapses in SPMS.

The Guideline provides the following advice on primary efficacy parameters in clinical trials for RRMS:

- The most relevant parameter in MS, the accumulation of disability, usually takes place over many years.
- Changes in progression of disability in a few years, which can be shown in clinical trials, could be accepted as a proof of efficacy, although it would be highly desirable to evaluate if the effect is maintained on a long-term basis.
- Changes in progression of disability should be distinguished between accumulation of disability in relation to relapses in RRMS and progression of disability in SPMS or in PPMS.
- In patients with RRMS or SPMS with superimposed relapses (RMS), the primary efficacy parameter may also be the relapse rate although the number, duration or severity of relapses cannot be taken as a surrogate for disease progression and this would be expressed accordingly in the Summary of Product Characteristics (SmPC; equivalent to the PI in Australia).
- Progression of disability should be evaluated and worsening of disability should be reasonably excluded by means of adequately powered long-term studies.
- In patients with CIS, the relapse rate and the percentage of patients with no further relapses are preferred efficacy variables instead of the time to the second clinical event. As in other MS forms, accumulation of disability is considered a relevant efficacy parameter that should be evaluated.

At the time of submission, fingolimod (Gilenya) was the only oral immunomodifier treatment for MS approved in Australia. Another oral immunomodifier, cladribine (Movectro) was approved in August 2010 for RRMS only and only for up to 2 years, but was subsequently withdrawn from the market by the sponsor. Other immunomodifier agents for MS include: IFN-β1a, IFN-β1b, GA, and natalizumab. Fampridine, an orally administered potassium channel blocker, is the most recently approved medicine for patients with MS. It was approved in May 2011 for the symptomatic improvement of walking ability in adult patients with MS who have shown improvement after 8 weeks of treatment. The interferons and GA have indications that include treatment after a single demyelinating event with associated brain MRI abnormalities characteristic of MS. Natalizumab is indicated only for treatment of RRMS. Interferon β-1b and natalizumab have indications which include delaying progression of disease/ disability and reduction in frequency of relapse. Given the revised McDonald's criteria, CIS with evidence of past demylination can now be considered as a form of relapsing MS. To date, only the interferons have indications that include treatment of all relapsing forms of MS.

Quality

This submission was considered by the PSC on 19 March 2012 when it resolved the following:

1. The PSC endorsed all the questions raised by the TGA in relation to pharmaceutic and biopharmaceutic aspects of the submission by Sanofi-Aventis Australia Pty Ltd to register Aubagio/Teriflunomide Sanofi/Teriflunomide Winthrop film coated tablets containing 14 mg of teriflunomide. In particular, the committee supported the evaluator's questions in relation to the stability of the product, drug substance and finished product specifications, and the validity of the bioavailability studies provided in support of this submission.
2. The committee advised that all outstanding issues should be addressed to the satisfaction of the TGA.
3. The PSC agreed that:

- The safety profile of the drug substance should be thoroughly investigated in view of the fact that the structure raises some safety signals/concerns.
- The sponsor should be asked to provide batch analysis data on three consecutive validation batches for the drug product.

4. With regards to the PopPK analysis, the PSC noted the unusual deviations from the analysis plan. The committee advised that:
   - The p-values for three of the four terms describing inter-subject variability were < 0.002 for the structural model(s) and the final covariate model, an indication that simulations involving between subject variability could be flawed.
   - The predictions do not adequately describe the variability in the data as evidenced by the under and over predictions for the 14 mg and the 70 mg dose, respectively.
   - The absence of the visual predictive checks categorised for the covariates makes it difficult to interpret the appropriateness of the model with regards to covariate effects.

The committee also recommended several revisions be made to chemistry and quality aspects of the PI, the details of which are beyond the scope of this AusPAR.

There was no requirement for this submission to be reviewed again by the PSC before it was presented for consideration by the ACPM.

The issues outstanding at the time of the PSC's consideration were successfully negotiated and there are no chemistry or quality control issues that would preclude approval.

Nonclinical

There are no nonclinical objections to the registration of teriflunomide for the proposed indication.

The nonclinical evaluator noted that teriflunomide is the ring-opened form of leflunomide (Arava, Sanofi-Aventis; registered for the treatment of rheumatoid arthritis in 1998; dose 20 mg/day) and accounts for virtually all of the activity of leflunomide.

Teriflunomide was extensively investigated in animal studies of safety pharmacology, PK, toxicity, carcinogenicity, genotoxicity and reproductive toxicity. The toxicological profile of teriflunomide across the range of studies is qualitatively and (based on AUC for teriflunomide) quantitatively similar to that of its parent compound leflunomide, with the main target tissues/organs being those with rapidly dividing cells (haematopoietic, GI, skin and reproductive in particular). Suppressed immune responses to antigens were shown in limited studies.

Considering its pharmacological activity and the known toxicities of leflunomide, teriflunomide studies did not reveal toxicities that were novel, unexpected or previously unidentified, with the possible exception of the pancreas. The nonclinical evaluator considered that risks associated with the use of leflunomide will almost certainly also apply to the use of teriflunomide.

Studies with human-derived CYP450 subtypes showed potential for teriflunomide to inhibit the activity of CYP2C8 and CYP2B6, to induce the activity of CYP3A4, and to induce or inhibit (depending on the concentration) the activity of CYP2C9.

Like leflunomide, teriflunomide is teratogenic and should be included in Pregnancy Category X.[22]

Clinical

Pharmacology

While an absolute bioavailability study was not performed, absorption is likely to be almost 100% after oral dosing, and enterohepatic circulation occurs. Food has minimal effect on the absorption of teriflunomide. The estimated half-life is approximately 19-20 days in patients with MS, with steady state achieved after approximately 100 days of treatment. Teriflunomide is highly protein bound and volume of distribution is approximately 11 L.

The predominant clearance pathway (approximately two thirds of the total clearance) for teriflunomide appears to be biliary excretion of parent compound together with possibly direct GI secretion. Metabolic clearance represents the remaining one third of total clearance. The primary biotransformation pathway for teriflunomide is hydrolysis, with oxidation being a minor pathway. Secondary pathways involve oxidation, N-acetylation and sulfate conjugation. Approximately 21.3% of a single dose is excreted as metabolites in the urine and 1.8% as metabolites in the faeces. Both activated charcoal and cholestyramine decrease the half-life of teriflunomide, suggesting that biliary recycling is a major contributor to its long elimination half-life. Studies of leflunomide have indicated that teriflunomide is not dialysable.

There is substantial variability in the PK of teriflunomide between individuals. In patients with MS, the inter-patient coefficient of variation for teriflunomide clearance was 55.2%. Suggested possible factors for the high variability seen after repeated doses were: intestinal secretion/reabsorption leading to enterohepatic recycling, and differences in time to achieve steady-state from the long terminal half-life.

Dose adjustment is not required in patients with mild to moderate hepatic impairment but has not been assessed for patients with severe hepatic impairment. Renal impairment does not significantly affect the PK of teriflunomide.

Potent CYP and transporter inducers may affect exposure to teriflunomide. An increase in exposure (especially of AUC) may occur with concomitant use of CYP2C8 substrates, such as paclitaxel, repaglinide, pioglitazone or rosiglitazone. When teriflunomide was given with the combined oral contraceptive, Minidril (0.03 mg ethinylestradiol and 0.15 mg levonorgestrel), there was a moderate increase in mean ethinylestradiol Cmax and $AUC_{0\text{-}24\,h}$ (1.58- and 1.54-fold, respectively) and levonorgestrel Cmax and $AUC_{0\,24\,h}$ (1.33- and 1.41-fold, respectively).

Teriflunomide co-administration with medicines metabolised by CYP1A2 (for example, duloxetine, alosetron, theophylline, tizanidine) may lead to a reduction of their efficacy.

The results of the PK studies for teriflunomide performed for this submission are consistent with those of earlier studies where teriflunomide PK were assessed as the active metabolite of leflunomide. The relative bioavailability of leflunomide (as measured by teriflunomide concentrations) was approximately 70% of that of teriflunomide: Cmax: 63% (90% CI 58%-69%) and $AUC_{0\text{-}72\,h}$ 73% (90% CI: 69%-77%). The proposed dose of 14 mg daily is 70% of the standard dose of leflunomide for active rheumatoid or psoriatic arthritis, therefore the proposed exposures of patients with MS to teriflunomide are similar to those currently occurring in patients given leflunomide.

[22] The definition of Category X is: Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

The primary PD effect of teriflunomide was identified during development of leflunomide. Teriflunomide is an immunomodulator with both anti-proliferative and anti-inflammatory activity by potent (IC_{50} = 1.25 μM), noncompetitive, selective and reversible inhibition of the mitochondrial enzyme DHO-DH. That leads to a blockade of *de novo* pyrimidine synthesis and a subsequent cytostatic effect on proliferating T and B lymphocytes in the periphery, resulting in diminished numbers of activated lymphocytes available to enter the CNS. Slowly dividing or resting cells which rely on salvage pathways for pyrimidine supply are unaffected by teriflunomide. Like leflunomide, teriflunomide is also associated with dose-related decreases in uric acid, and alopecia.

An *in vitro* study (IIVT0017) reported that inhibition of teriflunomide-induced proliferation in human T cells and B cells could be reversed by the addition of exogenous uridine.

Efficacy

Only data for monotherapy teriflunomide were submitted, including a pivotal efficacy/safety study and a double-blind extension study which is ongoing. Study 6049 (the TEMSO study) was a 2 year, multicentre, multinational, randomised, placebo-controlled, double-blind, parallel-group, stratified (by centre and by baseline EDSS score [≤ 3.5 (that is, fully ambulatory), versus > 3.5]) study of teriflunomide in patients with MS.

The primary objective was to determine the effect of teriflunomide in reducing the frequency of relapses in subjects with relapsing MS. The primary efficacy variable was the ARR. The effect of teriflunomide on delaying the accumulation of disability at 2 years, assessed using the Kurtzke EDSS, was a secondary efficacy objective. The primary efficacy variable was the ARR, defined as the number of confirmed relapses per patient-year. The key secondary efficacy variable was time to disability progression, defined as the time to at least 1 point increase on EDSS score from baseline (if the baseline EDSS score was ≤ 5.5), or time to at least 0.5 point increase on EDSS score from baseline (if the baseline EDSS score was > 5.5), and this increase in EDSS score was to be persistent for at least 12 weeks. Major inclusion criteria were:

- Patients with MS, aged 18 to 55 years, who were ambulatory (EDSS of ≤ 5.5);
- Exhibiting a relapsing clinical course, with or without progression (RRMS, SPMS or PRMS);
- Meeting McDonald's criteria for MS diagnosis;
- Experienced at least 1 relapse over the 1 year preceding the trial or at least 2 relapses over the 2 years preceding the trial;
- No relapse onset in the preceding 60 days prior to randomisation;
- During the 4 weeks prior to randomisation, patients must have been clinically stable, without adrenocorticotrophic hormone or systemic steroid treatment.

Significant exclusion criteria were:

- Prior or concomitant use of cladribine, mitoxantrone, or other immunosuppressant agents such as azathioprine, cyclophosphamide, cyclosporine, methotrexate, or mycophenolate;
- Prior use of interferons or cytokine therapy in the preceding 4 months;
- Prior use of GA therapy in the preceding 4 months or IV immunoglobulins in the preceding 6 months.

Screening occurred over up to 4 weeks. Subjects were randomised (1:1:1 stratified, based on centre, and by patient's EDSS score [≤ 3.5 or > 3.5]) to once daily: placebo; 7 mg

teriflunomide; or 14 mg teriflunomide. Treatment continued for up to 2 years and was followed by an optional long-term extension study (LTS6050) or an 11 day washout period with cholestyramine or activated charcoal to accelerate elimination of teriflunomide to levels to less than 0.02 µg/mL. An MRI scan of the brain and the spinal cord and an abdominal ultrasound of the pancreas (followed by pancreatic computed tomography (CT) or MRI scan if abnormal) were performed at baseline, at 6 month intervals for the first 72 weeks, and at the close-out visit.

A total of 1088 subjects were randomised, with 91.5% diagnosed with RRMS. Median baseline EDSS score was 2.50, equating to mild disability in one functional system or minimal disability in two functional systems. The mean EDSS at baseline was 2.68 with a range of 0 (that is, no symptoms) to 6 (that is, needing intermittent or unilateral constant assistance (cane, crutch or brace) to walk 100 meters with or without resting). Some 77.1% of subjects had an EDSS of ≤3.5. A median of 1 relapse had occurred in the preceding year. A total of 73% of randomised subjects had received no previous treatment with MS medication. Subjects had a mean of 1.6 (median of 0) gadolinium enhancing lesions on MRI at baseline and 36.2% of subjects had ≥1 enhancing lesion.

A similar proportion of subjects in each treatment group completed the 2 years of study (from 71.3% on placebo to 74.9% on teriflunomide 7 mg). During the 2 year course of the study, relapses were experienced by 50.7% of subjects given placebo, 42.2% given teriflunomide 7 mg, and by 39.4% given teriflunomide 14 mg (ITT population). The adjusted ARR was 0.539 (95% CI: 0.466 to 0.623) in the placebo group, 0.370 (95% CI: 0.318 to 0.432) in the teriflunomide 7 mg group, and 0.369 (95% CI: 0.308 to 0.441) in the teriflunomide 14 mg group. These results corresponded to a relative risk for relapse during the study period of 68.8% (p = 0.0002) in the teriflunomide 7 mg group and 68.5% (p = 0.0005) for the teriflunomide 14 mg group, compared with placebo. Results for the PP population were similar and were also statistically significant for relative risk of relapse for each dose of teriflunomide versus placebo.

Few patients had disability progression sustained for 12 weeks during the course of the study: placebo (86; 23.7%), teriflunomide 7 mg (68; 18.6%), teriflunomide 14 mg (62; 17.3%). The Kaplan-Meier estimate of the percentage of patients with 12 week sustained disability progression at Week 108 was 27.3%, 21.7%, and 20.2% in the placebo, teriflunomide 7 mg, and teriflunomide 14 mg groups, respectively. In the 14 mg/day teriflunomide group, the risk for disability progression was reduced by 29.8% (p = 0.0279) for the ITT population. The risk of disability progression in the 7 mg/day teriflunomide group was reduced by 23.7% compared with placebo, and this was not statistically significant. No large differences in the rate of disability progression were seen for the groups with baseline EDSS ≤ 3.5 versus > 3.5.

The PP population had similar results to the ITT population, that is, a statistically significant reduction in risk of disability progression compared with placebo for the 14 mg dose but not for the 7 mg dose.

There was a trend towards fewer subjects given either dose of teriflunomide having less disability progression sustained for 24 weeks, but the results did not reach statistical significance.

Changes in volume of abnormal brain tissue and in the number of gadolinium enhancing lesions over time were assessed using MRI. Of the 1086 patients in the ITT population, 358 patients in the placebo group, 359 patients in the teriflunomide 7 mg group, and 355 patients in the teriflunomide 14 mg group were included in the MRI examination at baseline. At Week 108, the mean change in absolute value of cubic root transformed burden of disease (BOD) from baseline was 0.111 for the placebo group, 0.072 for the teriflunomide 7 mg group and 0.045 for the teriflunomide 14 mg group. The model adjusted, least square mean difference from baseline was -0.053 (95% CI: -0.101 to

-0.005) for the teriflunomide 7 mg group and -0.089 (95% CI: -0.137 to -0.041) for the teriflunomide 14 mg group, with the corresponding p values of 0.0317 and 0.0003, respectively.

A total of 137 patients (38.2%) in the placebo group, 127 patients (35.4%) in the teriflunomide 7 mg group and 125 patients (35.2%) in the teriflunomide 14 mg group had at least 1 gadolinium-enhancing T1 lesion per MRI scan at baseline. After 108 weeks, there was a greater reduction in the number of gadolinium-enhancing T1 lesion per MRI scan in both teriflunomide groups compared to placebo. The adjusted gadolinium-enhancing T1 lesion per scan was 1.331 (95% CI: 1.059 to 1.673) in the placebo group, 0.570 (95% CI: 0.434 to 0.748) in the teriflunomide 7 mg group, and 0.261 (95% CI: 0.167 to 0.407) in the teriflunomide 14 mg group. There was a statistically significant difference from placebo in relative risk reduction of 57.2% ($p < 0.0001$) in the teriflunomide 7 mg group and of 80.4% ($p < 0.0001$) in the teriflunomide 14 mg group, compared with placebo.

Study 6050 is the long term extension of Study 6049 and is planned to last for 6 years. Data from October 2006 when the first patient was enrolled until January 2011 were presented in an Interim Analysis. The blind was maintained for patients on active treatment with either 7 mg or 14 mg teriflunomide, and subjects who had been randomised to placebo in Study 6049 were re-randomised to active treatment. This was primarily a safety and tolerability study with accumulation of disability a secondary endpoint. A total of 740 subjects were randomised and received treatment, including 237 subjects who were re-randomised from placebo to teriflunomide 7 mg (n = 129) or 14 mg (n = 108).

There was a trend towards higher exposure to teriflunomide and less risk of disability progression, but the differences were not statistically significant. Data are provided to 5 years, however only 135 patients had completed 5 years of treatment. The rates of 24 Week sustained disability were not statistically significant for any dose group, but there was a suggestion that those commencing either dose of teriflunomide early had less accumulated disability sustained to 24 Weeks than those commenced on placebo initially.

Study 2001 was a Phase II study with a similar design but with the primary efficacy variable of T2/proton density and gadolinium-enhanced T1 activity from MRI scans. The double-blind treatment period was 36 weeks. A total of 177 subjects were randomised to treatment: placebo (n = 61); teriflunomide 7 mg (n = 60); and teriflunomide 14 mg (n = 56). MRI assessment included the total number of lesions, number of enhancing lesions, number of new lesions and a measure of the volume of lesions (disease burden). Results were generally statistically significant, favouring teriflunomide and showing a dose response relationship. In contrast, the ARRs were 0.81 for placebo, 0.58 for teriflunomide 7 mg and 0.55 for teriflunomide 14 mg, and the placebo versus active comparisons were not statistically significant, as would be expected from such a small study over a comparatively short duration.

A meta-analysis of results from the Studies 6049 and 2001 showed no statistically significant relationship between mean teriflunomide concentration and ARR or burden of disease at Week 108.

Safety

The clinical development program for teriflunomide included 29 clinical studies: 18 Phase I studies and 11 Phase II/III studies of which 6 are ongoing. Evaluation of safety data from the completed Phase II/III studies was based on 2 types of pooled analyses: Pool 1, focusing on the placebo-controlled segments of studies; and Pool 2, focusing on the active treatment, including the core and the extension segment of the studies. Patients in the open extension phases of the primary extension study had been exposed to teriflunomide for 2.5 years on average, including during the initial double-blind 2 year

treatment period. A total of 691 patients had received teriflunomide for > 2 years in the monotherapy MS studies.

The major safety concerns for leflunomide, the parent compound of teriflunomide, are: increased risk of severe liver injury; bone marrow suppression (particularly if used in combination with other immune suppressants); and hypersensitivity reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis. Severe liver injury and bone marrow suppression are rare events with leflunomide, but have caused fatalities. Leflunomide may also increase the risk of malignancies with long term use, and is in pregnancy category X (*Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy*). Leflunomide is also associated with an increased risk of peripheral neuropathy, hypertension, and weight loss. Monitoring of haematological and hepatic function is recommended before commencement of treatment, monthly for the first 6 months, followed by 6-8 weeks thereafter. Teriflunomide is likely to have a very similar risk profile.

In the teriflunomide versus placebo studies, the following AEs were most frequently reported.

- diarrhoea (8.3%, 14.0%, 17.3% for placebo, teriflunomide 7 mg and teriflunomide 14 mg, respectively),
- alopecia (4.3%, 11.2%, 14.7%, respectively),
- nausea (6.9%, 9.3%, 14.2%, respectively),
- ALT increase (7.1%, 12.6%, 14.0%, respectively,) and
- paraesthesia (7.8%, 9.6%, 10.6%, respectively).

There was a clear dose relationship for the majority of these events. Diarrhoea, alopecia, nausea and paraesthesia infrequently led to permanent premature treatment discontinuation.

Increases of ALT > ULN and > 3 times ULN occurred with both doses of teriflunomide (29.5%, 47.7% and 49.6% for placebo, teriflunomide 7 mg and teriflunomide 14 mg groups, respectively). There were no differences between treatment groups for higher elevations or for serious hepatic TEAEs.

Neutropenia was reported more frequently with the 14 mg teriflunomide dose (0.5%, 2.3%, 4.6% for placebo, teriflunomide 7 mg and teriflunomide 14 mg groups, respectively). In the Pool 1 population, haematological AEs were reported in 6 (1.4%), 20 (4.7%) and 24 (5.8%) of the placebo, teriflunomide 7 mg and teriflunomide 14 mg groups respectively.

One subject in each teriflunomide group discontinued treatment due to a non-serious bone marrow disorder (decreased neutrophil count). Serious neutropenia/neutrophil count decreased was reported in 1 subject given placebo, 4 given teriflunomide 14 mg and none given teriflunomide 7 mg.

TEAEs potentially related to peripheral neuropathy were reported with a higher frequency in patients given teriflunomide 14 mg (4.8%, 3.7%, 6.0% for placebo, teriflunomide 7 mg and teriflunomide 14 mg groups, respectively), with 1 patient discontinuing in each teriflunomide treatment group. New-onset hypertension (TEAE) occurred in 2.8% and 3.5% of patients in the teriflunomide 7 mg and 14 mg groups, compared to 1.3% of patients given placebo. Exacerbation/worsening of pre-existing hypertension was more frequent in patients treated with teriflunomide compared to placebo (9.5% and 10.6% in teriflunomide 7 mg and 14 mg compared to 8.9% in placebo).

The maximum mean weight loss occurred at Week 48, was below 2 kg (< 4.4 pounds) for both teriflunomide treatment groups, and stabilised thereafter.

Forty-five pregnancies occurred in subjects enrolled in clinical studies. Among these, 10 pregnancies went to term. Teriflunomide was discontinued immediately after pregnancy diagnosis and the patients were required to undergo an accelerated elimination procedure. Those 10 patients delivered healthy newborn babies. None had malformations or functional problems reported that could suggest a link to a teratogenic effect. In addition, 8 pregnancies went to term in 12 pregnant female partners of male patients, also with healthy newborn babies. The weight and the gestational age of the newborns were not different from those observed in the typical MS population. Information on abnormalities in the remaining 35 pregnancies that did not go to term was not discussed in the available data.

In the Study EFC6049/TEMSO, the frequency of relapses during the washout period was numerically lower than the frequency on-treatment for both teriflunomide doses and placebo, suggesting there is no major rebound phenomenon.

At the time the submission was developed, 7 deaths had been reported in clinical studies, none in the Pool 1 studies, 4 in Pool 2 studies and 3 in ongoing studies. Of the deaths in Pool 2, there were 3 that involved cardiovascular disorder and one where the cause of death was unknown.

The clinical evaluator recommended ongoing monitoring of patients for hepatic, pancreatic and haematologic function as well as blood pressure. The evaluator also recommended that signals for the rarer complications associated with leflunomide should be sought: eosinophilia; leucopoenia; pancytopenia; hepatitis; jaundice/cholestasis; severe infections and interstitial lung disease (including interstitial pneumonitis); severe anaphylactoid reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme; agranulocytosis; severe liver injury such as hepatic failure, and acute hepatic necrosis; pancreatitis; and peripheral neuropathy.

Clinical evaluator's recommendation

The clinical evaluator recommended the indication be limited to a claim for reduction in the number of relapses in patients with RRMS and SPMS. The clinical evaluator recommended against a claim for reduction in disability, as the evidence from one randomised clinical trial (RCT) was not sufficiently supportive.

Risk management plan

The OPR has indicated the RMP is supportive to the application.

In addition to routine pharmacovigilance, the sponsor proposes the following additional activities:

- A long term prospective cohort study to investigate the incidence of selected safety events and overall safety in patients treated with teriflunomide. That study is to be conducted in Europe and its protocol has not yet been finalised.
- A pregnancy registry which would include Australian patients.
- A targeted questionnaire on specific AEs.
- Educational materials for health care professionals (HCPs) and carers, as described in the RMP evaluation.

The RMP evaluator has recommended implementation of RMP Version 1.0, dated 24 Feb 2012 with ASA Version 1.1 dated May 2012, including the sponsor's response to TGA

requests for information/documents and any future updates, as a condition of registration. The RMP evaluator has recommended PI amendments to align liver function monitoring and use in patients with pre-existing acute or chronic liver disease or those with ALT > 2 times ULN with the current recommendations for leflunomide.

If teriflunomide is not granted marketing authorisation in Europe, the planned study to assess long-term safety in routine clinical practice and to determine incidence of AEs of special interest is unlikely to be performed.

Risk-benefit analysis

Delegate considerations

The sponsor requested an indication that includes all forms of relapsing MS. The clinical evaluator recommended the indication be limited to a claim for reduction in the number of relapses in patients with RRMS and SPMS. The clinical evaluator recommended against a claim for reduction in disability, as the evidence from one RCT was not sufficiently supportive. A second RCT with similar design to the Phase III study included with this submission is due to report in 2015.

Given the current Guideline[23] recommendations, it is accepted that an indication in RMS will mainly rely on the effects shown in patients with RRMS and that an effect on relapses in RRMS may be extrapolated to an effect on relapses in SPMS. In the period since the TGA adopted the Guideline, the McDonald criteria for diagnosis of MS have been amended and it is now possible to confirm a diagnosis of MS in a patient who presents with a single symptomatic episode but who has MRI evidence at presentation of previous lesions. The older criteria required a subsequent MRI to confirm the diagnosis. At this time, the Delegate proposed to specify RRMS and SPMS in the indication. This is consistent with the TGA's adopted Guideline. Further evidence of efficacy would be required to extend the indication to include patients who have had a single symptomatic episode regardless of MRI findings.

The clinical evaluator considers that any claim for prevention of disability should await a second Phase III study (the TOWER Study, due to be reported on in 2015). This was recommended due to the small and inconsistent difference in rates of disability progression demonstrated in the single Phase III study included in this submission. The Delegate noted that the approximately 30% reduction in disability progression at Week 108 is similar to that demonstrated with fingolimod.[24] There were 2 Phase III efficacy and safety studies supporting the fingolimod submission; however, only one of these assessed disability progression to 24 months. That study showed statistically significant reductions in the hazard ratio for disability progression for both 3 month and 6 month sustained disability. Statistically significant differences in disability progression were not demonstrated by fingolimod in the second Phase III study that assessed progression over 12 months. Cross-study comparisons are necessarily limited and the definition of disability progression in the fingolimod study was slightly different from that used in the pivotal study for this submission. However, given the magnitude of difference in disability progression with teriflunomide is similar to that of fingolimod, the Delegate was inclined to consider that statements concerning an effect on disability progression could be included in the indications for teriflunomide.

23 Guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis (CPMP/EWP/561/98 Rev. 1,16 November 2006).
24 Information from the PI for Gilenya.

Proposed action

Three products (fingolimod, natalizumab and IFN-β1b) currently include in their indications a statement concerning reduction in progression of disability, rather than "prevention of accumulation" of disability as has been proposed for teriflunomide. The key secondary efficacy parameter concerning disability in the pivotal study for teriflunomide was 'confirmed 12 week sustained disability progression'. To be consistent with the recommendations in the Guideline and the key secondary efficacy endpoint in the pivotal study for efficacy of teriflunomide, the Delegate proposed that teriflunomide be approved for the following:

> *[Product] is indicated for the treatment of patients with ~~relapsing forms of multiple sclerosis~~* ***Relapsing Remitting Multiple Sclerosis and Secondary Progressive Multiple Sclerosis with superimposed relapses*** *to reduce the frequency of clinical relapses and to delay the ~~accumulation~~* ***progression*** *of physical disability.*

Proposed condition of registration

Adherence to the current RMP and subsequent amendments should be a condition of registration.

Advice requested from ACPM

The Delegate sought general advice on this application from the ACPM and requested the ACPM address the following issues in particular:

- Should the indications extend to include patients with any form of relapsing MS in the absence of data on efficacy and safety in patients with a single clinical episode and MRI evidence of past disease activity?
- Is there sufficient evidence that teriflunomide delays the progression of disability for a statement on disability progression to be included in the indications, noting that the level of evidence is somewhat lower than has previously been accepted to support this claim?
- Should concomitant treatment with other immune modulators specifically be excluded either in the *Indications* or *Precautions* sections of the PI?
- Should the indications specifically exclude individuals with MS aged < 18 years, or should the absence of efficacy and safety data for patients with MS in this age group be reflected in the *Paediatric Use* section of the PI?

Response from sponsor

The sponsor's comments on the issues for which the advice of the ACPM is sought, as outlined in the Delegate's overview, above, are presented below.

The sponsor agrees with the recommendation of the Delegate to approve the application for teriflunomide and to include reference 'to delay the progression of physical disability' in the indication. As part of the responses below, the sponsor provides a justification for retaining reference to the MS population as 'patients with RMS', as included in the original application. The sponsor proposed the following revised indication:

> *[Product] 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.*

Delegate's question: Should the indications extend to include patients with any form of relapsing MS in the absence of data on efficacy and safety in patients with a single episode and MRI evidence of past disease activity?

Sponsor's response: The evaluator discusses the indication in light of the evolving diagnosis criteria for MS. The sponsor would like to highlight that the evolution of the diagnosis criteria is not directly related to the forms of the disease, nor to the indication. The evolution of the criteria allows for an earlier and simpler diagnosis of MS, based on evidence of dissemination in space and in time which is considered appropriate for the diagnosis, but it is the same disease which is diagnosed, with good sensitivity and specificity. Furthermore, there was already the possibility to make the diagnosis of MS after a single episode based on the 2001 version of the McDonald criteria, the difference being that after the 2010 revision, it is no longer mandatory to wait for at least 3 months for a confirmatory MRI. This option was available in EFC6049/TEMSO, for which the diagnosis had to be based on the 2001 version of the McDonald criteria, with the additional requirement of at least 1 relapse in the past year or 2 relapses in the past 2 years. For example, a patient with 1 relapse 8 months before inclusion, with MRI performed 4 months later meeting criteria for dissemination in time and in space, would be eligible.

With respect to diagnosis of the form of the disease, such a patient, in the absence of progression of disability before the relapse, would be categorised 'relapsing-remitting'. On this point of the form of the disease, the sponsor would like to highlight that patients with any form of RMS ("exhibiting a relapsing clinical course, with or without progression", as written in the initial protocol) could be enrolled in EFC6049/TEMSO. Of note, although the subcategories used do not exactly match the ones proposed in the European Guideline, they cover the same population of patients with MS presenting with relapses.

A subgroup analysis was performed to investigate the consistency of the treatment effect across the levels of the subgroups defined by each of multiple baseline characteristics of the patients. The smaller numbers of patients in the SPMS or PRMS categories than in the RRMS category reflect the frequency of patients with relapses eligible to participate in a study like EFC6049/TEMSO. Because of these small numbers, SPMS or PRMS were pooled for the subgroup analyses, however the number of patients was still comparatively small. Importantly, there was no statistically significant interaction between treatment and MS subtype observed for the primary or the key secondary endpoint: the relative risk/hazard ratios consistently favoured teriflunomide, as shown in Table 14, below. Thus, the efficacy of teriflunomide appears to be consistent in all relapsing forms of MS, supporting the proposed indication wording submitted in the original application.

Table 14. Summary of efficacy analysis for selected disease characteristic subgroups: ITT population

	Annualized relapse rate Relative risk ratio (95% CI)		12 weeks disability progression Hazard ratio (95% CI)	
Subgroup	7 mg vs. Placebo	14 mg vs. Placebo	7 mg vs. Placebo	14 mg vs. Placebo
MS Subtype				
Secondary progressive and progressive relapsing (N=93)	0.639 (0.317, 1.287)	0.985 (0.447, 2.172)	0.371 (0.096, 1.438)	0.489 (0.128, 1.868)
Relapsing remitting (N=993)	0.691 (0.562, 0.850)	0.661 (0.531, 0.824)	0.802 (0.577, 1.115)	0.721 (0.514, 1.011)

On the basis of the above, the sponsor considers that the original wording of the indication, that references patients with RMS, is justified. The proposed indication recommended by the Delegate would therefore be revised as outlined below:

> *[Product] is indicated for the treatment of patients with* ***relapsing forms of*** ~~***Relapsing Remitting Multiple Sclerosis and Secondary Progressive***~~ ***Multiple Sclerosis*** ~~***with superimposed relapses***~~ *to reduce the frequency of clinical relapses and to delay the progression of physical disability.*

Delegate's question: Is there sufficient evidence that teriflunomide delays the progression of disability for a statement on disability progression to be included in the indications, noting

that the level of evidence is somewhat lower than has previously been accepted to support this claim?

Sponsor's response: The sponsor considers that there is robust evidence that teriflunomide 14 mg delays the progression of disability. In EFC6049/TEMSO, teriflunomide reduced the risk of sustained disability progression by 29.8% (p = 0.0279) at the dose of 14 mg. A trend to a reduction of risk of sustained disability progression, by 23.7% (p = 0.0835), was observed at the dose of 7 mg/day. The demonstration is strengthened by the consistency of sensitivity analyses and post hoc analyses.

As shown in Table 15, below, although statistical significance was not reached for 'time to disability progression sustained for 24 weeks' because of the smaller number of events, the hazard ratios are highly consistent with those of the main analysis. Various sensitivity analyses included in the submission are consistent in reporting this advantage for the 14 mg dose.

Table 15. Time to disability progression analyses: Hazard ratios

Description	7 mg vs. Placebo	14 mg vs. Placebo
Sustained for 12 weeks	0.763	0.702
Sustained for 24 weeks	0.750	0.749
Including extension for confirmation	0.799	0.720
Per protocol population	0.783	0.699

Furthermore, the more recent results of the second Phase III placebo controlled study, TOWER, confirm the effect of teriflunomide 14 mg on disability progression. These results were obtained after the submission in Australia and therefore were not included for evaluation. However, as discussed at the presubmission meeting with the TGA, they are intended to be provided as a post approval commitment. The top-line results were notified to the TGA prior to the formal press release and the results of the TOWER Study will be presented to the medical community at the European Committee for Treatment and Research in MS (ECTRIMS) conference in October. A 31.5% reduction in the risk of 12 week sustained accumulation of disability was observed with teriflunomide 14 mg compared to placebo (p = 0.0442). There was no statistically significant difference observed between teriflunomide 7 mg and placebo for the risk of 12 week sustained accumulation of disability.

In conclusion, there is now confirmed evidence that teriflunomide 14 mg reduces the accumulation of disability in patients with MS.

Delegate's question: Should concomitant treatment with other immune modulators specifically be excluded either in the indications or precautions sections of the PI?

Sponsor's response: The sponsor considers that the *'Precautions'* section of the PI is adequate for providing information and guidance on co-administration with other immunomodulators. In the PI, the following information is included:

> "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."

The sponsor considers that guidance is necessary, rather than specific exclusion, and proposes to complement the existing information by further revising the *Precaution* in the PI to add the following text

> "In any situation in which the decision is made to switch from [Product] to another agent with a known potential for hematologic suppression, it would be prudent to monitor for hematologic toxicity, because there will be overlap of systemic exposure to both compounds. Use of the accelerated elimination procedure may decrease this risk, but also may potentially induce disease worsening result in return of disease activity if the patient had been responding to [Product] treatment."

Delegate's question: Should the indications specifically exclude individuals with MS aged < 18 years or should the absence of efficacy and safety data for patients with MS in this age group be reflected in the Paediatric Use section of the PI?

The sponsor considers that the existing presentation of information on the lack of data in paediatric patients, both in the *Precautions* and *Dosage and Administration* sections of the PI, appropriately conveys the relevant information to prescribers, and specific reference in the indication is therefore unnecessary. This approach also aligns with the standard presentation of information on paediatric use in other medications approved for MS and in general for products on the Australia market.

Advisory committee considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered this product to have an overall positive benefit – risk profile, for the indication:

> *For the treatment of patients with relapsing remitting multiple sclerosis and secondary progressive multiple sclerosis with super imposed relapses to reduce the frequency of clinical relapses and to delay the progression of physical disability*

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- a statement in the *Dosage and Administration* / *Clinical Trials* / *Precautions* / *Contraindications* sections of the PI and relevant sections of the CMI in relation to both age limitations and the use of concomitant treatment.

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- monitoring of the EU conditions of registration specifically in relation to pregnancy registers.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Aubagio/Teriflunomide Winthrop/Teriflunomide Sanofi film coated tablets containing 14 mg teriflunomide for the following indication:

Teriflunomide 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.

Specific conditions of registration applying to these goods

The implementation in Australia of the teriflunomide Risk Management Plan (RMP), version 1.0 dated 24 February 2012 with ASA Version 1.1 dated May 2012, included with submission PM-2011-02772-3-1, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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