

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

AUBAGIO 14 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 14 mg of teriflunomide.

Excipient with known effect: Each tablet contains 72 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Pale blue to pastel blue, pentagonal film-coated tablets with imprint on one side ('14') and engraved with a corporate logo on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AUBAGIO is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (MS). (please refer to section 5.1 for important information on the population for which efficacy has been established).

4.2 Posology and method of administration

The treatment should be initiated and supervised by a physician experienced in the management of multiple sclerosis.

Posology

The recommended dose of AUBAGIO is 14 mg once daily.

Special populations

Elderly population

AUBAGIO should be used with caution in patients aged 65 years and over due to insufficient data on safety and efficacy.

Renal impairment

No dosage adjustment is necessary for patients with mild, moderate or severe renal impairment not undergoing dialysis.

Patients with severe renal impairment undergoing dialysis were not evaluated. Teriflunomide is contraindicated in this population (see section 4.3).

Hepatic impairment

No dosage adjustment is necessary for patients with mild and moderate hepatic impairment. Teriflunomide is contraindicated in patients with severe hepatic impairment (see section 4.3).

Paediatric population

The safety and efficacy of AUBAGIO in children aged from 10 to less than 18 years has not yet been established. There is no relevant use of teriflunomide in children aged from birth to less than 10 years for the treatment of multiple sclerosis.

No data are available.

Method of administration

The film-coated tablets are for oral use. The tablets should be swallowed whole with some water. AUBAGIO can be taken with or without food.

4.3 Contraindications

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

Patients with severe hepatic impairment (Child-Pugh class C).

Pregnant women, or women of childbearing potential who are not using reliable contraception during treatment with teriflunomide and thereafter as long as its plasma levels are above 0.02 mg/l (see section 4.6). Pregnancy must be excluded before start of treatment (see section 4.6).

Breast-feeding women (see section 4.6).

Patients with severe immunodeficiency states, e.g. AIDS.

Patients with significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia.

Patients with severe active infection until resolution (see section 4.4).

Patients with severe renal impairment undergoing dialysis, because insufficient clinical experience is available in this patient group.

Patients with severe hypoproteinaemia, e.g. in nephrotic syndrome.

4.4 Special warnings and precautions for use

Monitoring

Before treatment

Before starting treatment with teriflunomide the following should be assessed:

- Blood pressure
- Alanine aminotransferase (ALT/SGPT)
- Complete blood cell count including differential white blood cell and platelet count.

During treatment

During treatment with teriflunomide the following should be monitored:

- Blood pressure
- Alanine aminotransferase (ALT/SGPT)
- Complete blood cell counts should be performed based on signs and symptoms (e.g. infections) during treatment.

Accelerated elimination procedure

Teriflunomide is eliminated slowly from the plasma. Without an accelerated elimination procedure, it takes an average of 8 months to reach plasma concentrations less than 0.02 mg/l, although due to individual

variation in substance clearance it may take up to 2 years. An accelerated elimination procedure can be used at any time after discontinuation of teriflunomide (see section 4.6 and 5.2 for procedural details).

Hepatic effects

Elevations of liver enzymes have been observed in patients receiving teriflunomide (see section 4.8). These elevations occurred mostly within the first 6 months of treatment.

Liver enzymes should be assessed before initiation of teriflunomide therapy - every two weeks during the first 6 months of treatment, and every 8 weeks thereafter or as indicated by clinical signs and symptoms such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. For ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal, monitoring must be performed weekly. Teriflunomide therapy should be discontinued if liver injury is suspected; consider discontinuing teriflunomide therapy if elevated liver enzymes (greater than 3-fold ULN) are confirmed. Patients with pre-existing liver disease may be at increased risk of developing elevated liver enzymes when taking teriflunomide and should be closely monitored for signals of liver disease.

The medicinal product should be used with caution in patients who consume substantial quantities of alcohol.

Since teriflunomide is highly protein bound and as the binding is dependent upon the concentrations of albumin, unbound plasma teriflunomide concentrations are expected to be increased in patients with hypoproteinaemia, e.g. in nephrotic syndrome. Teriflunomide should not be used in patients with conditions of severe hypoproteinaemia.

Blood pressure

Elevation of blood pressure may occur during treatment with teriflunomide (see section 4.8). Blood pressure must be checked before the start of teriflunomide treatment and periodically thereafter. Blood pressure elevation should be appropriately managed before and during treatment with teriflunomide.

Infections

Initiation of treatment with teriflunomide should be delayed in patients with severe active infection until resolution.

In placebo-controlled studies, no increase in serious infections was observed with teriflunomide (see section 4.8). However, based on the immunomodulatory effect of AUBAGIO, if a patient develops a serious infection, suspending treatment with AUBAGIO should be considered and the benefits and risks should be reassessed prior to re-initiation of therapy. Due to the prolonged half-life, accelerated elimination with cholestyramine or charcoal may be considered.

Patients receiving AUBAGIO should be instructed to report symptoms of infections to a physician. Patients with active acute or chronic infections should not start treatment with AUBAGIO until the infection(s) is resolved.

The safety of AUBAGIO in individuals with latent tuberculosis infection is unknown, as tuberculosis screening was not systematically performed in clinical studies. For patients testing positive in tuberculosis screening, treat by standard medical practice prior to therapy with AUBAGIO.

Respiratory reactions

Interstitial lung disease (ILD) has been reported with teriflunomide in the postmarketing setting. ILD and worsening of pre-existing ILD have been reported during treatment with leflunomide, the parent compound of teriflunomide. The risk is increased in patients who had a history of ILD when treated with leflunomide.

ILD may occur acutely at any time during therapy with a variable clinical presentation. ILD may be fatal. New onset or worsening pulmonary symptoms, such as persistent cough and dyspnoea, may be a reason for discontinuation of the therapy and for further investigation, as appropriate. If discontinuation of the drug is necessary, consider initiation of an accelerated elimination procedure.

Haematological effects

A mean decrease less than 15% from baseline affecting white blood cell count has been observed (see section 4.8). As a precaution, a recent complete blood cell count, including differential white blood cell count and platelets, should be available before the initiation of treatment with AUBAGIO and the complete blood cell count should be assessed during AUBAGIO therapy as indicated by clinical signs and symptoms (e.g., infections).

In patients with pre-existing anaemia, leucopenia, and /or thrombocytopenia as well as in patients with impaired bone marrow function or those at risk of bone marrow suppression, the risk of haematological disorders is increased. If such effects occur, the accelerated elimination procedure (see above) to reduce plasma levels of teriflunomide should be considered.

In cases of severe haematological reactions, including pancytopenia, AUBAGIO and any concomitant myelosuppressive treatment must be discontinued and a teriflunomide accelerated elimination procedure should be considered.

Skin reactions

Cases of severe skin reactions have been reported postmarketing (including Stevens-Johnson syndrome and toxic epidermal necrolysis).

In patients treated with leflunomide, the parent compound, very rare cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported.

In case of ulcerative stomatitis, teriflunomide administration should be discontinued. If skin and /or mucosal reactions are observed which raise the suspicion of severe generalised major skin reactions (Stevens-Johnson syndrome, or toxic epidermal necrolysis-Lyell's syndrome), teriflunomide and any other possibly associated treatment must be discontinued, and an accelerated procedure initiated immediately. In such cases patients should not be re-exposed to teriflunomide (see section 4.3).

Peripheral neuropathy

Cases of peripheral neuropathy have been reported in patients receiving AUBAGIO (see section 4.8). Most patients improved after discontinuation of AUBAGIO. However, there was a wide variability in final outcome, i.e. in some patients the neuropathy resolved and some patients had persistent symptoms. If a patient taking AUBAGIO develops a confirmed peripheral neuropathy, consider discontinuing AUBAGIO therapy and performing the accelerated elimination procedure.

Vaccination

Two clinical studies have shown that vaccinations to inactivated neoantigen (first vaccination), or recall antigen (reexposure) were safe and effective during AUBAGIO treatment. The use of live attenuated vaccines may carry a risk of infections and should therefore be avoided.

Immunosuppressive or immunomodulating therapies

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

Co-administration with antineoplastic or immunosuppressive therapies used for treatment of MS has not been evaluated. Safety studies, in which teriflunomide was concomitantly administered with interferon beta or with glatiramer acetate for up to one year did not reveal any specific safety concerns, but a higher adverse reaction rate as compared to teriflunomide monotherapy was observed. The long term safety of these combinations in the treatment of multiple sclerosis has not been established.

Switching to or from AUBAGIO

Based on the clinical data related to concomitant administration of teriflunomide with interferon beta or with glatiramer acetate, no waiting period is required when initiating teriflunomide after interferon beta or glatiramer acetate or when starting interferon beta or glatiramer acetate, after teriflunomide.

Due to the long half-life of natalizumab, concomitant exposure, and thus concomitant immune effects, could occur for up to 2-3 months following discontinuation of natalizumab if AUBAGIO was immediately started. Therefore, caution is required when switching patients from natalizumab to AUBAGIO.

Based on the half-life of fingolimod, a 6-week interval without therapy is needed for clearance from the circulation and a 1 to 2 month period is needed for lymphocytes to return to normal range following discontinuation of fingolimod. Starting AUBAGIO during this interval will result in concomitant exposure to fingolimod. This may lead to an additive effect on the immune system and caution is, therefore, indicated.

In MS patients, the median $t_{1/2z}$ was approximately 19 days after repeated doses of 14 mg. If a decision is made to stop treatment with AUBAGIO, during the interval of 5 half-lives (approximately 3.5 months although may be longer in some patients), starting other therapies will result in concomitant exposure to AUBAGIO. This may lead to an additive effect on the immune system and caution is, therefore, indicated.

Lactose

Since AUBAGIO tablets contain lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions of other substances on teriflunomide

The primary biotransformation pathway for teriflunomide is hydrolysis, with oxidation being a minor pathway.

Potent cytochrome P450 (CYP) and transporter inducers: Co-administration of repeated doses (600 mg once daily for 22 days) of rifampicin (a CYP2B6, 2C8, 2C9, 2C19, 3A inducer), as well as an inducer of the efflux transporters P-glycoprotein [P-gp] and breast cancer resistant protein [BCRP] with teriflunomide (70 mg single dose) resulted in an approximately 40% decrease in teriflunomide exposure. Rifampicin and other known potent CYP and transporter inducers such as carbamazepine, phenobarbital, phenytoin and St John's Wort should be used with caution during the treatment with teriflunomide.

Cholestyramine or activated charcoal

It is recommended that patients receiving teriflunomide are not treated with cholestyramine or activated charcoal because this leads to a rapid and significant decrease in plasma concentration unless an accelerated elimination is desired. The mechanism is thought to be by interruption of enterohepatic recycling and/or gastrointestinal dialysis of teriflunomide.

Pharmacokinetic interactions of teriflunomide on other substances

Effect of teriflunomide on CYP2C8 substrate: repaglinide

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

Effect of teriflunomide on oral contraceptive: 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel

There was an increase in mean ethinylestradiol C_{max} and AUC₀₋₂₄ (1.58- and 1.54-fold, respectively) and levonorgestrel C_{max} and AUC₀₋₂₄ (1.33- and 1.41-fold, respectively) following repeated doses of teriflunomide. While this interaction of teriflunomide is not expected to adversely impact the efficacy of oral contraceptives, it should be considered when selecting or adjusting oral contraceptive treatment used in combination with teriflunomide.

Effect of teriflunomide on CYP1A2 substrate: caffeine

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

Effect of teriflunomide on warfarin

Repeated doses of teriflunomide had no effect on the pharmacokinetics of S-warfarin, indicating that teriflunomide is not an inhibitor or an inducer of CYP2C9. However, a 25% decrease in peak international normalised ratio (INR) was observed when teriflunomide was coadministered with warfarin as compared

with warfarin alone. Therefore, when warfarin is co-administered with teriflunomide, close INR follow-up and monitoring is recommended.

Effect of teriflunomide on organic anion transporter 3 (OAT3) substrates:

There was an increase in mean cefaclor C_{max} and AUC (1.43- and 1.54-fold, respectively), following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of OAT3 *in vivo*. Therefore, when teriflunomide is coadministered with substrates of OAT3, such as cefaclor, benzylpenicillin, ciprofloxacin, indometacin, ketoprofen, furosemide, cimetidine, methotrexate, zidovudine, caution is recommended.

Effect of teriflunomide on BCRP and/or organic anion transporting polypeptide B1 and B3 (OATP1B1/B3) substrates:

There was an increase in mean rosuvastatin C_{max} and AUC (2.65- and 2.51-fold, respectively), following repeated doses of teriflunomide. However, there was no apparent impact of this increase in plasma rosuvastatin exposure on the HMG-CoA reductase activity. For rosuvastatin, a dose reduction by 50% is recommended for coadministration with teriflunomide. For other substrates of BCRP (e.g., methotrexate, topotecan, sulfasalazine, daunorubicin, doxorubicin) and the OATP family especially HMG-Co reductase inhibitors (e.g., simvastatin, atorvastatin, pravastatin, methotrexate, nateglinide, repaglinide, rifampicin) concomitant administration of teriflunomide should also be undertaken with caution. Patients should be closely monitored for signs and symptoms of excessive exposure to the medicinal products and reduction of the dose of these medicinal products should be considered.

4.6 Fertility, pregnancy and lactation

Use in males

The risk of male-mediated embryo-foetal toxicity through teriflunomide treatment is considered low (see section 5.3).

Pregnancy

There are limited amount of data from the use of teriflunomide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Teriflunomide may cause serious birth defects when administered during pregnancy. Teriflunomide is contraindicated in pregnancy (see section 4.3).

Women of childbearing potential have to use effective contraception during treatment and after treatment as long as teriflunomide plasma concentration is above 0.02 mg/l. During this period women should discuss any plans to stop or change contraception with the treating physician.

The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, they must notify the physician immediately for pregnancy testing, and if positive, the physician and patient must discuss the risk to the pregnancy. It is possible that rapidly lowering the blood level of teriflunomide, by instituting the accelerated elimination procedure described below, at the first delay of menses, may decrease the risk to the foetus.

For women receiving teriflunomide treatment, who wish to become pregnant, the medicine should be stopped and an accelerated elimination procedure is recommended in order to more rapidly achieve concentration below 0.02 mg/l (see below).

If an accelerated elimination procedure is not used, teriflunomide plasma levels can be expected to be above 0.02 mg/l for an average of 8 months, however, in some patients it may take up to 2 years to reach plasma concentration below 0.02 mg/l. Therefore, teriflunomide plasma concentrations should be measured before a woman begins to attempt to become pregnant. Once the teriflunomide plasma concentration is determined to be below 0.02 mg/l, the plasma concentration must be determined again after an interval of at least 14 days. If both plasma concentrations are below 0.02 mg/l, no risk to the foetus is to be expected.

For further information on the sample testing please contact the Marketing Authorisation Holder or its local representative (see section 7).

Accelerated elimination procedure

After stopping treatment with teriflunomide:

- cholestyramine 8 g is administered 3 times daily for a period of 11 days, or cholestyramine 4 g three times a day can be used, if cholestyramine 8 g three times a day is not well tolerated,
- alternatively, 50 g of activated powdered charcoal is administered every 12 hours for a period of 11 days.

However, also following either of the accelerated elimination procedures, verification by 2 separate tests at an interval of at least 14 days and a waiting period of one-and-a-half months between the first occurrence of a plasma concentration below 0.02 mg/l and fertilisation is required.

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

Breast-feeding

Animal studies have shown excretion of teriflunomide in breast milk. Breast-feeding women must, therefore, not receive teriflunomide.

Fertility

Results of studies in animals have not shown an effect on fertility (see section 5.3). Although human data are lacking, no effect on male and female fertility is anticipated.

4.7 Effects on ability to drive and use machines

AUBAGIO has no or negligible influence on the ability to drive and use machines.

In the case of adverse reactions such as dizziness, which has been reported with leflunomide, the parent compound, the patient's ability to concentrate and to react properly may be impaired. In such cases, patients should refrain from driving cars and using machines.

4.8 Undesirable effects

Summary of the safety profile

A total of 2267 patients were exposed to teriflunomide (1155 on teriflunomide 7 mg and 1112 on teriflunomide 14 mg) once daily for a median duration of about 672 days in four placebo-controlled studies (1045 and 1002 patients for teriflunomide 7 mg and 14 mg, respectively) and one active comparator study (110 patients in each of the teriflunomide treatment groups) in patients with relapsing forms of MS (Relapsing Multiple Sclerosis, RMS).

Teriflunomide is the main metabolite of leflunomide. The safety profile of leflunomide in patients suffering from rheumatoid arthritis or psoriatic arthritis may be pertinent when prescribing teriflunomide in MS patients.

The placebo-controlled pooled analysis was based on 2047 patients with Relapsing Multiple Sclerosis treated with teriflunomide once daily. Within this safety population, the most commonly reported adverse reactions in the teriflunomide treated patients were: headache, diarrhoea, increased ALT, nausea, and alopecia. In general, headache, diarrhoea, nausea and alopecia, were mild to moderate, transient and infrequently led to treatment discontinuation.

Tabulated list of adverse reactions

Adverse reactions reported with AUBAGIO in placebo-controlled studies, reported for teriflunomide 7 mg or 14 mg at $\geq 1\%$ higher rate than for placebo, are shown below. Frequencies were defined using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations (see section 4.4)		Influenza, Upper respiratory tract infection, Urinary tract infection, Bronchitis, Sinusitis, Pharyngitis, Cystitis, Gastroenteritis viral, Oral herpes, Tooth infection, Laryngitis, Tinea pedis				Severe infections including sepsis ^a
Blood and lymphatic system disorders		Neutropenia, (see section 4.4) Anaemia	Mild thrombocytopenia (platelets <100G/l)			
Immune system disorders		Mild allergic reactions				Hyper-sensitivity reactions (immediate or delayed) including anaphylaxis and angioedema
Psychiatric disorders		Anxiety				
Nervous system disorders	Headache	Paraesthesia, Sciatica, Carpal tunnel syndrome	Hyperaesthesia, Neuralgia, Peripheral neuropathy			
Cardiac disorders		Palpitations				
Vascular disorders		Hypertension (see section 4.4)				
Respiratory, thoracic and mediastinal disorders						Interstitial lung disease
Gastrointestinal disorders	Diarrhoea, Nausea	Abdominal pain upper, Vomiting, Toothache				Pancreatitis, Stomatitis
Hepatobiliary disorders	Alanine aminotransferase (ALT) increase (see section 4.4)	Gamma-glutamyltransferase (GGT) increase (see section 4.4), Aspartate aminotransferase				Acute hepatitis

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
		e increase (see section 4.4)				
Skin and subcutaneous tissue disorders	Alopecia	Rash, Acne				Severe skin reactions ^a Nail disorders
Musculoskeletal and connective tissue disorders		Musculoskeletal pain, Myalgia, Arthralgia				
Renal and urinary disorders		Pollakiuria				
Reproductive system and breast disorders		Menorrhagia				
General disorders and administration site conditions		Pain				Asthenia
Investigations		Weight decrease, Neutrophil count decrease (see section 4.4), White blood cell count decrease (see section 4.4), Blood creatine phosphokinase increased				
Injury, poisoning and procedural complications			Post-traumatic pain			

a: please refer to the detailed description section

Description of selected adverse reactions

Alopecia

Alopecia was reported as hair thinning, decreased hair density, hair loss, associated or not with hair texture change, in 13.9% of patients treated with 14 mg teriflunomide versus 5.1% in patients treated with placebo. Most cases were described as diffuse or generalised over the scalp (no complete hair loss reported) and occurred most often during the first 6 months and with resolution in 121 of 139 (87.1%) patients treated with teriflunomide 14 mg. Discontinuation because of alopecia was 1.3% in the teriflunomide 14 mg teriflunomide group, versus 0.1% in the placebo group.

Hepatic effects

During placebo-controlled studies the following was detected:

ALT increase (based on laboratory data) according to baseline status - Safety population in placebo-controlled studies		
	Placebo (N=997)	Teriflunomide 14 mg (N=1002)
>3 ULN	66/994 (6.6%)	80/999 (8.0%)

ALT increase (based on laboratory data) according to baseline status - Safety population in placebo-controlled studies		
	Placebo (N=997)	Teriflunomide 14 mg (N=1002)
>5 ULN	37/994 (3.7%)	31/999 (3.1%)
>10 ULN	16/994 (1.6%)	9/999 (0.9%)
>20 ULN	4/994 (0.4%)	3/999 (0.3%)
ALT >3 ULN and TBILI >2 ULN	5/994 (0.5%)	3/999 (0.3%)

Mild increases in transaminase, ALT below or equal to 3-fold ULN were more frequently seen in teriflunomide-treated groups as compared to placebo. The frequency of elevations above 3-fold ULN and higher was balanced across treatment groups. These elevations in transaminase occurred mostly within the first 6 months of treatment and were reversible after treatment cessation. The recovery time varied between months and years.

Blood pressure effects

In placebo-controlled studies the following was established:

- systolic blood pressure was >140 mm Hg in 19.9% of patients receiving 14 mg/day teriflunomide as compared to 15.5% receiving placebo;
- systolic blood pressure was >160 mm Hg in 3.8% of patients receiving 14 mg/day teriflunomide as compared to 2.0% receiving placebo;
- diastolic blood pressure was >90 mm Hg in 21.4% of patients receiving 14 mg/day teriflunomide as compared to 13.6% receiving placebo.

Infections

In placebo-controlled studies, no increase in serious infections was observed with teriflunomide 14 mg (2.7%) as compared to placebo (2.2%). Serious opportunistic infections occurred in 0.2% of each group. Severe infections including sepsis, sometimes fatal have been reported postmarketing.

Haematological effects

A mean decrease affecting white blood cell (WBC) count (<15% from baseline levels, mainly neutrophil and lymphocytes decrease) was observed in placebo-controlled trials with AUBAGIO, although a greater decrease was observed in some patients. The decrease in mean count from baseline occurred during the first 6 weeks then stabilised over time while on-treatment but at decreased levels (less than a 15% decrease from baseline). The effect on red blood cell (RBC) (<2%) and platelet counts (<10%) was less pronounced.

Peripheral neuropathy

In placebo-controlled studies, peripheral neuropathy, including both polyneuropathy and mononeuropathy (e.g., carpal tunnel syndrome), was reported more frequently in patients taking teriflunomide than in patients taking placebo. In the pivotal, placebo-controlled studies, the incidence of peripheral neuropathy confirmed by nerve conduction studies was 1.9% (17 patients out of 898) on 14 mg of teriflunomide, compared with 0.4% (4 patients out of 898) on placebo. Treatment was discontinued in 5 patients with peripheral neuropathy on teriflunomide 14 mg. Recovery following treatment discontinuation was reported in 4 of these patients.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

There does not appear to be an increased risk of malignancy with teriflunomide in the clinical trial experience. The risk of malignancy, particularly lymphoproliferative disorders, is increased with use of some other agents that affect the immune system (class effect).

Severe skin reactions

Cases of severe skin reactions have been reported with teriflunomide post-marketing (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Symptoms

There is no experience regarding teriflunomide overdose or intoxication in humans. Teriflunomide 70 mg daily was administered up to 14 days in healthy subjects. The adverse reactions were consistent with the safety profile for teriflunomide in MS patients.

Management

In the event of relevant overdose or toxicity, cholestyramine or activated charcoal is recommended to accelerate elimination. The recommended elimination procedure is cholestyramine 8 g three times a day for 11 days. If this is not well tolerated, cholestyramine 4 g three times a day for 11 days can be used. Alternatively, when cholestyramine is not available, activated charcoal 50 g twice a day for 11 days may also be used. In addition, if required for tolerability reasons, administration of cholestyramine or activated charcoal does not need to occur on consecutive days (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressants, ATC Code: L04AA31.

Mechanism of action

Teriflunomide is an immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), required for the de novo pyrimidine synthesis. As a consequence teriflunomide reduces the proliferation of dividing cells that need de novo synthesis of pyrimidine to expand. The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood, but this is mediated by a reduced number of lymphocytes.

Pharmacodynamic effects

Immune system

Effects on immune cell numbers in the blood: In the placebo-controlled studies, teriflunomide 14 mg once a day led to a mild mean reduction in lymphocyte count, of less than $0.3 \times 10^9/l$, which occurred over the first 3 months of treatment and levels were maintained until the end of the treatment.

Potential to prolong the QT interval

In a placebo-controlled thorough QT study performed in healthy subjects, teriflunomide at mean steady-state concentrations did not show any potential for prolonging the QTcF interval compared with placebo: the largest time matched mean difference between teriflunomide and placebo was 3.45 ms with the upper bound of the 90% CI being 6.45 ms.

Effect on renal tubular functions

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

Clinical efficacy and safety

The efficacy of AUBAGIO was demonstrated in two placebo controlled studies, the TEMSO and the TOWER study, that evaluated once daily doses of teriflunomide 7 mg and 14 mg in patients with RMS.

A total of 1088 patients with RMS were randomised in TEMSO to receive 7 mg (n=366) or 14 mg (n=359) of teriflunomide or placebo (n= 363) for 108 weeks duration. All patients had a definite diagnosis of MS (based on McDonald criteria (2001)), exhibited a relapsing clinical course, with or without progression, and experienced at least 1 relapse over the year preceding the trial or at least 2 relapses over the 2 years preceding the trial. At entry, patients had an Expanded Disability Status Scale (EDSS) score ≤ 5.5 . The mean age of the study population was 37.9 years. The majority of patients had relapsing–remitting multiple sclerosis (91.5%), but a subgroup of patients had secondary progressive (4.7%) or progressive relapsing multiple sclerosis (3.9%). The mean number of relapses within the year before study inclusion was 1.4 with 36.2% of patients having gadolinium-enhancing lesions at baseline. The median EDSS score at baseline was 2.50; 249 patients (22.9%) had an EDSS score > 3.5 at baseline. The mean duration of disease, since first symptoms, was 8.7 years. A majority of patients (73%) had not received disease-modifying therapy during the 2 years before study entry. The study results are shown in Table 1.

A total of 1169 patients with RMS were randomised in TOWER to receive 7 mg (n=408) or 14 mg (n=372) of teriflunomide or placebo (n= 389) for a variable treatment duration ending at 48 weeks after last patient randomised. All patients had a definite diagnosis of MS (based on McDonald criteria (2005)), exhibited a relapsing clinical course, with or without progression, and experienced at least 1 relapse over the year preceding the trial or at least 2 relapses over the 2 years preceding the trial. At entry, patients had an Expanded Disability Status Scale (EDSS) score ≤ 5.5 . The mean age of the study population was 37.9 years. The majority of patients had relapsing–remitting multiple sclerosis (97.5%), but a subgroup of patients had secondary progressive (0.8%) or progressive relapsing multiple sclerosis (1.7%). The mean number of relapses within the year before study inclusion was 1.4. Gadolinium-enhancing lesions at baseline: no data. The median EDSS score at baseline was 2.50; 298 patients (25.5%) had an EDSS score > 3.5 at baseline. The mean duration of disease, since first symptoms, was 8.0 years. A majority of patients (67.2%) had not received disease-modifying therapy during the 2 years before study entry. The study results are shown in Table 1.

Table 1 - Main Results (for the approved dose, ITT population)

	TEMSO-study		TOWER-study	
	Teriflunomide 14 mg 358	Placebo 363	Teriflunomide 14 mg 370	Placebo 388
N				
Clinical Outcomes				
Annualised relapse rate	0.37	0.54	0.32	0.50
<i>Risk difference (CI_{95%})</i>	-0.17 (-0.26, -0.08)***		-0.18 (-0.27, -0.09)****	
Relapse-free _{week 108}	56.5%	45.6%	57.1%	46.8%
<i>Hazard ratio (CI_{95%})</i>	0.72, (0.58, 0.89)**		0.63, (0.50, 0.79)****	
3-month Sustained Disability Progression _{week 108}	20.2%	27.3%	15.8%	19.7%
<i>Hazard ratio (CI_{95%})</i>	0.70 (0.51, 0.97)*		0.68 (0.47, 1.00)*	
6-month Sustained Disability Progression _{week 108}	13.8%	18.7%	11.7%	11.9%
<i>Hazard ratio (CI_{95%})</i>	0.75 (0.50, 1.11)		0.84 (0.53, 1.33)	
MRI endpoints				
Change in BOD _{week 108} ⁽¹⁾	0.72	2.21		
<i>Change relative to placebo</i>	67%***			
Mean Number of Gd- enhancing lesions at week 108	0.38	1.18	Not measured	
<i>Change relative to placebo (CI_{95%})</i>	-0.80 (-1.20, -0.39)****			
Number of unique active lesions /scan	0.75	2.46		
<i>Change relative to placebo (CI_{95%})</i>	69%, (59%; 77%)****			

**** p<0.0001 *** p<0.001 ** p<0.01 * p<0.05 compared to placebo

(1) BOD: burden of disease: total lesion volume (T2 and T1 hypointense) in ml

Efficacy in patients with high disease activity:

A consistent treatment effect on relapses and time to 3-month sustained disability progression in a subgroup of patients in TEMSO (n= 127) with high disease activity was observed. Due to the design of the study, high disease activity was defined as 2 or more relapses in one year, and with one or more Gd-enhancing lesion on brain MRI. No similar subgroup analysis was performed in TOWER as no MRI data were obtained.

No data are available in patients who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon, having had at least 1 relapse in the previous year while on therapy, and at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gd-enhancing lesion, or patients having an unchanged or increased relapse rate in the prior year as compared to the previous 2 years.

TOPIC was a double-blind, placebo-controlled study that evaluated once daily doses of teriflunomide 7 mg and 14 mg for up to 108 weeks in patients with first clinical demyelinating event (mean age 32.1 years). The primary endpoint was time to a second clinical episode (relapse). A total of 618 patients were randomized to receive 7 mg (n=205) or 14 mg (n=216) of teriflunomide or placebo (n=197). The risk of a second clinical attack over 2 years was 35.9% in the placebo group and 24.0% in the teriflunomide 14 mg treatment group (hazard ratio: 0.57, 95% confidence interval: 0.38 to 0.87, p=0.0087). The results from the TOPIC study confirmed the efficacy of teriflunomide in RRMS (including early RRMS with first clinical demyelinating event and MRI lesions disseminated in time and space).

Teriflunomide effectiveness was compared to that of a subcutaneous interferon beta-1a (at the recommended dose of 44 µg three times a week) in 324 randomised patients in a study (TENERE) with minimum treatment

duration of 48 weeks (maximum 114 weeks). The risk of failure (confirmed relapse or permanent treatment discontinuation whichever came first) was the primary endpoint. The number of patients with permanent treatment discontinuation in the teriflunomide 14 mg group was 22 out of 111 (19.8%), the reasons being adverse events (10.8%), lack of efficacy (3.6%), other reason (4.5%) and lost to follow-up (0.9%). The number of patients with permanent treatment discontinuation in the subcutaneous interferon beta-1a group was 30 out of 104 (28.8%), the reasons being adverse events (21.2%), lack of efficacy (1.9%), other reason (4.8%) and poor compliance to protocol (1%). Teriflunomide 14 mg/day was not superior to interferon beta-1a on the primary endpoint: the estimated percentage of patients with treatment failure at 96 weeks using the Kaplan-Meier method was 41.1% versus 44.4% (teriflunomide 14 mg versus interferon beta-1a group, $p=0.595$).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with AUBAGIO in children from birth to less than 10 years in treatment of multiple sclerosis (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with AUBAGIO in one or more subsets of the paediatric population in multiple sclerosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Median time to reach maximum plasma concentrations occurs between 1 to 4 hours post-dose following repeated oral administration of teriflunomide, with high bioavailability (approximately 100%).

Food does not have a clinically relevant effect on teriflunomide pharmacokinetics.

From the mean predicted pharmacokinetic parameters calculated from the population pharmacokinetic (PopPK) analysis using data from healthy volunteers and MS patients, there is a slow approach to steady-state concentration (i.e., approximately 100 days (3.5 months) to attain 95% of steady-state concentrations) and the estimated AUC accumulation ratio is approximately 34-fold.

Distribution

Teriflunomide is extensively bound to plasma protein (>99%), probably albumin and is mainly distributed in plasma. The volume of distribution is 11 l after a single intravenous (IV) administration. However, this is most likely an underestimation since extensive organ distribution was observed in rats.

Biotransformation

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

Elimination

Teriflunomide is excreted in the gastrointestinal tract mainly through the bile as unchanged medicinal product and most likely by direct secretion. Teriflunomide is a substrate of the efflux transporter BCRP, which could be involved in direct secretion. Over 21 days, 60.1% of the administered dose is excreted via feces (37.5%) and urine (22.6%). After the rapid elimination procedure with cholestyramine, an additional 23.1% was recovered (mostly in feces). Based on individual prediction of pharmacokinetic parameters using the PopPK model of teriflunomide in healthy volunteers and MS patients, median $t_{1/2z}$ was approximately 19 days after repeated doses of 14 mg. After a single IV administration, the total body clearance of teriflunomide is 30.5 ml/h.

Accelerated Elimination Procedure: Cholestyramine and activated charcoal

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

Teriflunomide concentrations measured during an 11-day procedure to accelerate teriflunomide elimination with either 8 g cholestyramine three times a day, 4 g cholestyramine three times a day or 50 g activated

charcoal twice a day following cessation of teriflunomide treatment have shown that these regimens were effective in accelerating teriflunomide elimination, leading to more than 98% decrease in teriflunomide plasma concentrations, with cholestyramine being faster than charcoal. Following discontinuation of teriflunomide and the administration of cholestyramine 8 g three times a day, the plasma concentration of teriflunomide is reduced 52% at the end of day 1, 91% at the end of day 3, 99.2% at the end of day 7, and 99.9% at the completion of day 11. The choice between the 3 elimination procedures should depend on the patient's tolerability. If cholestyramine 8 g three times a day is not well-tolerated, cholestyramine 4 g three times a day can be used. Alternatively, activated charcoal may also be used (the 11 days do not need to be consecutive unless there is a need to lower teriflunomide plasma concentration rapidly).

Linearity/non-linearity

Systemic exposure increases in a dose proportional manner after oral administration teriflunomide from 7 to 14 mg.

Characteristics in specific groups of patients

Gender, Elderly, Paediatric patients

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

Hepatic impairment

Mild and moderate hepatic impairment had no impact on the pharmacokinetic of teriflunomide. Therefore no dose adjustment is anticipated in mild and moderate hepatic-impaired patients. However, teriflunomide is contraindicated in patients with severe hepatic impairment (see sections 4.2 and 4.3).

Renal impairment

Severe renal impairment had no impact on the pharmacokinetic of teriflunomide. Therefore no dose adjustment is anticipated in mild, moderate and severe renal-impaired patients.

5.3 Preclinical safety data

Repeated oral administration of teriflunomide to mice, rats and dogs for up to 3, 6, and 12 months, respectively, revealed that the major targets of toxicity were the bone marrow, lymphoid organs, oral cavity/gastro intestinal tract, reproductive organs, and pancreas. Evidence of an oxidative effect on red blood cells was also observed. Anemia, decreased platelet counts and effects on the immune system, including leukopenia, lymphopenia and secondary infections, were related to the effects on the bone marrow and/or lymphoid organs. The majority of effects reflect the basic mode of action of the compound (inhibition of dividing cells). Animals are more sensitive to the pharmacology, and therefore toxicity, of teriflunomide than humans. As a result, toxicity in animals was found at exposures equivalent or below human therapeutic levels.

Teriflunomide was not mutagenic *in vitro* or clastogenic *in vivo*. Clastogenicity observed *in vitro* was considered to be an indirect effect related to nucleotide pool imbalance resulting from the pharmacology of DHO-DH inhibition. The minor metabolite TFMA (4-trifluoromethylaniline) caused mutagenicity and clastogenicity *in vitro* but not *in vivo*.

No evidence of carcinogenicity was observed in rats and mice.

Fertility was unaffected in rats despite adverse effects of teriflunomide on male reproductive organs, including reduced sperm count. There were no external malformations in the offspring of male rats administered teriflunomide prior to mating with untreated female rats. Teriflunomide was embryotoxic and teratogenic in rats and rabbits at doses in the human therapeutic range. Adverse effects on the offspring were also seen when teriflunomide was administered to pregnant rats during gestation and lactation. The risk of male-mediated embryo-fetal toxicity through teriflunomide treatment is considered low. The estimated female plasma exposure via the semen of a treated patient is expected to be 100 times lower than the plasma exposure after 14 mg of oral teriflunomide.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

lactose monohydrate
maize starch
microcrystalline cellulose
sodium starch glycolate (Type A)
hydroxypropylcellulose
magnesium stearate

Tablet coating

hypromellose
titanium dioxide (E171)
talc
macrogol 8000
indigo carmine aluminum lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium-aluminium blisters inserted in wallets (14 and 28 film-coated tablets) and packed in cartons containing 14, 28, 84 (3 wallets of 28), and 98 (7 wallets of 14) film-coated tablets.
Each wallet is placed in a protective sleeve.

Aluminium-aluminium perforated unit-dose blister packs in cartons containing 10x1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

sanofi-aventis groupe
54, rue La Boétie
F-75008 Paris
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/838/001

EU/1/13/838/002

EU/1/13/838/003

EU/1/13/838/004

EU/1/13/838/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 August 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Sanofi Winthrop Industrie
56, Route de Choisy au Bac
F-60205 Compiègne Cedex
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

• Additional risk minimisation measures

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree an educational programme with the National Competent Authority.

The MAH shall ensure that, following discussion and agreement with the National Competent Authorities in each Member State where Aubagio is marketed, at launch and after launch, all healthcare professionals who are expected to use Aubagio are provided with the following items:

- Summary of Product Characteristics (SmPC)
- Educational material for Healthcare professionals
- Educational card for patients

The educational material for HealthCare Professionals (HCP) will include the following key elements:

1. HCPs should discuss with their patients the specific safety concerns of Aubagio detailed below including the tests and precautions needed for safe use as follows:

- Risk of hepatic effects
 - liver function tests are needed prior to treatment and periodically during treatment
 - To educate the patient about the signs and symptoms of liver disease and the need to report to their HCP if they experience any of them
- Potential risk of teratogenicity
 - To check pregnancy status before starting treatment
 - To educate female patients of child-bearing potential on the need for effective contraception before starting, and during treatment with teriflunomide
 - To inform their doctor immediately if they stop contraception, or prior to changing contraceptive measures
 - If female patients become pregnant despite using contraceptive measures, they should stop teriflunomide and contact their doctor immediately who should:
 - Consider and discuss with the patient the accelerated elimination procedure
 - encourage them to enrol in a pregnancy registry (in countries where a pregnancy registry is on-going),
- Risk of hypertension
 - to check for a history of hypertension and that blood pressure should be appropriately managed during treatment
 - the need for blood pressure checks before treatment and periodically during treatment,
- Risk of hematologic effects
 - the need for complete blood cell counts before treatment and periodically during treatment based on signs and symptoms
- Risk of infections/serious infections
 - To discuss the need to contact the doctor in the event of signs/symptoms of infection, or if the patient takes other medicines that affect the immune system

2. A reminder to provide patients with a Patient Education Card, including filling-in their contact details, and to provide replacement Patient Education Cards as necessary;

3. To encourage patients to contact their MS physician and/or General Practitioner if they experience any of the signs and symptoms discussed in the Patient Education Card;

4. Information on the optional service of a periodic reminder to patients about the continued need for effective contraception during treatment.

The educational card for the patients will include the following key elements:

1. A reminder for both patients and all HCPs involved in their treatment that the patient is being treated with teriflunomide, a drug which:

- Requires concomitant use of effective contraception in women of child-bearing potential
- Requires a pregnancy status check before treatment
- Affects liver function
- Affects blood cell counts and the immune system

2. Information to educate the patient:

- To pay attention to certain signs and symptoms which might indicate liver disease or infection, and if any of these occur, to contact their doctor/HCP promptly
- Of the need for the procedures/tests before and during teriflunomide treatment
- To remind female patients to tell their doctor if breastfeeding
- For women of child-bearing potential
 - to emphasise the need for effective contraception during treatment with teriflunomide
 - to stop treatment with teriflunomide immediately if they suspect they might be pregnant and also to contact their doctor immediately
- To remind patients to show the Patient Education Card to Doctors/HCPs involved with their medical care (especially in the event of medical emergencies and/or if new Doctors/HCPs are involved.)
- To record the first date of prescription and the contact details of their prescriber

3. To encourage the patients to read the PIL thoroughly

4. If they become pregnant:

- To remind both patients and HCPs about the accelerated elimination procedure

- To remind both patients and HCP about the Pregnancy Registry (in countries where pregnancy registry is on-going)

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

AUBAGIO 14 mg film-coated tablets
teriflunomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 14 mg teriflunomide.

3. LIST OF EXCIPIENTS

Also contains: lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
84 (3 wallets of 28) film-coated tablets
98 (7 wallets of 14) film-coated tablets
10x1 film-coated tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

sanofi-aventis groupe
54, rue La Boétie
F – 75008 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/838/001 14 tablets
EU/1/13/838/002 28 tablets
EU/1/13/838/003 84 tablets
EU/1/13/838/004 98 tablets
EU/1/13/838/005 10x1 tablet

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

AUBAGIO

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

PROTECTIVE SLEEVE CONTAINING WALLET

1. NAME OF THE MEDICINAL PRODUCT

AUBAGIO 14 mg film-coated tablets
teriflunomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 14 mg teriflunomide.

3. LIST OF EXCIPIENTS

Also contains: lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

sanofi-aventis groupe
54, rue La Boétie
F - 75008 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

WALLET

1. NAME OF THE MEDICINAL PRODUCT

AUBAGIO 14 mg film-coated tablets
teriflunomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 14 mg teriflunomide.

3. LIST OF EXCIPIENTS

Also contains: lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

Calendar days

Mon
Tue
Wed
Thu
Fri
Sat
Sun

Week 1 (wallets of 14 and 28)
Week 2 (wallets of 14 and 28)
Week 3 (wallets of 28)
Week 4 (wallets of 28)

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

sanofi-aventis groupe
54, rue La Boétie
F - 75008 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

UNIT-DOSE BLISTER

1. NAME OF THE MEDICINAL PRODUCT

AUBAGIO 14 mg tablets
teriflunomide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

sanofi-aventis groupe

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR WALLET

1. NAME OF THE MEDICINAL PRODUCT

AUBAGIO 14 mg

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

AUBAGIO 14 mg film-coated tablets teriflunomide

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What AUBAGIO is and what it is used for
2. What you need to know before you take AUBAGIO
3. How to take AUBAGIO
4. Possible side effects
5. How to store AUBAGIO
6. Contents of the pack and other information

1. What AUBAGIO is and what it is used for

What Aubagio is

AUBAGIO contains the active substance teriflunomide.

What AUBAGIO is used for

AUBAGIO is used in adults to treat relapsing- remitting multiple sclerosis (MS).

What multiple sclerosis is

MS is a long-term illness that affects the central nervous system (CNS). The CNS is made up of the brain and spinal cord. In multiple sclerosis, inflammation destroys the protective sheath (called myelin) around the nerves in the CNS. This loss of myelin is called demyelination. This stops nerves from working properly.

People with relapsing form of multiple sclerosis will have repeated attacks (relapses) of physical symptoms caused by their nerves not working properly. These symptoms vary from patient to patient but usually involve:

- difficulty walking
- vision problems
- balance problems.

Symptoms may disappear completely after the relapse is over, but over time, some problems may remain between relapses. This can cause physical disabilities that may interfere with your daily activities.

How Aubagio works

Aubagio helps to protect against attacks on the central nervous system by the immune system by limiting the increase of some white blood cells (lymphocytes). This limits the inflammation that leads to nerve damage in MS.

2. What you need to know before you take AUBAGIO

Do not take AUBAGIO:

- if you are allergic to the active substance or any of the other ingredients of this medicine (listed in section 6),
- if you have severe liver problems,
- if you are **pregnant**, think you may be pregnant, or are breast-feeding,
- if you suffer from a serious problem which affects your immune system (e.g. AIDS),
- if you have a serious problem with your bone marrow, or if you have low numbers of red or white cells in your blood or a reduced number of blood platelets,
- if you are suffering from a serious infection,
- if you have severe kidney problems which require dialysis,
- if you have very low levels of proteins in your blood (hypoproteinaemia),

If you are not sure, talk to your doctor or pharmacist before taking AUBAGIO.

Warnings and precautions

Talk to your doctor or pharmacist before taking AUBAGIO if:

- you have liver problems; your doctor will carry out blood tests before and during treatment to check how well your liver is working. If your test results show a problem with your liver, your doctor may stop your treatment with AUBAGIO. Please read section 4.
- you have high blood pressure (hypertension) whether it is controlled with medicines or not. AUBAGIO can cause an increase in blood pressure. Your doctor will check your blood pressure regularly during treatment. Please read section 4.
- you are going to have a vaccination.
- you have an infection. Before you take AUBAGIO, your doctor will make sure you have enough white blood cells and platelets in your blood. As AUBAGIO decreases the number of white cells in the blood this may affect your ability to fight the infection. Your doctor may do blood tests to check your white blood cells if you think you have an infection. Please read section 4.

AUBAGIO can occasionally cause some problems with lungs, or nerves in your arms or legs. For more information on these, please read section 4

If any of the above applies to you (or you are not sure), talk to your doctor or pharmacist before taking AUBAGIO.

Children and adolescents

AUBAGIO should not be used in children and adolescents under 18 years of age. This is because the effects of the medicine in this age group are not known.

Other medicines and AUBAGIO

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription.

In particular, tell your doctor or pharmacist if you are taking any of the following:

- leflunomide, methotrexate and other medicines that affect the immune system (often called immunosuppressants or immunomodulators)
- rifampicin (a medicine used to treat tuberculosis and other infections)
- carbamazepine, phenobarbital, phenytoin for epilepsy
- St John's wort (a herbal medicine for depression)
- repaglinide, pioglitazone, nateglinide, or rosiglitazone for diabetes
- daunorubicin, doxorubicin, paclitaxel, or topotecan for cancer
- duloxetine for depression, urinary incontinence or in kidney disease in diabetics
- alosetron for the management of severe diarrhea
- theophylline for asthma
- tizanidine, a muscle relaxant
- warfarin, an anticoagulant used to make the blood thinner (i.e. more fluid) in order to avoid blood clots
- oral contraceptives (containing ethinylestradiol and levonorgestrel)
- cefaclor, benzylpenicillin (penicillin G), ciprofloxacin for infections
- indometacin, ketoprofen for pain or inflammation
- furosemide for heart disease

- cimetidine for reducing gastric acid
- zidovudine for HIV infection
- rosuvastatin, simvastatin, atorvastatin, pravastatin for hypercholesterolemia (high cholesterol)
- sulfasalazine for inflammatory bowel disease or rheumatoid arthritis
- cholestyramine for high cholesterol or relief from itching in liver disease
- activated charcoal to reduce absorption of medicines or other substances

Pregnancy and breast-feeding

Do not take AUBAGIO if you are, or think you may be **pregnant**. If you are pregnant or become pregnant while taking AUBAGIO, the risk of having a baby with birth defects is increased. Women of childbearing potential must not take AUBAGIO without using reliable contraceptive measures.

Tell your doctor if you plan to become pregnant after stopping treatment with AUBAGIO, as you need to ensure that most of AUBAGIO has left your body before trying to become pregnant. This drug elimination may take up to 2 years to occur naturally. The time can be reduced to a few weeks by taking certain medicines which speed up removal of AUBAGIO from your body.

In either case it should be confirmed by a blood test that AUBAGIO has been sufficiently removed from your body and you need confirmation from your treating physician that the blood level of AUBAGIO is low enough to allow you to become pregnant.

For further information on the laboratory testing please contact your doctor.

If you suspect that you are pregnant while taking AUBAGIO or in the two years after you have stopped treatment, you must contact your doctor **immediately** for a pregnancy test. If the test confirms that you are pregnant, your doctor may suggest treatment with certain medicines to remove AUBAGIO rapidly and sufficiently from your body, as this may decrease the risk to your baby.

Contraception

You must use an effective method of contraception during and after treatment with AUBAGIO.

Teriflunomide remains in your blood for a long time after you stop taking it. Continue to use effective contraception after you stop treatment.

- Do this until the levels of AUBAGIO in your blood are low enough - your doctor will check this.
- Talk with your doctor about the best method of contraception for you and any potential need for contraception change.

Do not take AUBAGIO when you are breast-feeding, as teriflunomide passes into the breast milk.

Driving and using machines

AUBAGIO might make you feel dizzy which may impair your ability to concentrate and react. If you are affected, do not drive or use machines.

AUBAGIO contains lactose

AUBAGIO contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

3. How to take AUBAGIO

Treatment with AUBAGIO will be overseen by a doctor who is experienced in the treatment of multiple sclerosis.

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The recommended dose is one film-coated tablet (14 mg) daily.

Route/method of administration

AUBAGIO is for oral use. AUBAGIO is taken every day as a single daily dose at any time of the day.

You should swallow the tablet whole with some water.
AUBAGIO may be taken with or without food.

If you take more AUBAGIO than you should

If you have taken too much AUBAGIO, call your doctor straight away. You may experience side effects similar to those described in section 4 below.

If you forget to take AUBAGIO

Do not take a double dose to make up for a forgotten tablet. Take your next dose at the scheduled time.

If you stop taking AUBAGIO

Do not stop taking AUBAGIO or change your dose without talking to your doctor first.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
The following side effects may happen with this medicine.

Serious side effects

Tell your doctor immediately, if you notice any of the following serious side effects:

- allergic reactions which might include symptoms of rash, hives, swelling of lips, tongue or face or sudden difficulty breathing
- severe skin reactions which might include symptoms of skin rash, blistering, or ulcers in your mouth
- severe infections or sepsis (a potentially life-threatening type of infection) which might include symptoms of high fever, shaking, chills, reduced urine flow, or confusion
- serious liver disease which might include symptoms of yellowing of your skin or the whites of your eyes, darker urine than normal, unexplained nausea and vomiting, or abdominal pain
- inflammation of the lungs which might include symptoms of shortness of breath or persistent cough
- inflammation of the pancreas which might include symptoms of severe pain in the upper abdominal area that may also be felt in your back, nausea, or vomiting

Other side effects include

Very common side effects (may affect more than 1 in 10 people):

- Headache
- Diarrhoea, feeling sick
- Increase in ALT (increase in blood levels of certain hepatic enzymes) shown in tests
- Hair thinning

Common side effects (may affect up to 1 in 10 people):

- Influenza, upper respiratory tract infection, urinary tract infection, bronchitis, sinusitis, sore throat and discomfort when swallowing, cystitis, gastroenteritis viral, oral herpes, tooth infection, laryngitis, fungal infection of the foot
- Laboratory values: a decrease in the number of red blood cells (anaemia), changes in liver and white blood cell test results (see section 2), as well as elevations in a muscle enzyme (creatine phosphokinase) have been observed.
- Mild allergic reactions
- Feeling anxious
- Pins and needles, feeling weak, numb, tingling or pain in the lower back or leg (sciatica); feeling numb, burning, tingling or pain in the hands and fingers (carpal tunnel syndrome)
- Feeling your heartbeat
- Increase in blood pressure
- Being sick (vomiting), toothache, upper abdominal pain
- Rash, acne

- Pain of the tendons, joints, bones, muscle pain (musculoskeletal pain),
- Needing to urinate more often than usual
- Heavy periods
- Pain
- Weight loss

Uncommon side effects (may affect up to 1 in 100 people):

- Decrease in the number of blood platelets (thrombocytopenia)
- Increased feeling or sensitivity, especially in the skin; stabbing or throbbing pain along one or more nerves, problems in the nerves of the arms or legs (peripheral neuropathy)

Not known (frequency cannot be estimated from the available data):

- Nail disorders
- Lack of energy or feeling weak (asthenia)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store AUBAGIO

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, protective sleeve, and wallet after “EXP”. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What AUBAGIO contains

- The active substance is teriflunomide. Each tablet contains 14 mg of teriflunomide.
- The other ingredients are lactose monohydrate, maize starch, microcrystalline cellulose, sodium starch glycolate (Type A), hydroxypropylcellulose, magnesium stearate, hypromellose, titanium dioxide (E171), talc, macrogol 8000, indigo carmine aluminum lake (E132).

What AUBAGIO looks like and contents of the pack

AUBAGIO 14 mg film-coated tablets (tablets) are pale blue to pastel blue, pentagonal film-coated tablets with imprint on one side (‘14’) and engraved with a corporate logo on the other side.

AUBAGIO is available in cardboard cartons containing:

- 14, 28, 84 and 98 tablets in wallet packs with integrated aluminium blisters;
- 10x1 tablet in all aluminium perforated unit-dose blisters.

Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder

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Manufacturer

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Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

ANNEX IV
SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF
THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for teriflunomide, the scientific conclusions of the CHMP are as follows:

Cumulatively, a total of 39 unique case reports of potential Interstitial lung disease (ILD) were retrieved, of which 3 cases with a possible causal relationship with teriflunomide. Since ILD can be a serious event, possibly fatal, it should be included in section 4.4 of the SmPC as reported in the post-marketing setting and not just as reported for the parent compound leflunomide. Due to the long half-life of the compound recommendation for initiation of an accelerated elimination procedure in case of pulmonary symptoms should also be included. ILD should also be moved from “very rare” to “not known” without a reference to leflunomide in the table in section 4.8.

In the post-marketing setting, 121 hepatic disorders events (26 % of the total) were assessed as associated with teriflunomide. An increase of ALT (≥ 3 x ULN) in combination with an increase of total bilirubin (>2 x ULN) indicates drug induced liver injury showing that teriflunomide is not only associated with non-serious elevations of liver enzymes, but also with serious hepatic events, like “acute hepatitis” which should be included in the SmPC section 4.8 with a frequency unknown. In addition, the adverse reactions “Alanine aminotransferase (ALT) increase”, “Gamma-glutamyl transferase (GGT) increase” and “Aspartate aminotransferase increase” should be moved from the system organ class (SOC) term “Investigations” to the SOC “Hepatobiliary disorders”.

Based on the very high number of reported post-marketing cases of asthenia (cumulatively 5873 cases) and considering that asthenia is also listed in the SmPC for the parent compound leflunomide, it should be included as possible adverse reaction for teriflunomide in the table in SmPC section 4.8 with a frequency of unknown.

Ten post-marketing cases of nail disorders reported a possible causality with teriflunomide and 6 of them resulted positive for de-challenge. It is also noted that nail loss and other nail disorders were often reported together with hair loss or hair thinning, suggesting a possible shared pathophysiologic mechanism; and alopecia is a known side effect of teriflunomide. Therefore, “nail disorders” should be included in the table in SmPC section 4.8 as possible adverse reaction with a frequency of unknown.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for teriflunomide the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing teriflunomide is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.