European Medicines Agency – accessed 30/05/2022 for additional safety warnings

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# RMS DMTs

Article 20 procedures noted for **alemtuzumab**, **fingolimod** and **natalizumab**.

An Article 20 pharmacovigilance procedure should be initiated in case a Member State (MS) or the European Commission (EC), as a result of the evaluation of data relating to pharmacovigilance, considers that at least one of the measures envisaged under title IX (Pharmacovigilance) or XI (Supervision and sanctions) of Directive 2001/83/EC must be applied for centrally authorised medicinal products.

Additional note: US FDA safety warning alert for **mitoxantrone**.

## 

## Alemtuzumab: *Lemtrada*

Communications/press releases:

<https://www.ema.europa.eu/en/medicines/human/referrals/lemtrada>

<https://www.ema.europa.eu/en/news/measures-minimise-risk-serious-side-effects-multiple-sclerosis-medicine-lemtrada>

<https://www.ema.europa.eu/en/news/use-multiple-sclerosis-medicine-lemtrada-restricted-while-ema-review-ongoing>

Since recommendation: <https://www.ema.europa.eu/en/documents/procedural-steps-after/lemtrada-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf>

There are a number of changes, please refer to link above.

Of note:

03/09/2020: To update sections 4.4 and 4.8 of the SmPC to

amend the existing warning and adverse drug

reactions on Epstein-Barr virus (EBV) infections and

EBV associated hepatitis, following safety evaluation

report (SER). The package leaflet is updated

accordingly

09/07/2020: Submission of an update the RMP (version 7.2)

incorporating all amendments and additional

activities defined in the Article 20 referral procedure

(EMEA/H/A-20/1483/C/3718/0028).

C.I.11.b - Introduction of, or change(s) to, the

obligations and conditions of a marketing

authorisation, including the RMP - Implementation of

change(s) which require to be further substantiated

by new additional data to be submitted by the MAH

where significant assessment is required

14/11/2019: Pursuant to Article 20 of Regulation (EC) No

726/2004, the European Commission requested on

10 April 2019 the opinion of the European Medicines

Agency further to new emerging and serious

concerns related to fatal cases, cardiovascular

adverse events in close temporal association with

Lemtrada infusion and immune-mediated diseases.

The PRAC was requested to assess the impact

thereof on the benefit-risk balance of Lemtrada and

to give its recommendation whether the marketing

authorisation of this product should be maintained,

varied, suspended or revoked

20/09/2018: LEMTRADA may increase the risk of acute acalculous

cholecystitis. In controlled clinical studies, 0.2% of

LEMTRADA-treated MS patients developed acute acalculous

cholecystitis, compared to 0% of patients treated with

INFB-1a. During postmarketing use, additional cases of

acute acalculous cholecystitis have been reported in

LEMTRADA-treated patients. Symptoms of acute acalculous

cholecystitis include abdominal pain, abdominal tenderness,

fever, nausea, and vomiting. Acute acalculous cholecystitis

is a condition that may be associated with high morbidity

and mortality rates if not diagnosed early and treated. If

acute acalculous cholecystitis is suspected, evaluate and

treat promptly

15/11/2017: Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in

order to update the safety and long term use information in

the posology following final results from study

CAMMS03409 - An Extension Protocol For Multiple Sclerosis

Patients Who Participated in Genzyme-Sponsored Studies

of Alemtuzumab (ongoing at the time of the initial MAA) to

evaluate the long term safety and efficacy of alemtuzumab

in MS patients who received additional treatment courses of

alemtuzumab. The update in the posology includes the

option for a third and fourth treatment course with

alemtuzumab if needed. If an additional course is

administered, safety-follow up should be continued until 48

months after the last infusion. Updated safety information

on immune thrombocytopenic Purpura (ITP), thyroid

disorders, infusion-associated reactions and infections has

been included.

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/lemtrada-h-c-psusa-00010055-202009-epar-scientific-conclusions-grounds-variation-terms-marketing_en.pdf>

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for alemtuzumab, the scientific

conclusions of CHMP are as follows:

In view of available data on risks from clinical trials, the literature, spontaneous reports, including cases with a plausible temporal relationship, and in view of a plausible mechanism of action, the PRAC considers a causal relationship between alemtuzumab and thrombotic thrombocytopenic purpura (TTP) is established. TTP is a serious and rare risk that has significant impact on the patient with high mortality if not urgently treated. The PRAC concluded that the product information of products containing alemtuzumab should be amended accordingly. In addition, in view of available data, the PRAC considers that an amendment of the adverse reaction pneumonitis is justified. “Pneumonitis” should be presented under SOC “respiratory, thoracic and mediastinal disorders” instead of SOC “infections and infestations”. The PRAC concluded that the product information of products containing alemtuzumab should be amended accordingly. Update of section 4.4 of the SmPC to add a warning on thrombotic thrombocytopenic purpura and 4.8 to add the adverse reaction thrombotic thrombocytopenic purpura with a frequency rare. Also, an update of section 4.4 and 4.8 of the SmPC to amend the adverse reaction pneumonitis. The Package leaflet is

updated accordingly.

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 alemtuzumab the CHMP is of the opinion that the benefit- risk balance of the medicinal product(s) containing alemtuzumab 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

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/lemtrada-h-c-psusa-00010055-201909-epar-scientific-conclusions-grounds-variation-terms-marketing_en.pdf>

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for alemtuzumab, the scientific

conclusions of CHMP are as follows:

During the reporting period, three case reports were identified indicating a potential causal association of progressive multifocal leukoencephalopathy (PML) and alemtuzumab. PML is a severe demyelinating disease of the central nervous system that is caused by reactivation of the polyomavirus JC, which occurs almost exclusively in immunosuppressed individuals. On the basis of this, updated risk minimizing measures are warranted. The PRAC recommends an update of the SmPC, section 4.4 and the patient information leaflet.

Cases of pericarditis with a potential causal association with alemtuzumab were identified during the

reporting period. Due to the severity of pericarditis and the cases identified, an update of the SmPC is warranted to include a warning of the risk of pericarditis. The PRAC recommends an update of the

SmPC, section 4.4. During the Article 20 referral procedure, Acquired haemophilia A was found to be related to treatment with alemtuzumab. Taken the severity of Acquired haemophilia A into consideration, the PRAC suggests an update of the SmPC section 4.4 to re-enforce awareness of this risk. The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation

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

The CHMP recommends that the terms of the marketing authorisation should be varied

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/lemtrada-h-c-psusa-00010055-201909-epar-scientific-conclusions-grounds-variation-terms-marketing_en.pdf>

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for alemtuzumab, the scientific

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Grounds for the variation to the terms of the marketing authorisation

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

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

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/lemtrada-article-20-referral-scientific-conclusions_en.pdf>

Scientific conclusions

Background information

During the assessment of the periodic safety update report (PSUSA) for Lemtrada

(EMEA/H/C/PSUSA/00010055/201809), the following new emerging and serious safety concerns were highlighted in addition to the known safety profile of alemtuzumab, which raised major concerns to the Pharmacovigilance Risk Assessment Committee (PRAC):

- Fatal cases: Several fatal cases were identified during the PSUSA procedure, which indicate that the

current recommendations for monitoring may be insufficient.

- Cardiovascular adverse events in close temporal association with Lemtrada infusions (e.g. cardiac

ischaemia and myocardial infarction, ischaemic and haemorrhagic stroke, arterial dissection,

pulmonary haemorrhage and embolism, vasculitis and thrombocytopenia), including a possible

mechanistic relation to these adverse events.

- Immune-mediated diseases such as auto-immune hepatitis, hepatic injury, auto-immune-mediated

central nervous system disease and Guillain-Barre Syndrome (GBS).

Limited information, including lack of detailed information on the individual cases, was available on

these concerns during the PSUSA assessment, precluding a thorough evaluation.

On 10 April 2019 the European Commission (EC) therefore triggered a procedure under Article 20 of

Regulation (EC) No 726/2004 resulting from pharmacovigilance data and requested the PRAC to assess the above safety concerns and their impact on the benefit-risk balance of Lemtrada and to issue a recommendation on whether the relevant marketing authorisation should be maintained, varied, suspended or revoked.

Provisional measures were introduced at the start of procedure to protect patients while the detailed evaluation was ongoing. As a provisional measure, it was recommended that new treatment with Lemtrada should only be initiated in adult patients with highly active relapsing remitting multiple sclerosis despite a full and adequate course of treatment with at least two other disease modifying treatments, or in adult patients with highly active relapsing remitting multiple sclerosis where all other disease modifying treatments are contraindicated or otherwise unsuitable.

Overall summary of the scientific evaluation by the PRAC

The efficacy of alemtuzumab in relapsing remitting multiple sclerosis patients across multiple

parameters of the disease is well established and maintained over long term follow up. This level of

efficacy is present across a wide range of patient populations, as evidenced by the consistency of

findings across various subgroups of participants in alemtuzumab clinical studies.

As part of the current review, a number of serious, life-threatening and disabling risks associated with Lemtrada have been assessed. Acute coronary syndrome and cerebrovascular events including arterial dissection and haemorrhagic stroke, pulmonary haemorrhage and transient thrombocytopenia have been identified as risks in close temporal association with the infusion of alemtuzumab. These risks are considered to be related to cytokine release syndrome, which has been described in the literature for alemtuzumab1,2.

Following the review, it has been reconfirmed that Lemtrada causes secondary autoimmune disease

including auto-immune hepatitis, thyroiditis, immune thrombocytopenic purpura, acquired haemophilia A, nephropathies, cytopenias and serious immunological reactions such as haemophagocytic lymphohistiocytosis. Cases of poly-autoimmunity associated with Lemtrada have also been identified. During the procedure, other new adverse reactions were identified which are also considered related to Lemtrada such as Epstein-Barr virus re-activation.

One general characteristic of alemtuzumab which impacts on its safety profile and on risk management is the very long treatment effect, and thereby the infrequent administration regimen. Thus, due to the long term effect of alemtuzumab, treatment discontinuation has limited value from a risk management perspective.

No surrogate or biomarker for patients at risk for serious cytokine release or autoimmunity was

identified. Therefore many of the newly-identified risks associated to Lemtrada are unpredictable and largely unavoidable. In such circumstances it is necessary to restrict use of the alemtuzumab to

patients who can benefit the most from treatment and who may be ready to accept the serious risks

associated with treatment. This includes not just a restricted therapeutic indication but also

contraindications in subpopulations anticipated, due to risk factors, to be at higher risk of developing

the serious adverse reactions.

In this context, and taking also into account the advice of the SAG, PRAC concluded that Lemtrada

should be indicated as a single disease modifying therapy in adults with highly active relapsing

remitting multiple sclerosis (RRMS) for the following patient groups:

• Patients with highly active disease despite a full and adequate course of treatment with at least

one disease modifying therapy (DMT) or

• Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more

disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI

or a significant increase in T2 lesion load as compared to a previous recent MRI.

With this conclusion, PRAC acknowledges that early initiation of high-efficacy DMTs in patients with

highly active (aggressive) or rapidly evolving RRMS is increasingly viewed as a strategy to prevent or

postpone irreversible damage that occurs early in the disease course3. Recent studies of RRMS with

long-term follow-up have shown that disease-modifying therapies (DMTs) reduce the proportion of

patients who progress to SPMS compared to the proportion of untreated patients who progress.

Furthermore, when selecting the most appropriate and effective treatment for the patient, the safety profile and the possibility to manage risks effectively should also be taken into consideration.

Vulnerable patient groups such as patients with severe active infections until complete resolution,

uncontrolled hypertension, a history of arterial dissection of the cervicocephalic arteries, of stroke,

angina pectoris or myocardial infarction and patients with known coagulopathy, on anti-platelet or anti- coagulant therapy, should be contraindicated. Patients with other concomitant autoimmune diseases (besides MS) should also be contraindicated to minimise the risk of development of additional autoimmune disorders.

In order to ensure adequate monitoring of patients before, during and after the infusion of

alemtuzumab, rapid diagnosis and prompt and adequate treatment of the above mentioned risks, the infusion of alemtuzumab should take place in a hospital with availability of experts and adequate

equipment to manage the risks. The MAH proposed to include also specialised infusion centres with

ready access to intensive care. Specialists from other medical disciplines (e.g. cardiologists) and

equipment for timely diagnosis and management of adverse reactions however requires, in the view of PRAC, a hospital setting. The PRAC considered a recommendation for a longer follow-up period in

hospital (for up to 5 days after the last infusion) to allow for prompt identification and management of serious adverse reactions that may occur. However it was ultimately considered that this long

hospitalisation may not be feasible and that, as highlighted by the SAG, there is limited data to

indicate it will have a substantial impact in the management of post-infusion adverse reactions.

New infusion instructions are also proposed to allow early identification and management of serious

adverse reactions temporally associated with infusion. In addition to close monitoring of cardiovascular function before, during and after the infusion, this also includes new recommendations for platelet count measurement during the infusion cycle and for post-infusion monthly liver transaminase testing. Currently, safety follow-up of patients is recommended from initiation of the first treatment course and until 48 months after the last treatment course. However, in individual cases autoimmune conditions may occur or be diagnosed later so healthcare professionals should be aware of this possibility.

Cases of pulmonary embolism, vasculitis, central nervous system autoimmune disease and Guillain-

Barre Syndrome (GBS) have been reported. The current evidence is insufficient to conclude on a causal relationship with Lemtrada. There are uncertainties about a potential causal relationship with a number of other autoimmune adverse events reported in temporal association with Lemtrada, and these will have to continue to be closely monitored in the future.

In future PSURs, the MAH is expected to submit cumulative reviews and discuss the following safety

concerns: vasculitis, CNS inflammation, GBS, diabetes type 1, myasthenic syndrome, myositis,

sarcoidosis, GBS, pneumonitis and EBV hepatitis.

A matter of concern is the post-marketing reporting rate of fatalities, including those with short latency after alemtuzumab infusion. The relative young age of patients who died within a short period (30 days) from Lemtrada treatment is also noted. A post authorisation safety study is needed to address these concerns.

A study is also needed to assess the effectiveness of the risk minimisation measures adopted during

this review. Considering the serious and unpredictable nature of the newly-identified adverse reactions, it is important to understand whether the newly implemented measures are adhered to in clinical practice.

The MAH for Lemtrada will also disseminate a DHPC to inform healthcare professionals of the outcome of this review, and the educational material for both healthcare professionals and patients will be updated.

In view of the above, PRAC concluded that the benefit-risk balance of Lemtrada remains favourable

subject to changes to the product information, the educational materials and additional

pharmacovigilance activities described above. As a consequence, PRAC recommended the variation to the terms of the marketing authorisation for Lemtrada.

Grounds for PRAC recommendation

Whereas

• PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Lemtrada.

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• PRAC reviewed data currently available from post-marketing setting and from clinical trials on

fatal cases, cardiovascular adverse events in close temporal association with Lemtrada

infusions and immune-mediated diseases, including data provided in writing and at an oral

explanation. PRAC also considered the views expressed by the neurology scientific advisory

group.

• PRAC concluded that myocardial ischaemia, myocardial infarction, haemorrhagic stroke,

dissection of the cervicocephalic arteries, pulmonary alveolar haemorrhage and

thrombocytopenia may occur in close temporal association with the infusion of Lemtrada. PRAC

also concluded that alemtuzumab is associated with immune-mediated diseases such as

autoimmune hepatitis, haemophilia A and haemophagocytic lymphohistiocytosis (HLH), which

can happen with a delay of months to years after the latest treatment. PRAC noted that these

risks, which are serious and which can in some cases have a fatal outcome, are largely

unpredictable.

• As a consequence, PRAC recommended that treatment with Lemtrada should be restricted to

patients with highly active relapsing remitting multiple sclerosis for the following patient

groups:

o patients with highly active disease despite a full and adequate course of treatment with

at least one disease modifying therapy, or

o patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2

or more disabling relapses in one year, and with 1 or more Gadolinium enhancing

lesions on brain MRI or a significant increase in T2 lesion load as compared to a

previous recent MRI.

• Lemtrada should also be contraindicated in patients with:

o severe active infections until complete resolution,

o uncontrolled hypertension,

o history of arterial dissection of the cervicocephalic arteries,

o history of stroke,

o history of angina pectoris or myocardial infarction,

o coagulopathy, on antiplatelet or anti-coagulant therapy

o concomitant autoimmune diseases other than multiple sclerosis.

• Furthermore, PRAC recommended that Lemtrada should only be administered in a hospital

setting with ready access to intensive care.

• PRAC also made additional recommendations for monitoring of patients before, during and

after infusion to ensure timely diagnosis and management of adverse reactions.

• The PRAC considered that given the serious and unpredictable nature of the risks, and that

effective risk minimisation is key to support a positive benefit-risk balance, a drug utilisation

study is necessary to assess effectiveness of risk minimisation measures.

• PRAC also considered that the data currently available on mortality incidence is limited and

therefore the MAH shall investigate the incidence of mortality in patients treated with Lemtrada

compared with a relevant patient population.

In view of the above, PRAC concluded that the benefit-risk balance of Lemtrada remains favourable

subject to changes to the product information, the educational materials and additional

pharmacovigilance activities described above. As a consequence, PRAC recommended the variation to the terms of the marketing authorisation for

Lemtrada.

CHMP opinion

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

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<https://www.ema.europa.eu/en/documents/variation-report/lemtrada-article-20-referral-assessment-report-provisional-measures_en.pdf>

Whereas,

• The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting

from pharmacovigilance data for Lemtrada, in particular the need for provisional measures in

accordance with Article 20(3) of Regulation (EC) No 726/2004, taking into account the grounds

set out in Articles 116 of Directive 2001/83/EC.

• The PRAC reviewed the available data on cardiovascular reactions, including data provided by

the marketing authorisation holder in the context of the PSUSA procedure. Several cases with

various cardiovascular reactions were identified, including pulmonary alveolar haemorrhage,

myocardial infarction, and ischaemic and haemorrhagic stroke as well as arterial dissection.

Many of these cases were life-threatening or fatal. Common to these cardiovascular reactions

was a close temporal relationship to an alemtuzumab infusion, which is suggestive of a causal

association.

• The PRAC also reviewed the available data on immune-mediated adverse events, including

data provided by the marketing authorisation holder in the context of the PSUSA procedure.

New life-threatening and potentially fatal immune-mediated adverse reactions were identified,

including haemophagocytic lymphohistocytosis and autoimmune hepatitis. The PRAC also noted

that recent literature reports have highlighted B-cell mediated central nervous system (CNS)

lesions with temporal onset of 6 months after infusion of alemtuzumab.

• In addition, several fatal cases were identified both in the literature and in the Eudravigilance

database. Information from some fatal cases indicates that current recommendations for

monitoring may be insufficient.

Assessment report on provisional measures

EMA/249094/2019 Page 7/7

• The PRAC noted that although efficacy of alemtuzumab in relapsed remitting multiple sclerosis

patients is well established, these emerging and serious safety concerns can impact the

benefit-risk balance of Lemtrada, and that until a thorough review is finalised, it would be

appropriate as a provisional measure to limit the patients exposed to alemtuzumab. Therefore,

in view of the seriousness of the events observed, the PRAC recommended provisional

amendments to the product information to restrict use of alemtuzumab in new patients to

adults with highly active relapsing remitting multiple sclerosis despite a full and adequate

course of treatment with at least two other disease modifying treatments, or to adults with

highly active relapsing remitting multiple sclerosis where all other disease modifying

treatments are contraindicated or otherwise unsuitable.

• In addition the PRAC considered important that the risk minimisation measures recommended

within the assessment of the current PSUSA procedure are also implemented together with the

provisional measures. The PRAC recommended as part of the PSUSA procedure the addition of

warnings related to serious reactions temporally associated with alemtuzumab infusion

including pulmonary alveolar haemorrhage, myocardial infarction, stroke (including ischaemic

and haemorrhagic stroke), cervicocephalic (e.g. vertebral, carotid) arterial dissection. New

warnings on autoimmune hepatitis, hepatic injury and haemophagocytic lymphohistiocytosis

are also added. Furthermore, the following new adverse reactions are added: pulmonary

alveolar haemorrhage, haemophagocytic lymphohistiocytosis, myocardial infarction, stroke

(including ischemic and haemorrhagic stroke), cervicocephalic arterial dissection and

neutropenia.

In view of the above, the Committee considers that the benefit-risk balance of Lemtrada

(alemtuzumab) remains favourable subject to the agreed provisional amendments to the product

information. The Committee, as a consequence, recommends the variation to the terms of the

marketing authorisation for Lemtrada (alemtuzumab).

This recommendation is without prejudice to the final conclusions of the ongoing procedure under

Article 20 of Regulation (EC) No 726/2004.

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/lemtrada-h-c-psusa-00010055-201703-epar-scientific-conclusions-grounds-variation-terms-marketing_en.pdf>

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for alemtuzumab, the scientific

conclusions of CHMP are as follows:

Alemtuzumab acts through antibody-dependent cellular cytolysis and complement-mediated lysis

following cell surface binding to T and B lymphocytes with a subsequent reduction in the level of

circulating B and T cells increasing the risk for infections or worsening of existing infections. Based on

the mechanism of action and the biological plausibility for worsening of active infections, it is

recommended to add a contraindication to initiate alemtuzumab treatment in patients with severe

active infection until resolution.

Based on data from the review period, a causal association is identified between listeriosis/listeria

meningitis and alemtuzumab treatment prior and during the initiation of the treatment. A total of 26

serious events concerning listeriosis have been reported, among them a post-marketing fatal case was identified where a causal relationship with alemtuzumab could not be excluded. Moreover, an

evaluation of time to onset of listeriosis was undertaken within this review. A case report mentioned

that as in most other cases of listeriosis, symptoms started rapidly after the last alemtuzumab

infusion, which suggests that patients could have been infected with the bacteria already prior to the alemtuzumab infusions. The incubation period of invasive listeriosis is found to be wide (median 8 days, range 1–67 days). For cases with involvement of the central nervous system (CNS) the period is more narrow (median 9 days, range 1–14 days) (Goulet et al. 2013). In another study, the median

incubation period is 11 days and 90% occurs within 28 days. Based on this observation, and due to the wide incubation period of Listeria infectious agents which is usually two weeks, the PRAC recommends to add to the existing warning that possibly listeria contaminated food items should be avoided not only one month after, but also two weeks prior and during alemtuzumab infusion.

Based on data from the review period, a causal association is identified between pneumonitis and

alemtuzumab treatment. In clinical studies, 6 of 1217 (0.5%) LEMTRADA-treated patients had

pneumonitis of varying severity. Cases of hypersensitivity pneumonitis with fibrosis have occurred.

Additional cases reported, majority in postmarketing setting, of which some occurred less than a

month (n=18) after treatment with alemtuzumab, has prompted the marketing authorization holder to add information to warn about the possibility of developing pneumonitis in alemtuzumab treated

patients.

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 alemtuzumab the CHMP is of the opinion that the benefit- risk balance of the medicinal product(s) containing alemtuzumab 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

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/lemtrada-h-c-psusa-00010055-201509-epar-scientific-conclusions-grounds-variation-terms-marketing_en.pdf>

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for alemtuzumab, the scientific

conclusions of CHMP are as follows:

Listeriosis/Listeria meningitis

Medicines that have a modulating effect on the immune system as Lemtrada might be associated with an increased risk of opportunistic infections. A total of 5 case reports all originating from the EU were identified. One alemtuzumab -treated MS clinical trial patient, enrolled in study CAMMS223, developed listeria meningitis and four spontaneous post-marketing cases of either systemic listeriosis or Listeria monocytogenes meningitis.

Bradycardia as an infusion related adverse reaction Seventy-one cases (in 55 patients) of bradycardia (two of which were assessed as serious, the remainder as non-serious) were reported in clinical trials. A total of 1,505 alemtuzumab patients were exposed in these trials. In addition, thirty-nine cases of bradycardia (eight of which were assessed as serious, the remainder as non-serious) were reported from alemtuzumab post-marketing reports as of 01 May 2015. Each of the ten serious cases involving bradycardia occurred in the context of infusion-associated reactions.

Therefore, in view of the data presented in the reviewed PSUR, the PRAC considered that changes to

the product information of medicinal products containing alemtuzumab were warranted. The section 4.4 of the summary of product characteristics and the relevant sections of the package leaflet were updated.

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

Grounds for the variation to the terms of the marketing authorisation

On the basis of the scientific conclusions for alemtuzumab the CHMP is of the opinion that the

benefit-risk balance of the medicinal product containing alemtuzumab is unchanged subject to the

proposed changes to the product information.

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

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<https://www.ema.europa.eu/en/documents/referral/lemtrada-article-20-procedure-prac-assessment-report_en.pdf>

<https://www.ema.europa.eu/en/documents/referral/lemtrada-article-20-procedure-chmp-divergent-positions_en.pdf>

<https://www.ema.europa.eu/en/documents/scientific-conclusion/lemtrada-h-c-psusa-00010055-201509-epar-scientific-conclusions-grounds-variation-terms-marketing_en.pdf>

## Cladribine: *Mavenclad*

Communications/press releases:

<https://www.ema.europa.eu/en/medicines/dhpc/mavenclad-cladribine-risk-serious-liver-injury-new-recommendations-about-liver-function-monitoring>

Since recommendation: <https://www.ema.europa.eu/en/documents/procedural-steps-after/mavenclad-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf>

There are a number of changes, please refer to link above.

Of note:

04/03/2022: Hypersensitivity is added to the list of adverse drug

reactions with frequency “common”. It has been specified

that hypersensitivity events included pruritus, urticaria,

rash and rare cases of angio-oedema. PL updated

accordingly. For more information, please refer to the

Summary of Product Characteristics.

## Fingolimod: *Gilenya*

Communications/press releases:

<https://www.ema.europa.eu/en/medicines/dhpc/gilenya-fingolimod-updated-recommendations-minimise-risk-drug-induced-liver-injury-dili>

<https://www.ema.europa.eu/en/news/european-medicines-agency-gives-new-advice-better-manage-risk-adverse-effects-heart-gilenya>

<https://www.ema.europa.eu/en/news/new-recommendations-minimise-risks-rare-brain-infection-pml-type-skin-cancer-gilenya>

<https://www.ema.europa.eu/en/news/updated-restrictions-gilenya-multiple-sclerosis-medicine-not-be-used-pregnancy>

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Since recommendation: <https://www.ema.europa.eu/en/documents/procedural-steps-after/gilenya-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf>

There are a number of changes, please refer to link above.

Of note:

03/09/2019: The MAH provided a review of information from the published

literature (Vermersch et al (2017)), including

epidemiological evaluation, the Novartis safety database,

and clinical studies (FREEDOMS/FTY720D2301 and

FREEDOMS II/FTY720D2309) covering at least 3 months

after treatment withdrawal to support a labelling update

regarding rebound effect (in sections 4.4, 4.6 and 4.8). This

has generally been observed within 12 weeks after stopping

fingolimod, but has also been reported up to 24 weeks after

fingolimod discontinuation recommending the patient

monitoring if treatment discontinuation is deemed

necessary.

Furthermore, post marketing data was also provided to

support changes related to the LEG 037 procedure

concerning the increased risk of major congenital

malformations and contraindication of Gilenya use in

pregnant women and women of child-bearing potential, not

using effective contraception regarding its reproductive

toxicity. As a result SmPC sections 4.3, 4.4 and 4.6 have

been updated to include contraindication regarding pregnant

women and WCBP not using effective contraception.

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08/12/2017: Section 4.4 of the SmPC has been amended to add the

following detail to the existing warning on cryptococcal

meningitis: “Cases of cryptococcal meningitis (a fungal

infection) have been reported in the post-marketing setting

after approximately 2 3 years of treatment, although an

exact relationship with the duration of treatment is

unknown.”

In addition, the existing warning on leukoencephalopathy

(PML) has been updated with the following: “Cases of PML

have occurred after approximately 2 3 years of monotherapy

treatment without previous exposure to natalizumab,

although an exact relationship with the duration of treatment

is unknown. Additional PML cases have occurred in patients who had been treated previously with natalizumab, which

has a known association with PML.”

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25/01/2016: Case of Progressive Multifocal Leukoencephalopathy (PML)

occurring in post marketing patients under Gilenya

treatment. PML typically only occurs in patients who are

immunocompromised. Before initiating treatment with

fingolimod, a baseline Magnetic Resonance Imaging (MRI)

should be available (usually within 3 months) as a reference.

During routine MRI, physicians should pay attention to PML

suggestive lesions. In case of PML is suspected, MRI should

be performed immediately for diagnostic purposes and

treatment with fingolimod should be suspended until PML has

been excluded.

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23/11/2015: Based on the review of the available information the CHMP is

of the opinion that the quality, the safety and the efficacy of

this medicinal product continues to be adequately and

sufficiently demonstrated and therefore considers that the

benefit/risk profile of Gilenya continues to be favourable.

However, since the first launch of the product, the following

safety issues have been identified with Gilenya:

bradyarrhythmia, PRES, lymphoma, periodicity of complete

blood count (CBC), HPS, hypersensitivity following a bullous

erythema multiform , PML, cryptococcal infections,

opportunistic infections, BCC, urticarial, angioedema, Kaposi

sarcoma, Tumefactive relapses, T-wave inversion, peripheral

oedema, retinal disorders, RCVS, fatal cases including

unexplained death and safety concerns after treatment by

DMTs. These issues have led to updates of the SmPC and

updates of the Pharmacovigilance Plan. Therefore, based

upon the safety profile of Gilenya, which requires the

submission of yearly PSURs, the CHMP was of the opinion

that an additional five-year renewal on the basis of

pharmacovigilance grounds was required.

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03/07/2015: Isolated cases of cryptococcal meningitis (a fungal infection)

have been reported in the post-marketing setting. Patients

with symptoms and signs consistent with cryptococcal

meningitis (e.g. headache accompanied by mental changes

such as confusion, hallucinations, and/or personality

changes) should undergo prompt diagnostic evaluation. If

cryptococcal meningitis is diagnosed, fingolimod should be

suspended and appropriate treatment should be initiated. A

multidisciplinary consultation (i.e. infectious disease

specialist) should be undertaken if re-initiation of fingolimod

is warranted-

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23/05/2014: After review of the latest MAH safety analyses, the CHMP

recommended the following main safety changes:

- Neutropenia was replaced by cytopenia regarding the signs

of relevant treatment related abnormalities when switching

directly therapy to Gilenya.

- Some ADRs were grouped (hepatic enzymes increases) and

some frequencies were updated: hepatic enzyme increases,

sinusitis, macular oedema, atrioventricular blocks and

reduction in values for forced expiratory volume. This

resulted in changes from common to very common adverse

reactions (ADRs) for hepatic enzyme increases and sinusitis.

- The overall rate of infections was updated. Herpes infection

was added as a more common lower respiratory tract

infection seen in Gilenya treated patients but observed at a

lesser extent than bronchitis. The terms “influenza viral

infection” and “tinea infections” were replaced by “influenza”

and “tinea versicolor”, respectively, as considered as a more

accurate description of these ADRs.

- The following ADRs were deleted: gastroenteritis,

paraesthesia, eye pain and weight decreased.

- PRES was included as a warning with physicians advised to

stop Gilenya treatment if PRES is suspected.

- The existing warnings to ascertain appropriate assessment

of patient immunity to VZV prior to treatment and on the

concomitant use of corticosteroids were strengthened

25/11/2013: Following a safety signal regarding the occurrence of 2 fatal

cases of haemophagocytic syndrome with fingolimod, the

PRAC/CHMP recommended an update of section 4.8 of the

SmPC to reflect this information as well as to issue a Direct

Healthcare Professional Communication (DHPC) with the aim

of raising awareness on this risk and communicate about the

difficulties of diagnosing HPS and the risk of a worse outcome

when the diagnosis is delayed. Section 4.8 was updated as

follows:

- Very rare cases of haemophagocytic syndrome (HPS) with

fatal outcome have been reported in patients treated with

fingolimod in the context of an infection. HPS is a rare

condition that has been described in association with

infections, immunosupression and a variety of autoimmune

diseases.

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25/11/2013: Following their assessment of PSUR 1 for Gilenya, the CHMP

requested the MAH to review all serious cases reporting

leucopenia and lymphopenia with at least important

information such as time to onset and outcomes. Incidence

of infections in clinical trials was found greater in groups of

patients with a nadir lymphocyte count <0.2x109/L than in

group 0.2-0.4x109/L and >0.4x109/L. In post-marketing,

the lymphocytes counts were unknown for a significant

number of cases so a correlation between infections and

lymphocyte count could not be excluded. Subsequently to

these findings and taking also into account the data from last

PSUR regarding fatal cases related to infections, the CHMP

considered relevant to specify a periodicity for the complete

blood count (CBC) in the SmPC. An update of the existing

warning was made recommending assessment of CBC at

month 3 and at least yearly thereafter.

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25/11/2013: Following their assessment of PSUR 2 for Gilenya, the CHMP

requested the MAH to review available data regarding the

bradyarrhythmia effect of fingolimod and the occurrence of

lymphoma. Subsequently to assessment of the presented

analyses, the Product information has been updated to

include the following concepts:

- Section 4.4: after the first dose, the decline in heart rate

starts within one hour, and is maximal within 6 hours. This

post-dose effect persists over the following days, although

usually to a milder extent, and usually abates over the next

weeks. With continued administration, the average heart

rate returns towards baseline within one month. However

individual patients may not return to baseline heart rate by

the end of the first month.

- Section 4.8: there have been cases of lymphoma of

different varieties, in both clinical studies and the

post-marketing setting, including a fatal case of Epstein-Barr

virus (EBV) positive B-cell lymphoma. The incidence of

lymphoma (B-cell and T-cell) cases was higher in clinical

trials than expected in the general population.

In addition, section 4.8 has been updated to be in line with

section 4.4 regarding the information on the

bradyarrhythmia effect and to include hypotension as an

associated symptom as follows: bradycardia was generally

asymptomatic but some patients experienced mild to

moderate symptoms, including hypotension, dizziness,

fatigue and/or palpitations, which resolved within the first 24

hours after treatment initiation

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25/11/2013: Based on the SmPC recommendation, all patients starting

treatment with Gilenya should have their heart activity

monitored before receiving the first dose of the medicine and

continuously for at least six hours thereafter as some

patients may develop heart problems such as bradycardia (a

slow heart rate) or atrioventricular block (a problem with the

conduction of electricity in the heart). The SmPC of Gilenya

also recommends that this first dose monitoring be repeated

if a patient, who was treated for more than 1 month with

Gilenya and stopped taking it for two weeks or more,

re-starts treatment. The timeframe of Gilenya therapy

interruption has been investigated by the MAH using

pharmacokinetics, pharmacokinetic/pharmacodynamic

models and titration data to better define when such

monitoring should be considered. Based on these data, the

CHMP recommended to extend the current advice for heart

activity monitoring in case of re-initiation of treatment to the

following situations: 1) treatment is interrupted for one day

or more during the first 2 weeks of treatment, 2) treatment is

interrupted for more than 7 days during weeks 3 and 4 of

treatment. In addition, such monitoring should be repeated

for the second dose in patients requiring pharmacological

intervention during the first dose.

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22/11/2012: On the basis of the data submitted, the CHMP considered that

this present applicant fulfilled the request for updating the

Product Information to include that PRES were also observed

with the 0.5 mg dose used in the approved indication. The

following information has been reflected in the Product Information:

- Section 4.8: In clinical studies, rare events involving the

nervous system occurred in patients treated with fingolimod

at higher doses (1.25 or 5.0 mg) including ischemic and

haemorrhagic strokes, posterior reversible encephalopathy

syndrome and neurological atypical disorders, such as acute

disseminated encephalomyelitis (ADEM)-like events. Rare

cases of posterior reversible encephalopathy syndrome have

also been reported at doses of 0.5 mg in both the clinical and

the post-marketing setting.

- Section 4: Rare: A condition called posterior reversible

encephalopathy syndrome (PRES). Symptoms may be

headache, confusion, seizures and/or vision disturbances.

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14/12/2011: On the basis of the submitted data, the CHMP recommended

to revise the time of occurrence of liver enzymes elevations

and related recommendation on monitoring. The relevant

text resulting from this variation is as follows:

Section 4.4:

Recent (i.e. within last 6 months) transaminase and bilirubin

levels should be available before initiation of treatment with

Gilenya. In the absence of clinical symptoms, liver

transaminases should be monitored at Months 1, 3, 6 ,9 and

12 on therapy and periodically thereafter. If liver

transaminases rise above 5 times the ULN, more frequent

monitoring should be instituted, including serum bilirubin

and alkaline phosphatase (ALP) measurement. With

repeated confirmation of liver transaminases above 5 times

the ULN, treatment with Gilenya should be interrupted and

only re-commenced once liver transaminase values have

normalised.

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<https://www.ema.europa.eu/en/documents/variation-report/gilenya-h-c-2202-a20-0008-epar-assessment-report-article-20_en.pdf>

“Whereas

• The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004, for

Gilenya initiated by the European Commission.

• The Committee reviewed the available safety data from clinical trials and post-marketing data on

the cardiovascular adverse events reported and in particular during the 24 hours after first dose

administration of Gilenya.

• In view of the available data the Committee concluded that serious cases of bradyarrhythmia and

hypertension have been reported with fingolimod. These occur in particular by 6 hours after the

first dose administration of Gilenya.

• The Committee therefore recommended that all patients should have an ECG and blood pressure

measurement performed at baseline prior to the first dose of Gilenya. The committee agreed that

Gilenya should not be used in patients at risk of cardiovascular disease and as use of beta blockers

and calcium channel blockers during treatment initiation may be associated with severe

bradycardia and heart block, Gilenya should not be initiated in patients who are concurrently

treated with these substances. Furthermore, if treatment is considered in all these at risk patients,

advice from a cardiologist should be sought prior to initiation of treatment in order to determine

the most appropriate monitoring (at least overnight) for treatment initiation. These

recommendations are reflected in the updated summary of product characteristics.

• The Committee is of the opinion that Gilenya should not be used in patients of uncontrolled

hypertension until the hypertension is brought under control.

• The Committee, as a consequence, concluded that the benefit-risk balance of Gilenya in the

treatment of highly active relapsing remitting multiple sclerosis remains positive under normal

conditions of use, subject to the conditions, warnings, changes to the product information,

additional pharmacovigilance activities and risk minimisation measures agreed.

The CHMP has therefore recommended the variation to the terms of the marketing authorisation for

Gilenya in accordance to the Product Information set out in annexes I, II and IIIB and update of Annex related to Article 127a”

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/gilenya-h-c-2202-psuv-0023-epar-scientific-conclusions-grounds-recommending-variation-terms_en.pdf>

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for Gilenya, the scientific conclusions of PRAC are as follows: The adverse event profile in this Periodic Safety Update Report (PSUR) is consistent with the known safety profile of Gilenya to date. However new safety information emerged from this PSUR period in relation to disseminated herpes infection, interaction with carbamazepine and strong CYP450 inducers, cases of overdose:

- A detailed review of cases of cutaneous Varicella Zoster Virus (VZV) dissemination and VZV

reactivation with central nervous system involvement resulted in identification of 35 cases of

disseminated herpes viral infections as of October 2012. According to literature, the risk of

herpes viral infections increases with altered cell-mediated immune responses. From the PRAC

viewpoint, the risk of viral infection should be considered with fingolimod treatment due to its

mechanism of action. These disseminated herpes viral infections cases included: 1 case with

visceral involvement (pulmonary), 3 cases with brain or spinal cord involvement and

31 cutaneous dissemination (13 cases multidermatomal, 3 cases with bilateral lesions, 10 cases

unilateral and 5 cases unspecified). An additional case of varicella disseminated infection leading

to death was recently reported and occurred 6 months after fingolimod initiation. This case is

still under evaluation and should be discussed in the next PSUR. Furthermore, the PRAC also

noted the recent follow up received after the Data Lock Point of this PSUR regarding the autopsy

of the patient who died following an Haemophagocytic syndrome was compatible with a possible

origin of disseminated herpes infection. Overall, the PRAC considered that the Summary of

Product Characteristics (SmPC) should be amended to reflect that some cases of disseminated

herpes infection, including fatal cases, have been reported in post-marketing and clinical trials

even at the 0.5 mg dose. - In healthy volunteers, concomitant treatment of carbamazepine, at the maximal dose of 600 mg twice daily, decreases the exposure of fingolimod and fingolimod-P by approximately 40%. No conclusions can be drawn on which nuclear receptors are mostly activated or which enzymes are specifically impacted in this interaction. Whilst the mechanism causing such reduction in exposure of fingolimod remains to be elucidated, the results of this study question the real role of CYP3A4 in fingolimod metabolism. On this basis, the PRAC recommended a revision of the SmPC information regarding concomitant administration of CYP450 inducers and to include a

specific warning on possible reduced efficacy of fingolimod when combined to CYP450-inducing

stronger agents (i.e. rifampicin, phenytoin, phenobarbital, carbamazepine, efavirenz, St John’s

wort). - Cases of overdose have been reported. Thus, the PRAC also recommended deletion of the

following sentence in section 4.9 of the SmPC: “No cases of overdose have been reported.”

Therefore, in view of available data regarding disseminated herpes infection, interaction with

carbamazepine and strong CYP450 inducers and cases of overdose, the PRAC considered that changes to the Product Information were warranted. The next PSUR should be submitted 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. The CHMP agrees with the scientific conclusions made by the PRAC. Grounds recommending the variation to the terms of the Marketing Authorisation On the basis of the scientific conclusions for Gilenya, the CHMP is of the opinion that the benefit-risk balance of the medicinal product containing the active substance FINGOLIMOD is favourable subject to the proposed changes to the product information”

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/gilenya-h-c-psuv-0027-epar-scientific-conclusions-grounds-recommending-variation-terms-marketing_en.pdf>

“Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for Gilenya, the scientific conclusions

of PRAC are as follows: The adverse event profile in this Periodic Safety Update Report (PSUR) is consistent with the known safety profile of Gilenya to date. However, new safety information emerged from this PSUR period in relation to hypersensitivity and rash, cancers (cervix and brain):

- Following the results of the safety analysis requested by the PRAC on hypersensitivity, no cases of

toxic epidermal necrolysis, Stevens Johnson syndrome or anaphylaxis were reported from clinical

trials. Two non-serious cases of erythema multiform in the fingolimod 0.5mg group were reported.

The incidence rate of hypersensitivity reactions in clinical trials was not significantly different from

placebo. However, cumulatively, 802 cases describing “hypersensitivity” were reported. Among these cases, 784 cases were excluded from further analysis by the Marketing Authorisation Holder (MAH) because these cases were not considered “noteworthy” according to the following criteria: 1) did not have positive dechallenge/rechallenge, 2) had reported confounders, 3) did not require intervention, and/or 4) were not documented. Based on these criteria, the PRAC considered that a causal relationship with Gilenya could not be totally ruled out, especially for the non-documented cases. Considering that a clear causal relationship was established for the remaining 18 cases (all positive dechallenges or positive rechallenges) and taking into account the number of reported cases

(including one bullous erythema multiforme coded as Stevens-Johnson syndrome), the PRAC

concluded that “hypersensitivity” and “rash” should be added as new adverse reactions of Gilenya.

Therefore, in view of available data regarding hypersensitivity, the PRAC considered that changes to

the product information were warranted.

- Regarding the review of other malignant neoplasms (potential risk), 15 cases of cervix cancer and 7

cases of brain cancer have been reported cumulatively (6 were reported during the present PSUR

period). Limited information has been presented in this PSUR, particularly for four of the cases of

brain cancers, thus not allowing a proper causality assessment between Gilenya and the reported

cases. The MAH is requested to improve the quality of data regarding cervix cancer and brain cancer

in the next PSUR. A comprehensive clinical assessment of all cervix cancer (taking into account

epidemiological data in multiple sclerosis patients and general population) and all brain cancer cases

should be provided in the next PSUR (covering PSUR period and cumulatively).

In addition, the PRAC noted the following:

- Regarding infections (identified risk), 1250 cases of infections have been reported during the

reporting period (the proportion of infection among all the reported cases in this current period is

around 13.1%). Due to the seriousness of the infections reported with fingolimod, these events

should be closely monitored.

- Twelve cases of Progressive Multifocal Leukoencephalopathy (PML) were reported including 5 during the current period. In the last PSUR, 10 cases were reported cumulatively. Taking into account the case reported in the late breaking information, there are at least 13 cases reported cumulatively. These events should be closely monitored and a thorough review of all PML cases should be provided in the next PSUR.

- Thrombocytopenia (including immune thrombocytopenic purpura) and pancytopenia were signals

under review by the MAH. A safety review was performed by the MAH and reported 115 cases of

thrombocytopenia. Moreover 7 cases of immune thrombocytopenic purpura were reported. Since 11 cases of thrombocytopenia had positive dechallenges including one patient with a positive

Gilenya EMA/405985/2014 Page 3/3 rechallenge, a potential causal relationship between Gilenya and thrompocytopenia could not be excluded. Regarding pancytopenia, 33 cases were cumulatively reported. The majority of these cases did not have sufficient information to allow a proper causality assessment. However, one case had a positive dechallenge. Based on these data, the PRAC considered necessary to keep these signals under evaluation in the next PSUR for further characterisation.

- Regarding the review of leukopenia/lymphopenia (identified risk), the percentage of cases reporting

concomitantly leukopenia and lymphopenia (any) was found higher for more serious types of

infections (sepsis) when compared with the percentage of infections overall. Based on this finding, the MAH should discuss whether an update of the Summary of Product Characteristics (e.g additional warning for the prescribers on the higher risk of serious infections) should be considered in the next PSUR.

- The number of skin cancer (potential risk) to date and the duration of follow-up, remain relatively

limited and do not permit to draw definitive conclusions on any potential long-term risk for this type

of malignancy with fingolimod in particular for exposure greater than 2 years. The risk for basal cell

carcinoma (BCC) increases with age. According to some published data, the incidence of BCC in the

age group 30-59 years is rather low compared to older population. In addition, based on the available PSUR data, the majority of the patients diagnosed with melanoma were in the age group 30-49 years. In order to further characterise this potential risk, the MAH is requested to provide cumulative information in which age groups skin cancer occurred and match this to the general multiple sclerosis population in the next PSUR. The next PSUR should be submitted 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. As requested by the MAH, the PRAC agreed that the frequency of the PSUR submission should thereafter be revised to a yearly cycle. The PRAC considered that the Risk Management Plan (RMP) is acceptable. In addition, revisions (e.g upgrade of hypersensitivity from potential to identified risk) were recommended to be taken into account at the next RMP update. The CHMP agrees with the scientific conclusions made by the PRAC. Grounds recommending the variation to the terms of the Marketing Authorisation. On the basis of the scientific conclusions for Gilenya, the CHMP is of the opinion that the benefit-risk balance of the medicinal product containing the active substance FINGOLIMOD is favourable subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation(s) should be varied.”

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/gilenya-h-c-psusa-00001393-201502-epar-scientific-conclusions-grounds-recommending-variation-terms_en.pdf>

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for, the scientific conclusions of CHMP

are as follows:

During this PSUR (EU PSUR 7) the MAH discussed risks related to fingolimod, and presented the data

from spontaneous reporting, notably for skin cancers, infection risks including opportunistic infections and hypersensitivity. Especially vigilance for skin lesions is warranted and a dermatological assessment is needed in case suspicious lesions are detected. In addition, cases of infections with opportunistic pathogens such as viral or bacterial have been reported and this information should be made available to healthcare professionals. Upon treatment initiation hypersensitivity reactions including rash, urticaria and angioedema have been reported. The MAH proposed wording for amendments to the product information in relation to all the above mentioned cases.

In addition the MAH submitted data from spontaneous reporting for adverse events including cases of lymphoma, T-wave inversion, peripheral oedema and nausea. After review of this data the PRAC

considered that information should also be presented in the list of adverse events in the product

information to increase vigilance by the healthcare professionals. Especially for lymphoma a statement is already included under section 4.8 of the summary of product characteristics; this preferred term should also be listed in the ADR table in the same section, and in the relevant section of the package leaflet. In conclusion and in view of all available data, the PRAC considered that changes to the product information were warranted. The CHMP agrees with the scientific conclusions made by the PRAC. Grounds recommending the variation to the terms of the Marketing Authorisation. On the basis of the scientific conclusions for fingolimod the CHMP is of the opinion that the benefit- risk balance of the medicinal product(s) containing fingolimod is favourable subject to the proposed changes to the product information. The CHMP recommends that the terms of the Marketing Authorisation(s) should be varied”

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/gilenya-h-c-psusa-00001393-201602-epar-scientific-conclusions-grounds-variation-terms-marketing_en.pdf>

“Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for fingolimod, the scientific

conclusions of CHMP are as follows:

305 cases of thrombocytopenia (180 serious and 125 non serious) were reported cumulatively and

80 cases (41 serious and 39 non serious) during the reporting interval. Among the 180 serious

cases of thrombocytopenia cumulatively the MAH identified 31 Grade 4 among the cases where

laboratory value is reported. 24 cases of positive dechallenge were reported cumulatively including 5

new cases in this PSUR period. 4 cases of rechallenge were reported cumulatively.

3 cases of Kaposi’s sarcoma were reported cumulatively 16 months, 15 months and 3.5 years after

the start of fingolimod. Another case was also reported following the literature assessment after

the Data Lock Point of this PSUR on fingolimod treatment. All the 4 cases were biopsy confirmed and

occurred > 1 year (16 months, 15 months, 3.5 years and 4 years) after the start of fingolimod,

with no history of immunosuppressive agent, HIV negative serology. In those 4 cases there are no

other aetiology reported to explain Kaposi’s sarcoma except fingolimod exposure. Even if the

time to onset is short, the chronology is compatible with a relationship between Kaposi’s

sarcoma and fingolimod treatment. It is important to consider that healthcare professionals should

have this information to correctly monitor their patient on fingolimod therapy. 4 cases of Kaposi’s

sarcoma represent already a signal and Kaposi’s sarcoma should be added to the SmPC.

Therefore, in view of the data presented in the reviewed PSUR, the PRAC considered that changes to

the product information of medicinal products containing fingolimod were warranted.

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 fingolimod the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing fingolimod 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.”

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/gilenya-h-c-psusa-00001393-201702-epar-scientific-conclusions-grounds-variation-terms-marketing_en.pdf>

Scientific conclusions

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

Based on 48 cases (50 events), including 9 fatal cases, a potential link between fingolimod treatment and polymorphic ventricular arrhythmia (PVA) incidence was identified. In 17 cases, temporal relationship is strongly suggested. On the other hand, analysis of fatal cases showed potential risk factors such as cardiac underlying conditions. Overall, the PRAC recommended that the contra-indications section of the SmPC should be updated to include cardiac underlying conditions.

Based on a number of cases of malignant melanoma (MM), Squamous cell carcinoma (SCC) and Merkel cell carcinoma, the PRAC recommended that a warning should be added to sections 4.4 and 4.8 of the SmPC to alert prescribers of the possible occurrence of Merkel cell carcinoma, SCC and MM, including cautions regarding exposure to sunlight without protection, regarding concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy and specific screening of the skin to be performed every six to 12 months. Following the number of fatal outcome of cryptococcal meningitis (30 cases cumulatively including 9 with fatal outcome), the PRAC recommended that the SmPC should be updated to inform on the occurrence of fatal cases. Infections, in particular opportunistic infection and cancer risk are due to the immunosuppressive effect of fingolimod, therefore the PRAC recommended that a warning should be included in section 4.4 of the SmPC

to inform of the consequences of the immunosuppressive effect and that increased risks appear to be related to long term treatment with fingolimod and in patients that have history of immunosuppressive treatments or other risk factors that could increase this risk (for example, sun exposure, known active infections or malignancies). 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 fingolimod the CHMP is of the opinion that the benefit-risk-balance of the medicinal product(s) containing fingolimod 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.”

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/gilenya-h-c-psusa-00001393-201802-epar-scientific-conclusions-grounds-variation-terms-marketing_en.pdf>

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for fingolimod, the scientific conclusions of CHMP are as follows: A cumulative review of the post-marketing cases identified five cases reporting events of interest [myalgia (n=3) and arthralgia (n=3)], which were considered noteworthy. Three of these five cases were reported with positive re-challenge for the events of interest and the other two cases were reported with positive de-challenge without any plausible alternative explanation for the event of interest. Additionally, 38 cases, reporting 41 events of interest [myalgia (n=15) and arthralgia (n=26)], were reported with positive de-challenge; however, there was limited information about medical history and/or concomitant medication in these 38 cases. Based on the noteworthy cases identified in post-marketing, ‘myalgia’ and ‘arthralgia’ will

be added to the section of the adverse drug reactions in the SmPC and in the Package leaflet.

Regarding malignant neoplasms including skin and malignant lymphoma, there is a trend for an increased incidence rate (3.3% for the first period then 4.04% for the current period). Lymphoma represented 9.3% (cumulative data) to 10.6% (current period). Lymphomas are heterogeneous but, the number of mycosis fungoides increased during the reporting interval (5 cases). At least 2 published cases of T cell lymphoma reported regression of the cutaneous lesions after fingolimod discontinuation, suggesting strong fingolimod causality and immunosuppressant effect. Based on the increasing frequency of mycosis fungoides, the event will be added under the description on lymphomas in section 4.8 of the SmPC. In a search for ‘HPV and related cancers’ a total of 414 cases (464 events) were identified cumulatively with a stable incidence rate over time. The majority of cases reported HPV infection, papilloma, dysplasia and warts. There were 68 neoplasms reported (59 cervix and 9 anal). Underreporting is highly probable for these events and evaluation of causality is consequently hard to define. Nevertheless, reported noteworthy cases suggest temporal relation. More than transformation onto malignant neoplasm following HPV infection, reactivation is a more relevant event suggestive of immunological modifications. Given the pharmacological properties of fingolimod on immunity and cases of reactivation (in some cases after several years of latency)

with close temporal association with fingolimod, these data strongly support possible HPV infection

reactivation upon fingolimod treatment. These data support the change proposed for the SmPC and in the Package leaflet. 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 fingolimod the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing fingolimod 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.”

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/gilenya-h-c-psusa-00001393-201902-epar-scientific-conclusions-grounds-variation-terms-marketing_en.pdf>

“Scientific conclusions

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

Regarding the signal ‘autoimmune haemolytic anaemia (AIHA)’, the PRAC concluded that the cumulative review provided by the MAH as well as the plausible theoretical mechanism support a causal relationship

between therapy with fingolimod and occurrence of AIHA:

• Four cases without identified cofounders and with supportive chronology and clinical course with

improvement/recovery following discontinuation of fingolimod.

• One case with very suggestive chronology of the event with compatible outcome then de-challenge and re-challenge positive

• Fingolimod is an immunosuppressant and immunosuppression conditions are risk factors for

dysimmunity. Based on the noteworthy cases identified in post-marketing, AIHA should be added to the section of the adverse drug reactions in the SmPC and in the package leaflet.

For weight decreased, section 4.8 of SmPC and section 4 of the package leaflet should be updated to

include this AE following the current PSUSA with the frequency common. Regarding lymphoma, the MAH proposed to update the section 4.4 of the SmPC regarding the risk of lymphoma “There have been cases of lymphoma in clinical studies and the post-marketing setting. The cases reported were heterogeneous in nature, mainly non-Hodgkin’s lymphoma, including B-cell and T-cell lymphomas. Cases of cutaneous T-cell lymphoma (mycosis fungoides) have been observed.” And under the section 2 of the PL “A type of cancer of the lymphatic system (lymphoma) has been reported in

MS patients treated with Gilenya”. The section 4.8 of the SmPC regarding lymphomas specifies that cases of lymphoma include also a fatal case of Epstein-Barr virus (EBV) positive B-cell lymphoma. Detailed information of adverse reactions with no recommendation should not be included in this section. Therefore, information relating to fatal case of Epstein-Barr virus (EBV) positive B-cell lymphoma and a precaution for use regarding the interruption of treatment if lymphoma is suspected, should be included in the PI.

For PML, section 4.4 of the SmPC and section 2 of the PL should be updated in order to highlight the

importance of MRI finding.

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 fingolimod the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing fingolimod 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.”

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/gilenya-h-c-psusa-00001393-202002-epar-scientific-conclusions-grounds-variation-terms-marketing_en.pdf>

“Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for fingolimod, the scientific conclusions of CHMP are as follows:

Data has been presented on liver injury requiring transplant from spontaneous reports, including one case with a close temporal relationship with fingolimod, and on herpes zoster/herpes simplex infections with fingolimod where 9 new cases of VZV infection with visceral or CNS dissemination and 3 new cases of Herpes simplex infection with visceral or CNS dissemination were reported, adding up to 50 and 20 cumulative cases, respectively. Among these 70 cumulative cases, there were 20 cases of meningoencephalitis, 9 cases of encephalitis and 3 cases of meningitis.

In view of these data, the PRAC agrees that the information should be reflected in the section 4.4 and 4.8 of the SmPC and accordingly in sections 2 and 4 of the PL.

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 fingolimod the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing fingolimod 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.”

## Dimethyl fumarate: *Tecfidera*

Press/communications:

<https://www.ema.europa.eu/en/medicines/dhpc/tecfidera-dimethyl-fumarate-updated-recommendations-light-cases-progressive-multifocal>

Since authorization: <https://www.ema.europa.eu/en/documents/procedural-steps-after/tecfidera-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf>

There are a number of changes, please refer to link above.

Of note:

13/05/2022: Please refer to Scientific Discussion ‘Product Name-H-C-

Product Number-II-Var.No’

Section 4.4 Blood/laboratory tests has been updated to

inform that Lymphocyte counts should be followed until

recovery (section 5.1). Upon recovery and in the absence

of alternative treatment options, decisions about whether

or not to restart Tecfidera after treatment discontinuation

should be based on clinical judgement.

In section 4.8, the number of exposed subjects (PY) and

the periods of exposure have been updated; rhinorrhoea

has been added to the list of adverse drug reactions (ADRs)

with frequency unknown and subsections Hepatic function,

lymphopenia, Infections, including PML and opportunistic

infections based on final results from ENDORSE study.

Section 5.1 pharmacodynamic effects subsection has been

updated to inform about the dynamics of lymphocyte

counts after discontinuation of Tecfidera therapy and to

summarize the efficacy results from ENDORSE study.

For more information, please refer to the Summary of

Product Characteristics.

24/11/2020: The PI has been updated to reflect new information

available on Progressive Multifocal Leukoencephalopathy

(PML) risk monitoring.

The SmPC section 4.3 has been updated to reflect that

Tecfidera is now contraindicated in patients with suspected

or confirmed PML.

The SmPC section 4.4 has been updated to reflect that

Tecfidera should not be initiated in patients with severe

lymphopenia (lymphocyte counts < 0.5 x 109/L) and that

Tecfidera should be discontinued in patients with severe

lymphopenia persisting for more than 6 months. The SmPC

section 4.4 has also been updated to inform that PML cases

have occurred in the setting of lymphopenia (lymphocyte

counts below lower limit of normal as defined by local

laboratory reference range) and to recommend enhanced

vigilance in patients with lymphopenia taking into

consideration additional factors that may contribute to an

increased risk for PML in the setting of lymphopenia

including duration of Tecfidera therapy (1-5 years),

profound decreases in CD4+ and specially CD8+ T cell

counts and prior immunosuppressive or

immunomodulatory therapy. This section has been updated

to inform that Tecfidera must be permanently discontinued

if a patient develops PML

The SmPC section 4.8 has been updated with additional

findings on lymphocyte counts including CD4+ and CD8+ T

cells counts in patients treated with Tecfidera with and

without PML and new information on PML cases in patients

treated with Tecfidera. The PL have been updated accordingly

09/01/2020: Herpes zoster infections

Cases of herpes zoster have occurred with Tecfidera. The

majority of cases were non-serious, however, serious

cases, including disseminated herpes zoster, herpes zoster

ophthalmicus, herpes zoster oticus, herpes zoster infection

neurological, herpes zoster meningoencephalitis and herpes

zoster meningomyelitis have been reported. These events

may occur at any time during treatment. Monitor patients

taking Tecfidera for signs and symptoms of herpes zoster

especially when concurrent lymphocytopenia is reported. If

herpes zoster occurs, appropriate treatment for herpes

zoster should be administered. Consider withholding

Tecfidera treatment in patients with serious infections until

the infection has resolved (see section 4.8).

The SmPC section 4.8 has been updated as follows:

- to add the adverse reaction herpes zoster with a

frequency not known.

Infections

Herpes zoster infections have been reported with Tecfidera

use. In an ongoing long-term extension study, in which

1736 MS patients are treated with Tecfidera, approximately

5% experienced one or more events of herpes zoster, the

majority of which were mild to moderate in severity. Most

subjects, including those who experienced a serious herpes

zoster infection, had lymphocyte counts above the lower

limit of normal. Grade 2 and 3 lymphopenia prevailed in

subjects with concurrent lymphocytopenia. In the post-

marketing setting most cases of herpes zoster infection

were non-serious and resolved with treatment. Limited

data is available on ALC in patients with herpes zoster

infection in the post-marketing setting. However, when

reported, most patients experienced grade 2 (< 0.8 ×

109/L to 0.5 × 109/L) or grade 3 (<0.5 × 109/L to 0.2 ×

109/L) lymphopenia (see section 4.4).

20/09/2018: Based on the review of data on quality, safety and efficacy,

the CHMP considered that the benefit-risk balance of

TECFIDERA in the approved indication remains favourable,

but recommended that one additional five-year renewal be

required based on the following pharmacovigilance

grounds:

Further characterisation of the important identified risks

“decrease in leukocyte and lymphocyte counts” and

“progressive multifocal leukoencephalopathy” (PML) is

required. Safety studies to further characterise the risk of

PML are currently still ongoing. The impact of PML on the

benefit/risk balance can currently not be sufficiently

assessed. Moreover, a high number of cases of herpes

zoster have been reported. A potential association of this

risk with decreases in lymphocyte counts caused by

Tecfidera can still not be fully confirmed or excluded

based on current data.

28/05/2018: Cases of anaphylaxis/anaphylactoid reaction have been

reported following Tecfidera administration in the post-

marketing setting. Symptoms may include dyspnoea,

hypoxia, hypotension, angioedema, rash or urticaria. The

mechanism of dimethyl fumarate induced anaphylaxis is

unknown. Reactions generally occur after the first dose, but

may also occur at any time during treatment, and may be

serious and life threatening. Patients should be instructed

to discontinue Tecfidera and seek immediate medical care if

they experience signs or symptoms of anaphylaxis.

Treatment should not be restarted

28/05/2018: Concomitant administration of non-live vaccines during

Tecfidera therapy has been studied in study 109MS307. In

this clinical study which involved a total of 71 patients with

relapsing remitting multiple sclerosis, patients on Tecfidera

240 mg twice daily for at least 6 months (n=38) or non-

pegylated interferon for at least 3 months (n=33), mounted

a comparable immune response (defined as ≥2-fold

increase from pre- to post-vaccination titer) to tetanus

toxoid (recall antigen) and a conjugated meningococcal C

polysaccharide vaccine (neoantigen), while the immune

response to different serotypes of an unconjugated 23

valent pneumococcal polysaccharide vaccine (T-cell

independent antigen) varied in both treatment groups. A

positive immune response defined as a ≥4 -fold increase in

antibody titer to the three vaccines, was achieved by fewer

subjects in both treatment groups. Small numerical

differences in the response to tetanus toxoid and

pneumococcal serotype 3 polysaccharide were noted in

favour of non-pegylated interferon.

No clinical data are available on the efficacy and safety of

live attenuated vaccines in patients taking Tecfidera

12/04/2017: In clinical studies (both controlled and uncontrolled), 9% of

patients had lymphocyte counts ≥0.5 x 109/L and <0.8 x

109/L for at least six months (moderate prolonged

lymphopenia). If therapy is continued in the presence of

moderate to severe prolonged lymphopenia, the risk of an

opportunistic infection, including Progressive Multifocal

Leukoencephalopathy (PML), cannot be ruled out.

At the first sign or symptom suggestive of PML, withhold

Tecfidera and perform appropriate diagnostic evaluations.

The symptoms of PML may be similar to an MS relapse.

Typical symptoms associated with PML are diverse,

progress over days to weeks, and include progressive

weakness on one side of the body or clumsiness of limbs,

disturbance of vision, and changes in thinking, memory,

and orientation leading to confusion and personality

changes. The benefit/risk should be assessed in patients with

lymphocyte counts ≥0.5 x 109/L and <0.8 x 109/L for

more than six months.

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/tecfidera-h-c-psusa-00010143-202103-epar-scientific-conclusions-grounds-variation-terms-marketing_en.pdf>

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for dimethyl fumarate (multiple

sclerosis), the scientific conclusions of CHMP are as follows:

In view of available data on alopecia from spontaneous reports including in 2190 (consumer

reports)/760 (HCP reports) cases with a close temporal relationship, a positive de-challenge and/or re-challenge (consumer report: 242 and 10; HCP reports: 35 and 4, respectively) and in view of a

plausible mechanism of action, the PRAC Rapporteur considers a causal relationship between dimethyl fumarate and alopecia is at least a reasonable possibility. The PRAC Rapporteur concluded that the product information of products containing dimethyl fumarate should be amended accordingly. 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 dimethyl fumarate (multiple sclerosis) the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing dimethyl fumarate

(multiple sclerosis) 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

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/tecfidera-h-c-psusa-00010143-201903-epar-scientific-conclusions-grounds-variation-terms-marketing_en.pdf>

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for dimethyl fumarate (multiple

sclerosis), the scientific conclusions of CHMP are as follows:

There was no case explicitly reporting Fanconi syndrome in the Multiple Sclerosis (MS) indication;

however, it has been reported in literature that that female patients with psoriasis treated long-term

with fumaric acid esters seem to be at particular risk. The limited long-term experience with Tecfidera could contribute to the low evidence regarding a potential association of dimethyl fumarate and Fanconi syndrome in the MS indication. Since early diagnosis of Fanconi syndrome and discontinuation of the potentially causative drug, e.g. dimethyl fumarate, are important steps to prevent the onset of renal impairment and osteomalacia, the PRAC recommends the inclusion of a warning in SmPC section 4.4 to make physicians aware of the potential risk of Fanconi syndrome including the description of corresponding symptoms. The Package leaflet should be updated accordingly.

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 dimethyl fumarate (multiple sclerosis) the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing dimethyl fumarate

(multiple sclerosis) 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.

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## Glatiramer acetate: several brands available

*Copaxone*

No clear information available – authorized before EMA processes.

## Interferon beta-1a: *Rebif*

Since authorization: <https://www.ema.europa.eu/en/documents/procedural-steps-after/rebif-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf>

There are a number of changes, please refer to link above.

Of note:

26/08/2014: The MAH conducted a cumulative search for cases of

thrombotic microangiopathy. Further to the PRAC review of

these data, the CHMP concurred with the PRAC ́s view that

there might be a causal relationship between the class of

interferons and thrombotic microangiopathy, and that the

PI should be updated accordingly. Furthermore, the CHMP

concurred that a warning about the risk of thrombotic

microangiopathy, including recommendations for

monitoring of early symptoms, prompt treatment and

discontinuation of interferon beta products when the

reaction occurs, should be added to the Product

Information.

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26/08/2014: The MAH conducted a cumulative search for cases of

glomerulosclerosis and nephrotic syndrome. Further to their

review of these data, the CHMP was of the opinion that

there might be a causal relationship between interferon

beta 1-a and glomerulosclerosis and nephrotic syndrome,

and that the PI should be updated accordingly.

Furthermore, the CHMP concluded that a warning about the

risk of nephrotic syndrome (including examples of

underlying conditions) and a recommendation to

periodically assess renal function were of relevance to the

prescriber and should be added to the SmPC.

--

28/02/2014: Following conclusions of a previous PSUR assessment, the

MAH complied with the request of the CHMP to update the

Product Information by adding the adverse reactions

“pancytopenia” and “increased sweating”.

With respect to pancytopenia, the CHMP considered the

available literature data concerning the effects of interferon

on blood cells and the available clinical data from clinical

trials and post-marketing setting. The CHMP considered

that no serious cases of pancytopenia were observed in

clinical trial and no reports concerning pancytopenia were

identified in literature, but cases of pancytopenia were

reported in the post-marketing setting. Taken together with

the known effect of IFN on blood cells, the possibility of

decrease in several bone marrow cell-lines and a number of

cases of positive de-challenge and even a couple of cases

with positive re-challenge, the evidence available was

considered supportive of at least a possible causality. Thus,

the CHMP concluded on the need to update section 4.8 of

the SmPC by including pancytopenia as an adverse

reaction.

The level of evidence available with the previous PSUR was

sufficient to support adding increased sweating to the PI

without a need for additional data.

The CHMP endorsed the MAH ́s frequency estimations of

both pancytopenia and excessive sweating and considered

that these substantiated the frequency category “rare” for

pancytopenia and “uncommon” for excessive sweating.

The CHMP also acknowledged that the MAH followed the

SmPC guideline and estimated frequencies for all adverse

reactions previously categorised as frequency “not known”.

The CHMP endorsed the MAH ́s proposals for the new

frequency categories and agreed on the update of section

4.8 of the SmPC.

--

27/06/2012: This update of Product Information followed a cumulative

review of cases of autoimmune hepatitis and systemic

lupus erythematosus in multiple sclerosis patients exposed

to interferon-beta-1a. It was based on the company ́s

internal safety database, pooled clinical trial database, the

FDA adverse event reporting system (AERS) database, as

well as on a literature review. The CHMP considered that

the level of evidence available through safety reporting

allowed establishing a causal relationship with autoimmune

hepatitis and drug-induced lupus erythematosus and that it

indicated increased risk of occurrence of these reactions in

multiple sclerosis patients treated with Rebif.

--

06/08/2010: The product information was updated to include "hepatic

failure" in section 4.8 of the SmPC and to add information

on symptoms of severe liver problems in Section 4 of the

Package Leaflet. The update was based on a CHMP

requirement following assessment of the PSURs 19 and 20

and was further supported by a summary of available

safety data presented by the MAH.

In addition, the MAH took the opportunity to review the

SOC order within the table in section 4.8 of the SmPC to be

compliant with the order defined in the SmPC guideline and

to replace "hair loss" by "alopecia", as "alopecia" is the

preferred term (PT) and includes "hair loss"

--

22/04/2009: The MAH conducted cumulative reviews of the safety

information available regarding the risk of multiple sclerosis

pseudo-relapses, retinal vascular disorder, thrombotic

thrombocytopenic purpura and haemolytic uremic

syndrome, in patients treated with Rebif. This resulted in

the inclusion of these syndromes and disorders as possible

adverse drug reactions associated with Rebif treatment.

The frequency for such adverse drug reactions could not be

established based on the information available.

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20/05/2008: Based on their review of the available information and on

the basis of a re-evaluation of the benefit/risk balance, the

CHMP was of the opinion that the quality, safety and

efficacy continue to be adequately and sufficiently

demonstrated. Therefore, the benefit/risk profile of Rebif

continues to be favourable. However, the review of safety

data led to the inclusion of "dyspnoea" and "Stevens-

Johnson syndrome" in section 4.8 of the SPC. The MAH will

continue to submit yearly periodic safety update reports

until otherwise specified by the CHMP. The CHMP

recommended the renewal of the Marketing Authorisation for Rebif with unlimited validity.

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14/12/2007: The 48-week results of study 25632 submitted for the

approval of the HSA-free formulation of Rebif showed an

incidence rate of injection site reactions following

administration of 44 mcg subcutaneously, three times per

week, of 29.6 % in 260 subjects. This represents a lower

incidence rate than the 80 to 90% observed in the

historical comparator studies or "Historical cohort," which

comprised 727 subjects treated with the previous HSA-

containing formulation of Rebif at 44 mcg subcutaneously

three times per week in three controlled studies.

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01/09/2006: Further to the request of the CHMP, the CHMP

Pharmacovigilance Working Party (PhVWP) performed a

class review of all interferons beta authorised in the

treatment of multiple sclerosis to provide recommendations

on the need for and the nature of changes to the current

contraindications in pregnancy, patients with a history of

severe depressive disorders and/or suicidal ideation and

patients with epilepsy not adequately controlled by

treatment. Based on the data submitted by the MAH

(clinical trial, post-marketing data and literature) and the

PhVWP recommendations, the CHMP agreed on the

following changes:

- Removal of the absolute contraindication (section

4.3) in patients with epilepsy not adequately controlled

with treatment and revision of section 4.4 of the SPC to

indicate that interferon beta should be used with caution in

patients with epilepsy, particularly if their epilepsy is not

adequately controlled

- Revision of the contraindication (section 4.3) in pregnancy to indicate that initiation of treatment in

pregnancy is contraindicated but leave some room for

clinical judgement as to whether a patient who becomes

pregnant while taking interferon beta should continue or

stop treatment. Consequential changes were made to

section 4.6 of the SPC.

- Revision of the contraindication (section 4.3) in

patients with a history of severe depressive disorders

and/or suicidal ideation, to indicate that treatment of

patients with current severe depression and/or suicidal

ideation is contraindicated. Consequential changes were

made to section 4.4 of the SPC.

The Package Leaflet was amended accordingly.

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01/09/2006: The safety information of the SPC was updated based on

literature and post-marketing data provided by the MAH.

The recommendations for the monitoring of haematological

laboratory parameters were amended in section 4.4 to

provide more information on the timing of blood cell

counts. Section 4.8 was updated as follows:

- Change of frequency of the adverse reactions

neutropenia, lymphopenia, leucopenia, thrombocytopenia

and anemia from 'Common' to 'Very common"

- Addition of "injection site infections, including

cellulitis"

- Update of the endocrine disorders related

information with the replacement of the wording "elevated

T3 and T4, reduced TSH" by "most often presenting as

hypothyroidism or hyperthyroidism"

## Interferon beta-1b: Betaferon

Since authorization: <https://www.ema.europa.eu/en/documents/procedural-steps-after/betaferon-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf>

There are a number of changes, please refer to link above.

Of note:

22/10/2021: Section 4.4 (subsection Thrombotic microangiopathy

(TMA)) has been updated (subsection TMA and Haemolytic

anaemia [HA]) to inform that cases of HA not associated

with TMA have been reported with interferon beta products.

Cases may occur several weeks to several years after

starting treatment with interferon beta and may be severe

(Life-threatening and fatal cases have been reported).

Section 4.8 has been updated to inform that the most

serious adverse drug reactions (ADRs) include TMA and HA

which has been added to the list of ADRs with frequency

unknown.

For more information, please refer to the Summary of

Product Characteristics.

--

08/09/2016: This grouped procedure amends sections 4.8 of the SmPC

in order to add "drug-induced lupus erythematosus" (DILE)

as ADR and "pulmonary arterial hypertension" (PAH)

following PRAC recommendation. The Package Leaflet is

updated accordingly.

--

26/08/2014: The MAH conducted a cumulative search for cases of

thrombotic microangiopathy. Further to the PRAC review of

these data, the CHMP concurred with the PRAC ́s view that

there might be a causal relationship between the class of

interferons and thrombotic microangiopathy, and that the

PI should be updated accordingly. Furthermore, the CHMP

concurred that a warning about the risk of thrombotic

microangiopathy, including recommendations for

monitoring of early symptoms, prompt treatment and

discontinuation of interferon beta products when the

reaction occurs, should be added to the Product

Information.

--

26/08/2014: The MAH conducted a cumulative search for cases of

glomerulosclerosis and nephrotic syndrome. Further to their

review of these data, the CHMP was of the opinion that

there might be a causal relationship between interferon

beta 1-b and glomerulosclerosis and nephrotic syndrome,

and that the PI should be updated accordingly.

Furthermore, the CHMP concluded that a warning about the

risk of nephrotic syndrome (including examples of

underlying conditions) and a recommendation to

periodically assess renal function were of relevance to the

prescriber and should be added to the SmPC.

--

25/05/2012: In order to adapt Betaferon Product Information to the

current Corporate Core Data Sheet, the MAH proposed to

update section 4.8 of the SmPC with adding adverse

reactions based on the post-marketing reporting. The CHMP

considered the MAH ́s assessment of causality for

arthralgia, diarrhoea, dizziness, menorrhagia,

vasodilatation and weight increased and concluded that

adding these reactions into section 4.8 of the SmPC was

justified, since these events were considered as “possibly

related”. The CHMP was also of the view that “weight

decreased” can be moved from section “Investigation” to

section “Metabolism and nutrition disorder” and that the

following terms: capillary leak syndrome, hepatic injury and

hepatic failure, already captured in section 4.4, can also be

listed in section 4.8 of the SmPC. Following a request from

the CHMP, adverse reaction frequencies in table 2 were

updated based on incidence rates of the pooled clinical trial

data, when feasible.

--

01/06/2006: The contra-indications in pregnancy, patients with a history

of severe depressive disorders and/or suicidal ideation, any

patients with epilepsy not adequately controlled by

treatment were also reviewed, with consequential

amendments of sections 4.3, 4.4 and 4.6. As these

contraindications are common to all interferons beta, the

CHMP Pharmacovigilance Working Party (PhVWP)

performed a class review of all interferons beta authorised

to provide recommendations on the need for and the

nature of changes to the current contraindications. Based

on the data submitted by the MAH (clinical trial, post-

marketing data and literature) and the PhVWP recommendations,

the CHMP agreed on the following

changes:

- Removal of the absolute contraindication in

patients with epilepsy not adequately controlled with

treatment and revision of section 4.4 of the SPC to indicate

that interferon beta should be used with caution in patients

with epilepsy, particularly if their epilepsy is not adequately

controlled

- Revision of the contraindication in pregnancy to

indicate that initiation of treatment in pregnancy is

contraindicated but leave some room for clinical judgement

as to whether a patient who becomes pregnant while taking

interferon beta should continue or stop treatment.

Consequential changes were made to section 4.6 of the

SPC.

- Revision of the contraindication in patients with a

history of severe depressive disorders and/or suicidal

ideation, to indicate that treatment of patients with current

severe depression and/or

--

27/10/2005: Based on the review of clinical trial data, postmarketing

data and literature provided by the MAH, the following warnings were

added to section 4.4 of the SPC:

“Thyroid function tests are recommended regularly in

patients with a history of thyroid dysfunction or as clinically

indicated.

Asymptomatic elevations of serum transaminases, in most

cases mild and transient, occurred very commonly in

patients treated with Betaferon during clinical trials. As for

other beta interferons, severe hepatic injury, including

cases of hepatic failure, has been reported rarely in

patients taking Betaferon. The most serious events often

occurred in patients exposed to other drugs or substances

known to be associated with hepatotoxicity or in the

presence of comorbid medical conditions (e.g.

metastasizing malignant disease, severe infection and

sepsis alcohol abuse).

Patients should be monitored for signs of hepatic injury.

## Mitoxantrone: off-label

*Novantrone*

No clear information available, authorized before EMA processes in place.

<https://www.ema.europa.eu/en/medicines/human/referrals/novantrone-associated-names>

US FDA has issued a safety warning alert: <https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/mitoxantrone-hydrochloride-marketed-novantrone-and-generics-healthcare-professional-sheet-text>

“FDA ALERT [7/29/2008]: FDA is informing health care professionals about additional recommendations for cardiac monitoring and reminding of the importance of monitoring cardiac function in patients with multiple sclerosis (MS) who are treated with mitoxantrone.

In March 2005, the labeling for mitoxantrone was changed to recommend that left ventricular ejection fraction (LVEF) be evaluated before initiating treatment and prior to administering each dose of mitoxantrone to patients with MS. These changes were established in response to post-marketing reports and case reports in the medical literature that described decreases in LVEF or frank congestive heart failure in patients with multiple sclerosis (MS) who had received cumulative doses of mitoxantrone that were lower than 100 mg/m2.

Since that time, FDA has received information from a post-marketing safety study that demonstrated there is poor adherence to these recommendations in clinical practice. FDA is working with the manufacturers to educate healthcare providers to adhere to cardiac monitoring recommendations for patients with MS.

In addition to adherence to the recommendations made in 2005, FDA and the manufacturers of mitoxantrone are now advising that all patients with MS who have finished treatment with mitoxantrone receive yearly quantitative LVEF evaluation to detect late-occurring cardiac toxicity.

This information reflects FDA’s current analysis of available data concerning this drug. FDA intends to update this document when additional information or analyses become available.”

## Natalizumab: *Tysabri*

Communications/press releases:

<https://www.ema.europa.eu/en/news/updated-recommendations-minimise-risk-rare-brain-infection-pml-tysabri>

<https://www.ema.europa.eu/en/news/ema-confirms-recommendations-minimise-risk-brain-infection-pml-tysabri>

<https://www.ema.europa.eu/en/news/european-medicines-agency-update-progressive-multifocal-leukoencephalopathy-pml-tysabri>

<https://www.ema.europa.eu/en/news/european-medicines-agency-recommends-additional-measures-better-manage-risk-progressive-multifocal>

<https://www.ema.europa.eu/en/news/european-medicines-agency-recommends-update-product-information-tysabri-risk-progressive-multifocal>

Since authorization: <https://www.ema.europa.eu/en/documents/procedural-steps-after/tysabri-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf>

There are a number of changes, please refer to link above.

Of note:

23/04/2020: In a pre-specified, retrospective, analysis of US anti-JCV

antibody positive TYSABRI patients (n = 15,120), the

extended interval dosing of TYSABRI (average dosing

interval of approximately 6 weeks) was associated with

lower PML risk (95% CI of hazard ratio = 0.01- 0.22)

compared to approved dosing. If utilising extended interval

dosing, caution is required because the efficacy of extended

interval dosing has not been established and the associated

benefit risk balance is currently unknown. For further

information, refer to the Physician Information and

Management Guidelines. Current

pharmacokinetic/pharmacodynamic statistical modelling

and simulation indicate that the risk of MS disease activity

for patients switching to longer dosing intervals may be

higher for patients with body weight >80kg or those with

dosing intervals ≥7 weeks. No prospective clinical studies

have been completed to validate these findings. According

to previous comments sections 4.4 and 5.1 together with

Annex IID are updated in the product information.

--

11/09/2017: Acute retinal necrosis (ARN) is a rare fulminant viral

infection of the retina caused by the family of herpes

viruses (e.g. varicella zoster). In post-marketing

experience, rare cases of ARN have been observed in

patients receiving TYSABRI. Some cases have occurred in

patients with central nervous system (CNS) herpes

infections (e.g. herpes meningitis and encephalitis). Serious

cases of ARN, either affecting one or both eyes, led to

blindness in some patients. The treatment reported in

these cases included anti-viral therapy and in some cases,

surgery. Patients presenting with eye symptoms such as

decreased visual acuity, redness and painful eye should be

referred for retinal screening for ARN. Following clinical

diagnosis of ARN, discontinuation of TYSBABRI should be

considered in these patients.

--

25/04/2016: Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 29 April 2015 the opinion of the European Medicines Agency further new scientific evidence on progressive multifocal leukoencephalopathy (PML) in patients treated with Tysabri. The CHMP was requested to assess the impact thereof on the benefit-risk balance of Tysabri and to give its recommendation whether the marketing authorisation of this product should be maintained,

varied, suspended or revoked. As the request results from the evaluation of data resulting from pharmacovigilance activities, the CHMP opinion should be adopted on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee. Please refer to the assessment report: Tysabri EMEA/H/A-20/1416/C/000603/0

--

18/04/2016: Based on the review of data on quality, safety and efficacy,

the CHMP considered that the benefit-risk balance of

Tysabri in the approved indication remains favourable and

therefore recommended the renewal of the marketing

authorisation with unlimited validity.

In addition, sections 4.4 and 4.8 of the Summary of

Product Characteristics (SmPC) were updated to include

new safety information on Granule Cell Neuronopathy

(GCN), a condition which is also caused by John

Cunningham Virus (JCV) and that has occurred in some

patients who have been given Tysabri. Symptoms of JCV

GCN are similar to symptoms of Progressive Multifocal

Leukoencephalopathy (i.e. cerebellar syndrome). The

Package leaflet is being updated accordingly.

--

13/06/2013: Based on the review of the submitted data in patients who

had onset of suspicion of PML after Tysabri discontinuation,

the CHMP considered that the Marketing Authorisation

Holder (MAH) assumption that PML occurs as Tysabri

continues to have some pharmacological effect is one

possible explanation and therefore accepted to include the

following information in the SmPC:

- Section 4.4: PML has been reported following

discontinuation of TYSABRI in patients who did not have

findings suggestive of PML at the time of discontinuation.

Patients and Physicians should continue to be alert for any

new signs or symptoms that may be suggestive of PML for

approximately six months following discontinuation of

TYSABRI.

--

19/11/2012: Based on the review of the submitted data, the CHMP

considered that a six-monthly anti-JCV antibody testing

would allow for an earlier identification of patients who

have changed their antibody status from negative to

positive. In addition, data on seroconversion, seroreversion

and intermittent positivity over 30 months suggested a

significant intrinsic variance of anti-JCV antibody status

over time supporting the increased monitoring from every

12 months to 6 months. Considering that the

recommended frequency of anti-JCV antibody testing was

part of the Risk management plan only, the CHMP accepted

to include a SmPC recommendation as well to further

strengthen this monitoring. The following updated

information on anti-JCV antibody testing appears in the

SmPC:

- Section 4.4: Anti-JCV antibody testing provides

supportive information for risk stratification of TYSABRI

treatment. Testing for serum anti-JCV antibody prior to

initiating TYSABRI therapy or in patients receiving TYSABRI

with an unknown antibody status is recommended. Re-

testing of anti-JCV antibody negative patients every 6

months is recommended. The anti-JCV antibody assay

(ELISA) should not be used to diagnose PML. Anti-JCV

antibody testing should not be performed during, or for at

least two weeks following, plasma exchange due to the

removal of antibodies from the serum.

--

19/11/2012: Based on 11 reported cases of hyper-eosinophilia

(eosinophil count >1.5 x 10 9/L), section 4.8 of the SmPC

was updated in order to inform the healthcare professionals

of the occurrence of this adverse reaction. No clinical

symptoms associated with the hyper-eosinophilia were

reported. However, stopping treatment resolved the

situation.

--

25/05/2012: Based on continuing evaluation of the progressive

multifocal leukoencephalopathy (PML) incidence rates the

risk stratification algorithm has been updated based on

postmarketing data, resulting in changes to the PML

incidence figures for patients with antibodies against JCV or

more additional risk factors. The CHMP considered that

these revised PML incidence rates are not significantly

different from the numbers that were included in the

previous version and has concluded that the current

benefit/risk assessment for the use of Tysabri in the

indicated population remains unaltered. However, given

that these numbers have changed, and will most likely

continue to vary, the CHMP agreed to amend the statement

in the SmPC by removing specific reference to the PML

incidence estimates in order to replace it with a qualitative

statement on the level of PML risk in the high risk

subgroup, particularly since updated estimates will continue

to be presented in the Physician Information and

Management Guidelines and the treatment forms. The text

on treatment continuation in patients with all three risk

factors was updated to clarify that TYSABRI should only be

continued if the benefits outweigh the risks.

For JCV antibodies, the CHMP also agreed to reflect that

this test should not be used for PML diagnosis in the

absence of supportive data. In addition, on the basis of the

review of further data, the CHMP agreed that anti-JCV

antibodies samples must not been drawn during or for at

least two weeks following the plasma exchange treatment

(PLEX), since this may reduce the risk of collecting

inaccurate data and hence accepted that this information is

added into the SmPC.

--

16/06/2011: PML is associated with an uncontrolled increase of the JC

virus in the brain, although the reason for this increase in

some patients treated with TYSABRI is unknown. JC virus is

a common virus which infects many people but does not

normally cause noticeable illness.

The risk of PML with TYSABRI is higher:

" The longer that you are on treatment especially if

you have been on treatment for more than two years. It is

not known if the chance of getting PML continues to rise,

remains the same, or falls after you have been on TYSABRI

for more than three years.

" If you have previously taken a medicine called an

immunosuppressant. These medicines reduce the activity of

your body's immune system.

" If you have antibodies to the JC virus in your blood.

These antibodies are a sign that you have been infected by

JC virus.

Patients who have all three risk factors for PML (i.e., have

received more than 2 years of TYSABRI therapy, and have

received prior immunosuppressant therapy and are anti-

JCV antibody positive) have the highest risk of PML at

approximately 9 in 1,000 patients treated.

Testing for serum anti-JCV antibody prior to initiating

TYSABRI therapy or in patients who are already being

treated with TYSABRI but who have not previously been

tested may provide additional information on the level of

risk for PML.

--

29/11/2010: The MAH has analysed the data of 52 Tysabri treated

patients with confirmed PML in respect of an association

with prior immunosuppressant use (IS). The presented

data indicate that prior IS use increases the risk of PML

independent of the duration of Tysabri therapy.

Sections 4.2 and 4.4 of the SmPC have been updated to

reflect the above and the following text has been added to

section 2 of the package leaflet:

"The risk of PML is also greater if you have previously taken

a medicine that weakens your immune system."

In addition, it was agreed that the following warning

statement would be added in the treatment initiation and

treatment continuation forms: "The risk of PML is also

greater if you have previously taken a medicine called an

immunosuppressant that reduces the activity of your body's

immune system".

Finally, the Product Information has been updated in

accordance with the latest QRD template (version 7.3.1

dated March 2010).

--

23/01/2009: The MAH reviewed in the 3rd PSUR symptoms often

reported concomitantly with possible hypersensitivity

reactions with Tysabri. The most common symptoms

included chest pain, dyspnoea, blood pressure increases or

decreases, skin and cutaneous disorders (mostly of an

urticarial nature). Angioedema was also rarely reported.

The MAH included the following text to the hypersensitivity

section in section 4.8 of the Summary of Product

Characteristics: "In post-marketing experience, there have

been reports of hypersensitivity reactions which have

occurred with one or more of the following associated

symptoms: hypotension, hypertension, chest pain, chest

discomfort, dyspnoea, angioedema, in addition to more

usual symptoms such as rash and urticaria."

--

30/10/2008: Approximately 38,700 patients have been treated

worldwide with Tysabri (natalizumab) since it has been

approved, and 4,650 patients received Tysabri during

clinical trials. Two cases of a rare brain infection called

progressive multifocal leukoencephalopathy (PML) have

been confirmed since the product is on the market phase in

multiple sclerosis patients treated with Tysabri. Two PML

cases were previously reported during clinical trials in

patients treated with Tysabri in combination with interferon

beta, leading to special warnings in the product information

and extensive risk minimisation measures, including

physician information and management Guidelines.

In the two new above mentioned cases reported from the

market, Tysabri was given as monotherapy, and for

approximately 17 and 14 months. Both patients have

undergone plasma exchange to reduce natalizumab levels.

The marketing authorisation holder has performed a study

investigating the effect of plasma exchange on Tysabri

levels which showed that this leads to reduction of

natalizumab levels faster than simply discontinuing Tysabri.

However, the impact of plasma exchange on the restitution

of immune function and ultimately its clinical usefulness is

unknown.

Patients treated with Tysabri must be regularly monitored

for any clinical signs suggestive of PML. If PML is

suspected, treatment must be suspended and further

evaluations carried out as described in the physician

information and management guidelines. Administration of

Tysabri may resume only once the clinician has excluded

PML, if necessary by repeating clinical, imaging and/or

laboratory investigations if clinical suspicion remains. The

benefit/risk profile of Tysabri remains positive in the

authorised indication.

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20/06/2008: A number of serious suspected hepatic reactions, including

increased liver enzymes and hyperbilirubinaemia, were

reported in patients receiving Tysabri since the medicine

was put on the market in November 2004. All cases but

one were reported from post marketing surveillance and

occurred as early as six days after the first dose of Tysabri.

All cases had at least one confounding risk factor but two

cases were assessed as likely to be related to Tysabri. In

these two cases, liver problems improved when Tysabri was

stopped, but reappeared after readministration.

--

25/04/2008: The MAH reviewed the data (spontaneous reports and

clinical trials) made available during the post-marketing

phase on allergic reactions occurring in patients treated

with Tysabri. Based on this review, it is concluded that the

risk for allergy is greatest with early infusions and in

patients re-exposed to TYSABRI following an initial short

exposure (one or two infusions) and extended period (three

months or more) without treatment. Since patients who

have received an initial short exposure to TYSABRI and

then had an extended period without treatment are more at

risk for allergy upon re-dosing, continuous dosing with

TYSABRI is important, especially during the first few

months of treatment.

The MAH also reviewed the data (spontaneous reports and

clinical trials) made available during the post-marketing

phase on herpes infections. Based on this review, it is

concluded that in clinical trials, herpes infections (Varicella-

Zoster virus, Herpes simplex virus) occurred slightly more

frequently in patients treated with Tysabri than in patients

receiving placebo.

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<https://www.ema.europa.eu/en/medicines/human/referrals/tysabri>

“EMA confirms recommendations to minimise risk of brain infection PML with Tysabri

More frequent MRI scans should be considered for patients at higher risk

On 25 February 2016, EMA completed its review of the known risk of progressive multifocal leukoencephalopathy (PML) with the multiple sclerosis medicine Tysabri (natalizumab), and confirmed initial recommendations1 aimed at minimising this risk.

PML is a rare brain infection caused by John Cunningham (JC) virus. This virus is very common in the general population and is normally harmless; however, it can lead to PML in persons whose immune system is weakened. The most common symptoms of PML are progressive weakness, speech and communication difficulties, vision changes, and sometimes changes in mood or behaviour. PML is a very serious condition that may result in severe disability or death.

Recent studies suggest that early detection and treatment of PML when the disease is asymptomatic (is still in the initial stages and shows no symptoms) may improve patients' outcomes. Asymptomatic cases of PML can be detected on MRI scans, and experts in the field of MRI and multiple sclerosis agree that simplified MRI protocols (which allow for shorter procedures, and also limit the burden for patients undergoing the scans) permit the identification of PML lesions. All patients taking Tysabri should undergo full MRI scans at least once a year, but on the basis of the new data EMA recommended that for patients at higher risk of PML more frequent MRI scans (e.g. every 3 to 6 months) performed using simplified protocols should be considered. If lesions suggestive of PML are discovered, the MRI protocol should be extended to include 'contrast-enhanced T1-weighted MRI', and testing the spinal fluid for the presence of JC virus should be considered.

New data from large clinical studies also suggest that, in patients who have not been treated with immunosuppressants (medicines that reduce the activity of the immune system) before starting Tysabri, the blood level of antibodies against JC virus ('antibody index') relates to the level of risk for PML. In light of the new evidence, patients are considered at higher risk of developing PML if they:

* have tested positive for JC virus, and
* have been treated with Tysabri for more than 2 years, and
* either have used an immunosuppressant before starting Tysabri, or have not used immunosuppressants and have a high JC virus antibody index.

In these patients, treatment with Tysabri should only be continued if benefits outweigh the risks.

If PML is suspected at any time, treatment with Tysabri must be stopped until PML has been excluded.

EMA's recommendations are based on an initial review by its Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), which confirmed them and adopted its final opinion. The CHMP's opinion was then sent to the European Commission, which issued a legally-binding decision valid throughout the EU.”

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<https://www.ema.europa.eu/en/documents/variation-report/tysabri-h-c-603-a20-0029-epar-assessment-report-article-20_en.pdf>

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/tysabri-h-c-603-psuv-0062-epar-scientific-conclusions-grounds-recommending-variation-terms-marketing_en.pdf>

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<https://www.ema.europa.eu/en/documents/variation-report/tysabri-h-c-603-a20-1416-epar-assessment-report-article-20_en.pdf>

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/tysabri-epar-scientific-conclusion_en.pdf>

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/tysabri-h-c-psusa-00002127-201908-epar-scientific-conclusions-grounds-variation-terms-marketing_en.pdf>

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/tysabri-h-c-psusa-00002127-202008-epar-scientific-conclusions-grounds-variation-terms-marketing_en.pdf>

“Taking into account the PRAC Assessment Report on the PSUR(s) for natalizumab, the scientific

conclusions of CHMP are as follows: In view of available data on thrombocytopenia (TCP) and immune (or idiopathic) thrombocytopenic purpura (ITP) from clinical and nonclinical studies, literature sources, post-marketing reports and third-party safety databases, the PRAC considers a causal relationship between natalizumab and thrombocytopenia (TCP) and immune (or idiopathic) thrombocytopenic purpura (ITP) is at least a reasonable possibility. The PRAC concluded that the product information of products containing natalizumab should be amended accordingly.”

## Ocrelizumab: *Ocrevus*

Since authorisation: <https://www.ema.europa.eu/en/documents/procedural-steps-after/ocrevus-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf>

There are a number of changes, please refer to link above.

Of note:

03/12/20: The warning in section 4.4 of the SmPC on Progressive Multifocal Leukoencephalopathy (PML) is updated to include lymphopenia and advanced age as new risk factors for PML present in the ocrelizumab-treated patient who developed PML without prior disease-modifying therapy use. For more information, please refer to the Summary of Product Characteristics.

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/ocrevus-h-c-psusa-00010662-201809-epar-scientific-conclusions-grounds-variation-terms-marketing_en.pdf>

“Taking into account the PRAC Assessment Report on the PSUR(s) for ocrelizumab, the scientific

conclusions of CHMP are as follows: In previous PSUR the MAH was requested to provide a cumulative review of all available data regarding the association between hypogammaglobulinemia and serious infections. During the reporting interval, a cumulative review was prepared that analysed the incidence, nature, severity and outcome of serious infections occurring in patients treated with ocrelizumab. At the time of initial Marketing Authorisation approval the exposure from clinical trials was very limited and no define conclusion could be drawn. With the data provided by the MAH in this reporting interval the PRAC concluded that there is an association between low Immunoglobulins level and risk of serious infections, which can be further supported by biological plausibility. Therefore, the PRAC recommended to update section 4.8 of the SmPC to reflect the association between treatment with ocrelizumab, decreased level of immunoglobulins and risk of serious infections.”

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/ocrevus-h-c-psusa-00010662-201903-epar-scientific-conclusions-grounds-variation-terms-marketing_en.pdf>

“Taking into account the PRAC Assessment Report on the PSUR(s) for ocrelizumab, the scientific

conclusions of CHMP are as follows: Considering the first report of hepatitis B reactivation published for ocrelizumab and described in the previous PSUR, the PRAC recommended a minor revision of the statements in section 4.4 of the SmPC on the risk of hepatitis B reactivation.”

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/ocrevus-h-c-psusa-00010662-202003-epar-scientific-conclusions-grounds-variation-terms-marketing_en.pdf>

“Taking into account the PRAC Assessment Report on the PSUR(s) for orelizumab, the scientific

conclusions of the CHMP are as follows: In view of available data on the risk of late onset of neutropenia from the literature and spontaneous reports, and in view of a plausible class effect in therapeutic CD20 antibodies, the PRAC considers a causal relationship between ocrelizumab and late onset of neutropenia is at least a reasonable possibility. The PRAC concluded that the product information of products containing ocrelizumab should be amended accordingly.”