European Medicines Agency – accessed 18/05/2022 for additional safety warnings

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# PMS DMTs

Article 20 procedures noted for **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.

## Azathioprine – off-label, several brands exist

*Imuran*

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

## Fingolimod

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.”

## 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.

--

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.

--

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.

--

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.

--

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.

--

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.

## Methotrexate – off-label, several brands exist

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

Communications/press releases:

<https://www.ema.europa.eu/en/news/new-measures-avoid-potentially-fatal-dosing-errors-methotrexate-inflammatory-diseases>

## 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

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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.

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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.

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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).

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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."

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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.

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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.”

## Rituximab – off-label, several brands exist

*MabThera*

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

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

Of note:

20/11/2013: “The Summary of Product Characteristics for MabThera is updated in section 4.4 with further information on the cases of hepatitis B reactivation and recommending hepatitis B virus screening to be performed in all patients before initiation of treatment, as per local guidelines. This information is to be communicated directly to the treating physicians and relevant Healthcare professionals via a ‘Dear Healthcare Professional Communication’.”

22/04/2013: “Sections 4.4, and 5.1 of the SmPC have been updated to reflect that a small proportion of patients had prolonged peripheral B cell depletion lasting 2 years or more after their last dose of MabThera. Based on the mechanism of action of MabThera and the knowledge that B cells play an important role in maintaining normal immune response, patients have an increased risk of infection following MabThera therapy. A small number of spontaneous and literature cases of hypogammaglobulinaemia have been observed in pediatric patients treated with MabThera, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion in paediatric patients are unknown. This information was added in section 4.8 of the SmPC. In addition, a numerical value given for response to vaccination was corrected and the statement referring to the occurrence of progressive multifocal leukoencephalopathy, under section 4.4 was reworded. Pneumocystis jirovecii infection was added in section 4.8. as “rare” and PML was added as very rare. The Package Leaflet was proposed to be updated accordingly. In addition editorial changes were made to the product information to comply with QRD template version 8 (revision 3) among these was the addition of a ‘Fertility’ sub-section and a statement under 4.6 on the lack of data on fertility. The MAH took this opportunity to make some minor typographical amendments to the SmPC and PL text”

14/12/2011: “The MAH has submitted a group of type II variations to update the Mabthera SmPC section 4.4, 4.8 and 5.1 with safety data further to several requests from the CHMP. Section 4 of the PL is also amended as a consequence. The changes are as follows; 1. Reassignement of the frequency of several adverse drug reactions (ADRs) listed as "unknown" to very rare or rare, as applicacle, in Table 1 of the SmPC (Section 4.8 Undesirable Effects) according to the current EC SmPC Guideline. 2. Update of the information regarding the risk of prolonged B-cell depletion further to a cumulative review. 3. Update of the warning related to hepatitis B, particularly with regard to the screening and surveillance. 4. Update of the information regarding the risk of prolonged neutropenia in the Chronic Lymphocytic Leukaemia (CLL) indication. 5. Addition of a warning on cardiac events in the rheumatoid arthritis (RA) indication further to the conduct of a cumulative review.”

23/03/2010: “This variation application was submitted in order to amend section 4.2 of the SPC to add reference to the MabThera Rheumatoid arthritis patient alert card. The PL has been updated accordingly. In addition to this, section 4.8 has been updated to add reference to the following adverse events: infusion related acute reversible thrombocytopenia, interstitial lung disease, Progressive Multifocal Leukoencephalopathy (PML) and serum sickness-like reaction. Furthermore, section 4.4 has been updated based on the experience gained from all of the reported cases of PML and in order to be consistent with information given in section 4.8. These sections have been updated to reflect the safety data from post marketing experience.”

04/07/2008: “The following sections of the Product Information have

been amended: - Section 4.4: Opportunistic and reactivation infections: update of text regarding reactivation of Hepatitis B infections. - Section 4.5: Deletion of redundant information from the interactions section of the SmPC; interaction of MabThera with chemotherapy other than cyclophosphamide, doxorubicin, vincristine, prednisolone [CHOP] or cyclophosphamide, vincristine, prednisolone [CVP]. - Section 4.6: Adverse events during pregnancy and lactation and the use of MabThera - to include safety observations from a limited number of pregnancies. Section 4.8: Information in relation to "Progression of Kaposi's sarcoma" to include progression of Kaposi's sarcoma following treatment with MabThera + chemotherapy". In addition:, as committed during the license renewal procedure and in order to better comply with the current approved SPC guideline (2005) whilst considering the latest proposal for SPC guidance (revision released in December 2007 for consultation) the Marketing Authorisation Holder has overall revised section 4.8. Also the MAH has taken the opportunity to address comments received as a part of the recent 10-years renewal of the MA, including editorial revisions of the Labelling and the Package Leaflet”

03/09/2007: “In February 2007, the CHMP requested that the European Marketing Authorisation Holder, Roche, issue a DDL across the EU concerning the two reported cases of PML. Subsequently a new case of PML in a vasculitis patient was reported and the DDL was revised and issued as of 2 April 2007. The current variation is to update section 4.4. of the SPC and also section 4 of the PIL with appropriate wording covering PML in Non-Hodgkins Lymphoma and autoimmune diseases. Since then, the position on the interpretation of PML cases reported in NHL patients has not changed. However, considering the severity of the conditions and the proposal to update the "Warnings" Section of the SPC with a statement regarding the observed cases of PML with off- label use of rituximab in SLE/vasculits patients, it is appropriate to include a text on PML in the "Warnings" Section of the SPC, in addition to the text in the post marketing experience of the "Undesirable Effects" section.”

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<https://www.ema.europa.eu/en/documents/scientific-conclusion/mabthera-h-c-psusa-00002652-202011-epar-scientific-conclusions-grounds-variation-terms-marketing_en.pdf>

“Taking into account the PRAC Assessment Report on the PSUR for rituximab, the scientific conclusions of the CHMP are as follows: In view of available data on the risk of malignancy from clinical trials, the literature, spontaneous reports and observational post-authorisation safety studies indicating no increased risk of malignancy in the autoimmune indications, the PRAC considers amendments to the product information are warranted. Moreover, based on evidence from literature articles of rituximab excretion into human breast milk, the PRAC considers amendments to the product information are warranted”

## Siponimod: *Mayzent*

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

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

Of note:

<https://www.ema.europa.eu/en/documents/scientific-conclusion/mayzent-psusa-00010818-202003-epar-scientific-conclusions-grounds-variation-terms-marketing_en.pdf>

“Taking into account the PRAC Assessment Report on the PSUR(s) for siponimod, the scientific conclusions of CHMP are as follows: Given the Basal Cell Carcinoma siponimod data and background data, there is evidence for an increase in the risk of BCC with siponimod. The underlying mechanism is unknown, but a hypothetical mechanism related to systemic immunosuppression and reduced immune-surveillance for increased risk of BCC in patients treated with siponimod has been suggested. The Product Information should be varied accordingly.”

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<https://www.ema.europa.eu/en/documents/variation-report/mayzent-h-c-4712-x-07-epar-assessment-report-variation_en.pdf>