Drug Safety Update

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

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Contents

The Medicines and Healthcare products Regulatory Agency is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

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This month, we have updated advice about the risk of diabetic ketoacidosis in patients being treated with SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin) for type 2 diabetes (page 2). It is important to discuss with patients the risk factors for, and signs and symptoms of, diabetic ketoacidosis.

Also this month, we have important advice for the neurology community: see our articles regarding natalizumab (page 4), dimethyl fumarate (page 7), and fingolimod (page 9) for the treatment of multiple sclerosis, which focus particularly on new advice on the risk of progressive multifocal leukoencephalopathy. We also update you about minimising the risk of cardiac side effects when using apomorphine with domperidone (page 11) in Parkinson's disease.

Furthermore this month, we would like to inform you that cases of osteonecrosis of the jaw have been reported in patients with cancer who have been treated with aflibercept. Dental examination and appropriate preventive dentistry should be considered before treatment, especially for patients also treated with an intravenous bisphosphonate (page 12).

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1 **SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis**

Test for raised ketones in patients with ketoacidosis symptoms, even if plasma glucose levels are near-normal.

Advice for healthcare professionals:

When treating patients who are taking a sodium-glucose co-transporter 2 (SGLT2) inhibitor (canagliflozin, dapagliflozin, or empagliflozin):

- inform them of the signs and symptoms of diabetic ketoacidosis (DKA) – see below – and advise them to seek immediate medical advice if they develop any of these
- discuss the risk factors for DKA with patients (see below)
- discontinue treatment with the SGLT2 inhibitor immediately if DKA is suspected or diagnosed
- do not restart treatment with any SGLT2 inhibitor in patients who experienced DKA during use, unless another cause for DKA was identified and resolved
- interrupt treatment with the SGLT2 inhibitor in patients who are hospitalised for major surgery or acute serious illnesses; treatment may be restarted once the patient's condition has stabilised
- report suspected side effects to SGLT2 inhibitors or any other medicines on a Yellow Card

Reports of diabetic acidosis

EU medicines regulators have completed a review of DKA associated with SGLT2 inhibitor treatment; this article summarises the review's recommendations. We published preliminary advice on this in June 2015.

SGLT2 inhibitors are licensed for use in adults with type 2 diabetes to improve glycaemic control. Serious, life-threatening, and fatal cases of DKA have been reported in patients taking an SGLT2 inhibitor (canagliflozin, dapagliflozin, or empagliflozin). The EU review concluded that this side effect is rare (affecting between 1 in 1000 and 1 in 10,000 patients). Up to 26 February 2016, we had received 118 Yellow Card reports of DKA and associated reactions in patients taking an SGLT2 inhibitor in the UK.

In several cases, blood glucose levels were only moderately elevated (eg <14 mmol/L)—representing an atypical presentation for DKA, which could delay diagnosis and treatment. Therefore inform patients of the signs and symptoms of DKA (eg rapid weight loss, feeling sick or being sick, stomach pain, fast and deep breathing, sleepiness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat) and test for raised ketones in patients with these signs and symptoms.

A substantial proportion of the cases concerned off-label use in patients with type 1 diabetes. We remind you that SGLT2 inhibitors should not be used in patients with type 1 diabetes.

Many of the cases of DKA occurred during the first 2 months of treatment and some shortly after stopping the SGLT2 inhibitor. In some cases, just before or at the first development of DKA, patients had dehydration, low food intake, weight loss, infection, surgery, vomiting, a decrease in insulin dose, or poor control of diabetes.

Risk factors

The mechanism by which SGLT2 inhibitors might lead to DKA has not been established. However, the following factors may predispose patients taking an SGLT2 inhibitor to DKA:

- a low beta cell function reserve (eg patients with type 2 diabetes who have low C-peptide levels, latent autoimmune diabetes in adults [LADA], or a history of pancreatitis)
- conditions leading to restricted food intake or severe dehydration
- sudden reduction in insulin
- increased insulin requirements due to acute illness
- surgery
- alcohol abuse

Discuss these risk factors with patients and use SGLT2 inhibitors with caution in patients who have them.

SGLT2 inhibitors: medicines in this class

The SGLT2 inhibitors marketed in the UK are listed below. Click on the brand name to see the summary of product characteristics (SPC).

Brand name	Active substance(s)
Forxiga ▼	Dapagliflozin tablets (5 mg and 10 mg)
Xigduo ▼	Dapagliflozin/metformin tablets (5 mg/850 mg and 5 mg/1000 mg)
Invokana ▼	Canagliflozin tablets (100 mg and 300 mg)
Vokanamet ▼	Canagliflozin/metformin tablets (50 mg/850 mg, 50 mg/1000 mg, 150mg/850mg, 150mg/1000mg)
Jardiance ▼	Empagliflozin tablets (10 mg and 25 mg)
Synjardy ▼	Empagliflozin/metformin tablets (5/850mg, 5/1000mg, 12.5/850mg, 12.5/1000mg)

Further information
European Medicines Agency announcement February 2016
Letter sent to health professionals in March 2016

Article citation: Drug Safety Update volume 9 issue 9 April 2016: 1

2 **Natalizumab (Tysabri▼): progressive multifocal leukoencephalopathy— updated advice to support early detection**

Perform a quantitative serum anti-JCV antibody test—including index value—to support risk stratification for progressive multifocal leukoencephalopathy. For high-risk patients, consider more frequent MRI screening.

Updated risk estimates are available as a result of an EU review of natalizumab (see below).

Advice for healthcare professionals:

Before starting natalizumab treatment

New advice:

- Perform a baseline quantitative serum anti-JCV antibody test—including the index value—to support risk stratification for progressive multifocal leukoencephalopathy (PML)

Reminder of previous advice:

- Perform a baseline cranial MRI scan as a reference, usually within 3 months of starting natalizumab treatment
- Counsel patients and carers on the risk of PML — an updated Treatment Initiation Form will be available in due course
- Advise patients and carers on symptoms to watch out for and to get medical advice urgently if they occur

During natalizumab treatment

New advice:

- Perform a quantitative serum anti-JCV antibody test—including the index value—every 6 months for the patients specified in the algorithm below (see figure 2)
- For high-risk patients (see below), consider the following extra precautions:
    - more frequent MRI screening for PML, such as every 3–6 months using an abbreviated protocol (FLAIR, T2-weighted, and DW imaging): earlier detection of PML in asymptomatic patients may be associated with improved PML outcome
    - If you suspect PML, extend the MRI protocol to include contrast-enhanced T1-weighted imaging and consider testing for JCV DNA in the cerebrospinal fluid using ultrasensitive polymerase chain reaction (PCR)

Reminder of previous advice (for all patients):

- If you suspect PML at any time, stop natalizumab treatment and investigate appropriately until PML has been excluded
- Perform a quantitative serum anti-JCV antibody test—including the index value—for any patient with unknown antibody index (all patients should be tested at least once)
- Perform a full cranial MRI scan at least yearly for the entire duration of treatment, to have up-to-date reference images
- Monitor patients for signs and symptoms or appearance of new neurological dysfunction (eg motor, cognitive, or psychiatric symptoms), bearing in mind that PML can present with features similar to multiple sclerosis
- Consider PML in the differential diagnosis of any patient presenting with neurological symptoms or new brain lesions in their MRI scan – cases of asymptomatic PML, diagnosed based on MRI scans and positive JCV DNA in the cerebrospinal fluid, have been reported
- After 2 years of treatment, remind patients of the risk of PML with natalizumab using the updated Treatment Continuation Form, which will be available in due course

After stopping natalizumab treatment:

New advice:

- Advise patients and carers to continue to watch out for signs and symptoms of PML for 6 months after the last dose—use the new Treatment Discontinuation Form, which will be available in due course, to aid this discussion
- Continue the same monitoring protocol for 6 months after the last dose, as PML has been reported during this time

Natalizumab (Tysabri) is a single disease-modifying therapy for adults with multiple sclerosis who have high disease activity despite treatment with beta-interferon, or who have rapidly evolving severe relapsing remitting disease.

Natalizumab is associated with a risk of PML— a rare, progressive, and demyelinating disease of the central nervous system that can be fatal. It is caused by activation of John Cunningham virus (JCV), which usually remains latent and typically only causes PML in immunocompromised patients.

Up to August 2015, there had been 582 reports worldwide from clinical practice of PML in patients receiving natalizumab. Up to 30 March 2016, we had received 33 Yellow Card reports of PML in patients receiving natalizumab in the UK. Evidence from these reports and several studies has led to new advice to reduce the risk of PML. This advice is summarised above, along with a reminder of the previous advice which still applies.

Clinically asymptomatic PML: importance of early detection

Recent analyses suggest that earlier detection of PML is associated with improved outcomes. Cases of asymptomatic PML, diagnosed based on MRI scans and positive JCV DNA in the cerebrospinal fluid, have been reported. PML which is clinically asymptomatic at diagnosis has more localised or unilobar lesions on MRI scans compared with symptomatic patients. Occasionally, particularly in patients with small lesions, exclusively grey matter involvement of PML has been observed on MRI scans.

Note that these analyses have important potential limitations, including lead time bias and length time bias. There was also information missing on MRI frequency in symptomatic PML cases, preventing comparison with PML cases asymptomatic at onset.[1]

Therefore the risk-proportionate MRI screening protocol for PML described in this article is recommended for patients receiving natalizumab. It is also important that patients do not have any signs or symptoms of PML before switching to other disease-modifying treatments (see other articles in this issue on dimethyl fumarate and fingolimod).

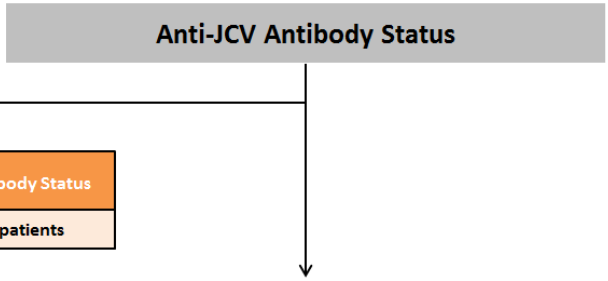
PML risk factors

The risk of PML in patients receiving natalizumab is already known to be higher in patients who:

- are serum anti-JCV antibody positive
- have had immunosuppressant therapy
- have been receiving natalizumab for a long time (especially for more than 2 years)

Recent data show that in patients who have not had immunosuppressant therapy and are serum anti-JCV antibody positive, the risk of PML rises with increased serum anti-JCV antibody index (see figure 1).

1 Dong-Si et al. Outcome and survival of asymptomatic PML in natalizumab-treated MS patients. Ann Clin Transl Neurol 2014; 1: 755–64.



Natalizumab Exposure	PML risk estimates per 1000 patients				
	Patients without prior IS use				Patients with prior IS use
	No index value	Antibody Index ≤ 0.9	Antibody Index > 0.9 ≤ 1.5	Antibody Index > 1.5	
1-12 months	0.1	0.1	0.1	0.2	0.3
13-24 months	0.6	0.1	0.3	0.9	0.4
25-36 months	2	0.2	0.8	3	4
37-48 months	4	0.4	2	7	8
49-60 months	5	0.5	2	8	8
61-72 months	6	0.6	3	10	6

Figure 1: PML risk estimates in serum anti-JCV antibody positive patients were derived using Life Table method based on the pooled cohort of 21,696 patients who participated in the STRATIFY-2, TOP, TYGRIS, and STRATA studies. Further stratification of PML risk by serum anti-JCV antibody index interval for patients with no history of immunosuppressant use were derived from combining the overall yearly risk with the antibody index distribution. The risk of PML in serum anti-JCV antibody negative patients was estimated based on data from clinical practice from approximately 125,000 exposed patients.

Figure 1 shows that the risk of PML is low at index values ≤0.9, and increases substantially at index values >1.5 in patients who have been receiving natalizumab for more than 2 years.

Therefore, the following groups of patients have been defined as being at high risk of PML:

1. those who have all three risk factors for PML (ie immunosuppressant therapy, serum anti-JCV antibody positive, and more than 2 years of natalizumab exposure)
2. those who have not had immunosuppressant therapy but have a high serum anti-JCV antibody index and more than 2 years of natalizumab exposure

For these high-risk groups, consider the extra precautions listed in the ‘during natalizumab treatment’ section above, and in figure 2 below.

6-monthly serum anti-JCV antibody testing

Perform a quantitative serum anti-JCV antibody test—including the index value—every 6 months in the following patients (see algorithm below):

- those who test negative for serum anti-JCV antibodies
- those who have low serum anti-JCV antibody index values, less than 2 years of natalizumab exposure, and who have not had immunosuppressant therapy

It is important to test these patients every 6 months because their serum anti-JCV antibody status might fluctuate, they might develop a new JCV infection, or they might have had a false negative finding. Also, patients who had a low serum anti-JCV antibody index at baseline may change to a high serum anti-JCV antibody index during treatment.

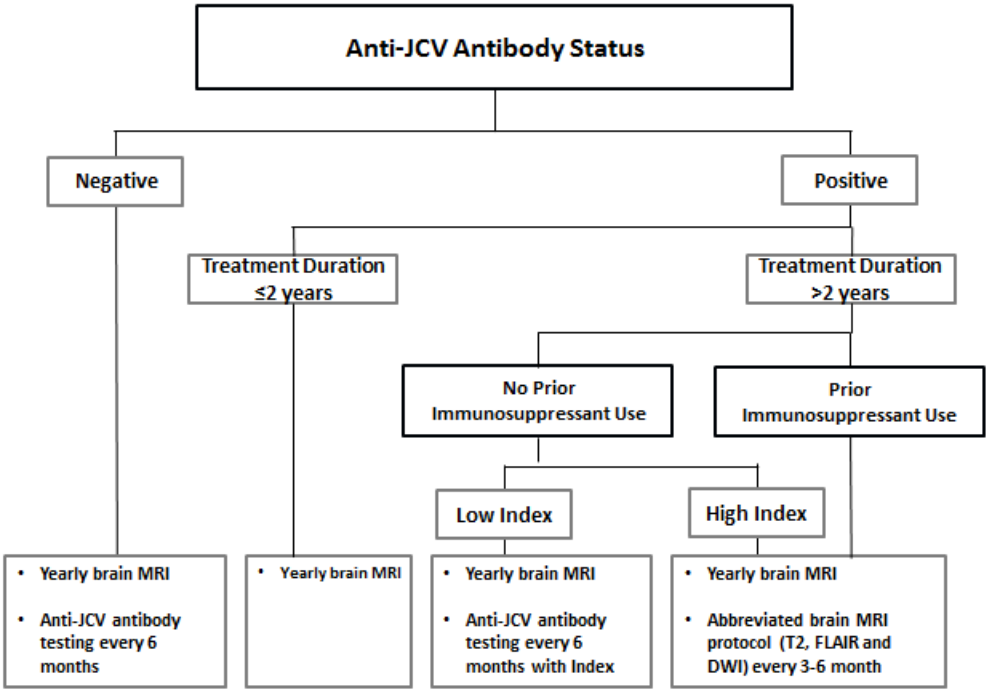


Figure 2: Algorithm of recommended patient monitoring (figure reproduced with permission from Biogen)

Further information

Letter sent to health professionals in March 2016

European Medicines Agency announcement February 2016

Risk of PML with other multiple sclerosis treatments

Other multiple sclerosis treatments—dimethyl fumarate (Tecfidera) and fingolimod (Gilenya)—have also been linked to a risk of PML (see articles below).

Article citation: Drug Safety Update volume 9 issue 9 April 2016: 2

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3 Dimethyl fumarate (Tecfidera): updated advice on risk of progressive multifocal leukoencephalopathy

Cases of progressive multifocal leukoencephalopathy have been reported in patients taking dimethyl fumarate for multiple sclerosis, who all had prolonged lymphopenia.

Advice for healthcare professionals:

Before starting dimethyl fumarate treatment

New advice:

- Perform a baseline cranial MRI scan as a reference, usually within 3 months of starting dimethyl fumarate treatment

Reminder of previous advice:

- Perform a full blood count including lymphocyte subsets
- Counsel patients and carers on the risk of progressive multifocal leukoencephalopathy (PML); advise them on symptoms to watch out for and to get medical help urgently if they occur
- If John Cunningham virus (JCV) testing is undertaken, consider that the influence of lymphopenia on the accuracy of the anti-JCV antibody test has not been studied in patients treated with dimethyl fumarate

During dimethyl fumarate treatment

New advice:

- In any patient, if PML is suspected, stop dimethyl fumarate immediately and investigate appropriately, eg MRI scan; ultrasensitive polymerase chain reaction (PCR) assay for JCV DNA
- Monitor full blood count every 3 months
- Consider interrupting dimethyl fumarate if lymphocyte counts fall below $0.5x10^9$/L for more than 6 months
- If treatment is stopped, monitor lymphocyte counts until they return to normal
- Note that patients might still develop a JCV infection, even if they have a normal lymphocyte count and previously tested negative for anti-JCV antibodies

Reminder of previous advice:

- Monitor patients for signs and symptoms or appearance of new neurological dysfunction (eg motor, cognitive, or psychiatric symptoms), bearing in mind that PML can present with features similar to multiple sclerosis

If dimethyl fumarate treatment is continued in patients with severe prolonged lymphopenia

New advice:

- Consider further MRI imaging as part of increased vigilance for PML, in accordance with national and local recommendations
- Counsel patients again on the risk of PML and remind them of the symptoms to watch out for

Dimethyl fumarate (Tecfidera) is authorised to treat relapsing-remitting multiple sclerosis. This medicine can cause lymphopenia.

Dimethyl fumarate is associated with an increased risk of PML—a rare, progressive, and demyelinating disease of the central nervous system that can be fatal. It is caused by activation of the JC virus, which usually remains latent and typically only causes PML in immunocompromised patients.

Confirmed cases of PML

In March 2015 we informed you of a fatal case of PML in a patient participating in the open-label ENDORSE study of dimethyl fumarate in multiple sclerosis. In November 2015, the licence-holder sent a letter to health professionals regarding another 2 cases of PML in patients who had been taking dimethyl fumarate for multiple sclerosis. All three patients were male and had not received any other medicines known at the time to be associated with a risk of PML. All three were seropositive for anti-JCV antibodies at the time of PML diagnosis (see table). A 4th confirmed case of PML has also been reported.

	Case 1	**Case 2**	**Case 3**
Date report received	October 2014	June 2015	August 2015
Country	Germany	USA	Germany
Setting	Clinical trial	Real-world practice	Real-world practice
Fatal / non-fatal	Fatal	Non-fatal	Non-fatal
Age	54 years	64 years	59 years
Anti-JCV antibody serostatus	Seropositive	Seropositive	Seropositive
Dimethyl fumarate treatment duration	4.5 years	2 years	1.5 years
Lymphocyte counts	fluctuated between 200 and 580 cells/µL	≤$0.5x10^9$/L with nadir of $0.3x10^9$/L	Mainly <$0.5x10^9$/L
Total lymphopenia duration	>3.5 years	At least 1.5 years	At least 1 year

Table: Confirmed cases of PML as a result of dimethyl fumarate treatment (as of October 2015).

Further information

Letter sent to health professionals in November 2015

European Medicines Agency announcement October 2015

Unlicensed use of dimethyl fumarate

Medicines containing dimethyl fumarate and other fumaric acid esters are not licensed in the UK for use in psoriasis. However, these medicines are sometimes imported as 'specials'.[1] If you are considering such use, be aware of the risks of severe, prolonged lymphopenia and serious opportunistic infections, including JCV infection which can lead to PML.

1 British Association of Dermatologists. 'Fumaric acid esters' information for patients, August 2013.

Other treatments for multiple sclerosis

Other multiple sclerosis treatments—natalizumab (Tysabri) and fingolimod (Gilenya)—have also been linked to a risk of PML (see other articles in this issue).

Article citation: Drug Safety Update volume 9 issue 9 April 2016: 3

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4 **Fingolimod (Gilenya▼): risks of progressive multifocal leukoencephalopathy, basal-cell carcinoma, and opportunistic infections**

Fingolimod (Gilenya) is authorised to treat relapsing-remitting multiple sclerosis in patients whose disease has failed to respond to beta-interferon or is severe and getting worse rapidly.

Risk of PML

There have been reports of progressive multifocal leukoencephalopathy (PML) in patients taking fingolimod (none in the UK). PML is a rare, progressive, and demyelinating disease of the central nervous system that can be fatal. It is caused by activation of John Cunningham virus (JCV), which usually remains latent and typically only causes PML in immunocompromised patients.

New advice for healthcare professionals:

Before starting fingolimod treatment:

- Perform a full blood count including lymphocyte subsets
- Perform a baseline cranial MRI scan as a reference, usually within 3 months of starting fingolimod treatment
- Counsel patients and carers on the risk of PML; advise them on the symptoms to watch out for and to get medical help urgently if they occur
- If testing for JCV is undertaken, consider that the influence of lymphopenia on the accuracy of the anti-JCV antibody test has not been studied in fingolimod-treated patients

During fingolimod treatment

- If PML is suspected, stop fingolimod treatment immediately and investigate appropriately, eg MRI scan; ultrasensitive polymerase chain reaction (PCR) assay for JCV DNA
- Monitor full blood count 3 months after starting fingolimod treatment and at least yearly thereafter
- We remind you to interrupt fingolimod treatment if lymphocyte count falls below $0.2x10^9$/L, do not restart treatment until lymphocyte levels have recovered
- When analysing routine MRI scans, pay attention to PML-suggestive lesions
- Consider further MRI scans as part of increased vigilance in patients considered at high risk of PML, in accordance with national and local recommendations
- Monitor patients for signs and symptoms or appearance of new neurological dysfunction (eg motor, cognitive, or psychiatric symptoms), bearing in mind that PML can present with features similar to multiple sclerosis
- Note that patients might still develop a JCV infection, even if they have a normal lymphocyte count and previously tested negative for anti-JCV antibodies

Reports of PML worldwide

As of December 2015, 3 confirmed cases of PML had been reported in patients taking fingolimod who had not received natalizumab. In fingolimod patients previously treated with natalizumab, 17 suspected cases of PML had been reported. It is estimated that approximately 20,000 patients had received fingolimod after previous natalizumab treatment.[1]

Other multiple sclerosis treatments—natalizumab (Tysabri) and dimethyl fumarate (Tecfidera)—have also been linked to a risk of PML (see other articles in this issue).

Risk of basal-cell carcinoma

Basal-cell carcinoma has been reported in patients taking fingolimod in clinical trials and in clinical practice. Up to 28 February 2015, 151 cases had been reported worldwide (exposure estimated at approximately 219,000 patient-years at this time).[1] Up to 30 March 2016, we had received 2 Yellow Card reports of basal-cell carcinoma in patients taking fingolimod.

1 European Medicines Agency announcement December 2015

New advice for healthcare professionals:

- Do not prescribe fingolimod to any patient with an active malignancy
- Patients' skin should be evaluated before starting fingolimod treatment and then at least yearly during treatment
- Inform patients about the common signs of basal-cell carcinoma and the need to seek medical advice if they occur. These include skin nodules (eg shiny pearly nodules), patches, or open sores that do not heal within weeks
- Refer patients with any signs of basal-cell carcinoma to a dermatologist

Risk of other opportunistic infections

The immunomodulatory effects of fingolimod can increase the risk of other central nervous system infections. These can be viral (eg herpes simplex, varicella zoster), fungal (eg cryptococcal meningitis), or bacterial (eg atypical mycobacterium). Up to 30 March 2016, we had received 49 Yellow Card reports of opportunistic infections in patients taking fingolimod.

Reminder of previous advice for healthcare professionals:

- Do not start fingolimod in any patient with severe infection
- Monitor full blood count 3 months after starting fingolimod treatment, at least yearly thereafter, and in case of any signs of infection
- Stop fingolimod treatment if a patient develops a serious infection; before restarting fingolimod treatment:
    - ensure the infection has resolved
    - carefully balance the benefit of fingolimod treatment against the risk of another infection
- Fingolimod can take up to 2 months to be eliminated from the body after the last dose, so remain vigilant for infections during this period

Further information
Letters sent to health professionals in January 2016 and April 2015

Article citation: Drug Safety Update volume 9 issue 9 April 2016: 4

5 **Apomorphine with domperidone: minimising risk of cardiac side effects**

Patients receiving apomorphine and domperidone require an assessment of cardiac risk factors and ECG monitoring to reduce the risk of serious arrhythmia related to QT-prolongation.

Advice for healthcare professionals:

- Before starting treatment, carefully consider whether the benefits of concomitant apomorphine and domperidone treatment outweigh the small increased risk of cardiac side effects
- Discuss the benefits and risks of apomorphine with patients and carers and advise them to contact their doctor immediately if they develop palpitations or syncopal symptoms during treatment
- Check the QT-interval before starting domperidone, during the apomorphine initiation phase and if clinically indicated thereafter (eg if a QT-prolonging or interacting drug is started or if symptoms of cardiac side effects are reported)
- Regularly review domperidone treatment to ensure patients take the lowest effective dose for the shortest duration
- Advise patients to inform their doctor of any changes that could increase their risk of arrhythmia, such as:
    - symptoms of cardiac or hepatic disorders
    - conditions that could cause electrolyte disturbances (eg gastroenteritis or starting a diuretic)
    - starting any other medicines
- Please continue to report suspected side effects to apomorphine, domperidone, or any other medicine on a Yellow Card

Apomorphine (brand names: APO-go, Dacepton) is a dopamine agonist used to treat refractory motor fluctuations in people with Parkinson's disease. Domperidone (brand names: Motilium, Dismotil) is usually started at least two days before apomorphine to control the expected side effects of nausea and vomiting.

Domperidone and the risk of cardiac side effects

In 2014, a review by EU medicines regulators concluded that domperidone is associated with a small increased risk of QT-interval prolongation, serious ventricular arrhythmias, and sudden cardiac death. A higher risk was observed in people older than 60 years, people taking daily oral doses of more than 30 mg, and in those taking other QT-prolonging medicines or cytochrome P450 3A4 inhibitors at the same time as domperidone. As a result of this review, the licensed indication for domperidone was restricted to relief of nausea and vomiting, the licensed dose was reduced, and several contraindications were introduced (see Drug Safety Update article from May 2014 for further details).

Apomorphine with domperidone and the risk of QT-prolongation

Apomorphine can increase the risk of QT-prolongation at high doses.

A review by EU medicines regulators of the safety of concomitant apomorphine and domperidone use has recently finished. This review concluded that health professionals should take the precautions listed above to reduce the risk of QT-prolongation. The risk of QT-prolongation may be increased in people on concomitant apomorphine and domperidone who have certain risk factors, including:

- pre-existing QT-interval prolongation
- serious underlying cardiac disorders such as heart failure
- severe hepatic dysfunction
- significant electrolyte disturbances
- concomitant drug therapy that may increase domperidone levels (eg cytochrome P450 3A4 inhibitors)

Further information
Drug Safety Update article on domperidone from May 2014

Article citation: Drug Safety Update volume 9 issue 9 April 2016: 5

6 **Aflibercept (Zaltrap▼): minimising the risk of osteonecrosis of the jaw**

Dental examination and appropriate preventive dentistry should be considered before treatment, especially for patients also treated with an intravenous bisphosphonate.

Advice for healthcare professionals:

- Cases of osteonecrosis of the jaw (ONJ) have been reported in patients with cancer who have been treated with aflibercept (Zaltrap)
- Patients who have also previously or concomitantly received an intravenous bisphosphonate may be at particular risk
- Before starting treatment, consider whether a dental examination and any appropriate preventive dentistry are needed
- Avoid invasive dental procedures, where possible, in patients being treated with Zaltrap who have previously received, or are currently receiving, an intravenous bisphosphonate
- During treatment, advise patients to: maintain good oral hygiene; receive routine dental check-ups; and to report any oral symptoms such as dental mobility, pain, or swelling
- Suspected adverse reactions should be reported to us on a Yellow Card

Zaltrap is authorised in combination with irinotecan, 5-fluorouracil, and folinic acid (FOLFIRI) chemotherapy for treatment of adults with metastatic colorectal cancer that is resistant to, or has progressed after, treatment with an oxaliplatin-containing regimen. More than 22,000 patients worldwide to date are estimated to have received Zaltrap.

Cases of ONJ

There have been 8 post-marketing cases of ONJ reported worldwide up to 3 August 2015, 3 of which stated concomitant treatment with intravenous bisphosphonates and 5 previous invasive dental procedure or infection (all of which are known risk factors for ONJ).

A meta-analysis of 3 phase III cancer clinical trials (EFC10262/VELOUR[1], EFC10261/VITAL[2], EFC10547/VANILLA[3]) found that 3 of 1,333 patients assigned Zaltrap had ONJ, compared with 1 of 1,329 assigned placebo (relative risk for all-grade osteonecrosis 2.99 [95% CI 0.31–28.72]).

A further phase III cancer trial (EFC6546/VENICE[4]) identified a higher frequency of ONJ in patients treated with Zaltrap and docetaxel independent of bisphosphonate use (7 of 209 patients receiving Zaltrap, docetaxel, and bisphosphonates compared with 2 of 224 patients receiving placebo, doxetaxel, and bisphosphonates).

Potential mechanism

The mechanism by which Zaltrap may increase the risk of ONJ is not fully known. However, it is an antiangiogenic agent and might therefore interfere with, and decrease, new capillary growth during wound healing at sites of physical trauma such as after dental procedures.

ONJ is a known risk with other antiangiogenic agents, such as sunitinib or bevacizumab, which target endothelial growth factor pathways.

Overall, although there are many known risk factors for ONJ, there is sufficient evidence to suggest that Zaltrap may independently increase or contribute to this risk.

Footnote: Eylea

Aflibercept is also the active ingredient in Eylea intravitreal injection, which is authorised for treatment of macular degeneration. ONJ has not been identified as a risk for Eylea.

1. EFC10262/VELOUR study: aflibercept versus placebo in combination with irinotecan and 5-FU in the treatment of patients with metastatic colorectal cancer after failure of an oxaliplatin based regimen (VELOUR).

2. EFC10261/VITAL: a study of aflibercept versus placebo in patients with second-line docetaxel for locally advanced or metastatic non-small-cell lung cancer (VITAL).

3. EFC10547/VANILLA: aflibercept compared to placebo in term of efficacy in patients treated with gemcitabine for metastatic pancreatic cancer (VANILLA).

4. EFC6546/VENICE study: aflibercept in combination with docetaxel in metastatic androgen independent prostate cancer (VENICE).

Further information
Letter sent to health professionals in March 2016

Article citation: Drug Safety Update volume 9 issue 9 April 2016: 6

7 **Live attenuated vaccines: avoid use in those who are clinically immunosuppressed**

Healthcare professionals working in primary and secondary care should ensure that clinically significant immunosuppression in a patient is identified before administration of a live attenuated vaccine.

Reminder for healthcare professionals:

- Live attenuated vaccines should not routinely be given to people who are clinically immunosuppressed (either due to drug treatment or underlying illness)
- It is important for healthcare professionals who are administering a particular vaccine to be familiar with the contraindications and special precautions before proceeding with immunisation
- Specialists with responsibility for an immunosuppressed patient who may be in a group eligible for a live attenuated vaccine should include in their correspondence with primary care a statement of their opinion on the patient's suitability for the vaccine
- If primary care professionals are in any doubt as to whether a person due to receive a live attenuated vaccine may be immunosuppressed at the time, immunisation should be deferred until secondary care specialist advice has been sought, including advice from an immunologist if required
- Remember that close contacts of immunosuppressed individuals should be fully immunised to minimise the risk of infection of vaccine-preventable diseases in immunosuppressed individuals

Background

Some recommended vaccines contain live, attenuated (weakened) organisms, which work by mimicking a natural infection. Live attenuated vaccines should not be given to people who are clinically immunosuppressed (either due to drug treatment or underlying illness) because the vaccine strain could replicate too much and cause an extensive, serious infection.

A minor immunodeficiency may not necessarily contraindicate vaccination, and the Summary of Product Characteristics* for a particular vaccine will explain specific contraindications and warnings. The Green Book (Immunisation against infectious disease) should also be consulted.

*Summaries of Product Characteristics for vaccines and other medicines can be found on the electronic medicines compendium (eMC) website or on the website of the European Medicines Agency.

Recent Yellow Card reports

We are aware of recent Yellow Card adverse reaction reports in which immunosuppressed patients have received a live attenuated vaccine, some of which resulted in severe infection and death.

Fatal BCG infection in neonates after in utero exposure to TNFα antagonist

We have received 4 Yellow Card reports regarding neonates who have died from disseminated BCG or tuberculosis infection after exposure to a TNFα antagonist in utero; they were probably not known to be immunosuppressed at the time of vaccination.

As a precaution, any infant who has been exposed to immunosuppressive treatment from the mother either in utero during pregnancy or via breastfeeding should have any live attenuated vaccination deferred for as long as a postnatal influence on the immune status of the infant remains possible.

In the case of in utero exposure to TNFα antagonists and other biological medicines, this period should be until the infant is age 6 months, after which time vaccination should be considered.

Shingles vaccination in elderly patients with immunosuppression

We have received Yellow Cards reporting that several elderly patients have received shingles vaccine (Zostavax) at a time when they were possibly immunosuppressed (eg due to treatment for a transplant or due to lymphoproliferative disorders). The suspected adverse reactions reported in these Yellow Cards are possibly a consequence of a disseminated viral infection caused by the vaccine strain.

It is important for all healthcare professionals to be familiar with the contraindications and special precautions associated with the shingles vaccine before proceeding with immunisation.

Reminder regarding close contacts of immunosuppressed individuals

Public Health England advise that to minimise the risk of infection in immunosuppressed individuals for whom live vaccines are contraindicated, their close contacts should be fully immunised according to the UK schedule, as a matter of priority. Close contacts of severely immunosuppressed individuals should also be offered vaccination against varicella and influenza. This will reduce the risk of exposure of vulnerable individuals to the serious consequences of vaccine-preventable infections.

Reporting of suspected adverse reactions to vaccines or medicines

Please continue to report suspected adverse reactions to vaccines and other medicines to the Yellow Card Scheme.

When a medication error has occurred (eg vaccination of a contraindicated patient), we are responsible for reviewing reports of medication errors resulting in harm and these should be reported via the Yellow Card Scheme. Reports of medication errors in the absence of harm should be reported to NHS England via the National Reporting and Learning System.

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8 **Meprobamate: licence to be cancelled**

Following an EU wide review of meprobamate, the remaining licence holder in the UK has ceased manufacturing and the licence will be cancelled by the end of 2016.

Advice for healthcare professionals:

- Prescribers should review the treatment of any patient who is currently receiving a meprobamate-containing medicine with a view to switching them to an alternative treatment
- Prescribers should not start any new patients on medicines that contain meprobamate

Background

Meprobamate is a carbamate used for short-term treatment of anxiety states or musculoskeletal disorders where, in either case, there is muscle tension or painful muscle spasm.

In 2012, the European Medicines Agency recommended withdrawal of meprobromate-containing medicines from the market following a review of their safety and effectiveness. The review concluded that the benefits of meprobamate do not outweigh its risks (which include dependence, withdrawal reactions, and abuse: see the Drug Safety Update article from February 2008).

Withdrawal of licence

No new stock will be released into the normal distribution chain after 31 December 2016, although existing stock placed on the market (and therefore already in the supply chain) before that date is likely to be dispensed until the products approach their expiry date.

Since 2012, prescribing of meprobamate in the UK has decreased; however, a small number of patients continue to receive it. These patients should be reviewed and where possible switched to an alternative safer treatment.

As with any unlicensed medicine there is a provision for the supply of unlicensed meprobamate, on the responsibility of the prescriber, who can judge the risks and benefits in consultation with the patient. However, the continued supply of a particular unlicensed medicine cannot be guaranteed.

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9 **Paraffin-based skin emollients on dressings or clothing: fire risk**

Smoking or a naked flame could cause patients' dressings or clothing to catch fire when being treated with paraffin-based emollient that is in contact with the dressing or clothing.

Reminder for healthcare professionals:

- Advise patients not to: smoke; use naked flames (or be near people who are smoking or using naked flames); or go near anything that may cause a fire while emollients are in contact with their medical dressings or clothing
- Change patient clothing and bedding regularly—preferably daily—because emollients soak into fabric and can become a fire hazard
- Incidents should be reported to NHS England's Serious Incident Framework (includes Wales), Healthcare Improvement Scotland, or to the Health and Social Care Boards in Northern Ireland

When patients are being treated with a paraffin-based emollient product that is covered by a dressing or clothing, there is a danger that smoking or using a naked flame could cause dressings or clothing to catch fire. We informed healthcare professionals of this risk in January 2008.

Examples of paraffin-based emollients include:

- white soft paraffin
- white soft paraffin plus 50% liquid paraffin
- emulsifying ointment

The risk is greater when these preparations are applied to large areas of the body, or when dressings or clothing become soaked with emollient.

We are aware of a recent fatal incident reported to the NHS England National Reporting and Learning System, in which a naked flame ignited emollient in contact with a patient's dressings and clothing.

Posters have previously been available from the National Patient Safety Agency, and may be a useful source of information for local use.

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10 **Letters sent to healthcare professionals in March 2016**

In March 2016, letters were sent to healthcare professionals regarding:

- SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis during treatment (see also the article in this issue)
- insulin lispro (Humalog 200 units/mL KwikPen): correct use to minimise medication errors
- natalizumab (Tysabri▼): updates to PML risk minimisation measures (see also the article in this issue)
- noradrenaline (norepinephrine) 0.08 mg/mL (4 mg in 50 mL) solution for infusion in a vial: potential risk of medication errors
- radium-223 dichloride (Xofigo▼): change in NIST standard reference material – information on implementation
- aflibercept (Zaltrap▼): information on the risk of osteonecrosis of the jaw (see also the article in this issue)
- idelalisib (Zydelig▼): restrictions in use for the treatment of chronic lymphocytic leukaemia and relapsed follicular lymphoma following new clinical trial results

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