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 (MHRA) is the government agency 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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In our first article this month, we inform you of the forthcoming removal of Omniscan and intravenous Magnevist gadolinium-containing contrast agents and restrictions to the use of some other (linear) agents in the class (page 2). For all gadolinium-containing contrast agents that remain on the market, use at the lowest doses that enhance images sufficiently and only when unenhanced body scans are not suitable.

In our second article, we highlight reports of progressive multifocal encephalopathy (PML) with cladribine when used for haematological conditions and the need to stop treatment in suspected cases of PML (page 4).

In our third article, we inform you of the start of a new European review into the safety of radium-223 dichloride following preliminary data from a clinical trial suggesting an increased incidence of deaths and fractures (page 5). Until full analysis is complete, do not use radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone.

Next, we describe a risk of pancreatitis and sphincter of Oddi spasm with eluxadoline, newly licenced for irritable bowel syndrome with diarrhoea (page 6). Do not use in patients without a gallbladder or in those with biliary disorders. Eluxadoline should only be initiated and supervised in secondary care.

In our final two articles, read about new contraindications related to cardiac risk (page 7) and strengthened warnings for immunosuppressive effects (page 8) with fingolimod, indicated for relapsing-remitted multiple sclerosis.

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Gadolinium-containing contrast agents: removal of Omniscan and iv Magnevist, restrictions to the use of other linear agents

A review has found that low levels of gadolinium can be retained in the brain and other tissues after administration of gadolinium-containing contrast agents (GdCAs). There is currently no evidence that gadolinium deposition in the brain has caused adverse neurological effects in patients; however, licences for gadodiamide (Omniscan) and intravenous gadopentetic acid (also known as gadopentetate dimegulumine; Magnevist) will be suspended from 1 February 2018 and these products will be recalled. The use of gadobenic acid (also known as gadobenate dimeglumine; MultiHance) and gadoxetic acid (Primovist) will be limited to delayed phase liver imaging only.

Advice for healthcare professionals:

- linear gadolinium-containing contrast agents (GdCAs) are associated with higher retention of gadolinium in the brain than macrocyclic GdCAs
- licences will be suspended for linear agents gadodiamide (Omniscan) and intravenous gadopentetic acid (Magnevist)
- suspended products will be recalled from 1 February 2018, by which time healthcare professionals are expected to have switched over to alternative GdCAs
- the authorised indication of the linear agents gadobenic acid (also known as gadobenate dimeglumine; MultiHance) and gadoxetic acid (Primovist) will be limited to delayed phase liver imaging
- macrocyclic agents gadoteridol (Prohance), gadobutrol (Gadovist), and gadoteric acid (Dotarem) will remain authorised, as will gadopentetic acid for intra-articular use
- use GdCAs only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI); do not exceed the recommended dose per kilogram of body weight and use the lowest dose that is effective for diagnosis

Background and 2007 European review

Gadolinium-containing contrast agents (GdCAs) are indicated for the enhancement of magnetic resonance imaging (MRI). GdCAs contain gadolinium bound to a ligand molecule and can be divided into two groups based on their chemical structure — linear and macrocyclic.

A 2007 European-level review identified a risk of nephrogenic systemic fibrosis (NSF) following use of GdCAs in patients with severely impaired renal function. Linear GdCAs were categorised as having a higher risk of causing NSF than macrocyclic GdCAs. In 2010, we published advice aiming to minimise the risk of NSF. Since 2006, the use of linear GdCAs has decreased markedly in the UK, and most patients now receive macrocyclic GdCAs.

Gadolinium retention in the brain and other tissues

A European-level scientific review to investigate gadolinium retention in brain and other tissues has now completed. Low levels of gadolinium deposition in the brain, particularly in the dentate nucleus of the cerebellum and in the sub-cortical structure the globus pallidus, have been confirmed by mass spectrometry and studies of MRI data. Data on stability, as well as in-vitro and non-clinical studies, show that macrocyclic agents have a significantly lower potential to cause retention of gadolinium in the body. This is because they are more stable and do not release gadolinium to any significant extent from the ligand molecule.

Central Alerting System message to healthcare professionals. 13 December 2017.

EMA's final opinion confirms restrictions on use of linear gadolinium agents in body scans.

In view of the evidence of retention of gadolinium in brain and other tissues following exposure to these agents, the risks of gadodiamide and intravenous gadopentetic acid are considered to outweigh their benefits.

There is currently no evidence that gadolinium deposition in the brain has caused adverse neurological effects in patients; however, data on long-term effects of gadolinium deposition in the brain or other tissues are very limited. The European Medicines Agency has issued information to patients about the review.

When using one of the linear GdCAs that will remain on the market, weigh the possible diagnostic advantages in patients who will require repeated scans against the potential for deposition of gadolinium in the brain and other tissues.

Status of gadolinium-containing contrast agents after the review

Brand leader product name	Active substance	Structure	Recommendation from EU review
Omniscan	gadodiamide	Linear	Suspension
Magnevist	gadopentetic acid (USAN[1] gadopentetate dimeglumine)	Linear	Suspension
Magnevist (intra-articular product)	gadopentetic acid, dimeglumine salt	Linear	Updates to product information
MultiHance	gadobenic acid (USAN[1] gadobenate dimeglumine)	Linear	Indication revised to delayed phase liver imaging only; updates to product information
Primovist	gadoxetic acid	Linear	Indication revised to delayed phase liver imaging only; updates to product information
ProHance	gadoteridol	Macrocyclic	Updates to product information
Gadovist	gadobutrol	Macrocyclic	Updates to product information
Dotarem[2]	gadoteric acid	Macrocyclic	Updates to product information

[1] United States Adopted Name. [2] Other products available are Clariscan, Dotagraf, and Cyclolux. One linear agent, gadoversetamide (OptiMARK), has been withdrawn by the Marketing Authorisation Holder and is not available in the UK.

Reporting of suspected adverse reactions

Gadolinium-containing contrast agents are authorised as medicines. Suspected adverse reactions should be reported to us on a Yellow Card.

Article citation: Drug Safety Update volume 11 issue 5; December 2017: 1.

Cladribine (Litak, Leustat) for leukaemia: reports of progressive multifocal encephalopathy (PML); stop treatment if PML suspected

Consider progressive multifocal encephalopathy (PML) in the differential diagnosis for patients with new or worsening neurological signs or symptoms, even several years after treatment with cladribine.

Advice for healthcare professionals:

- we are aware of 3 confirmed cases of progressive multifocal encephalopathy (PML) worldwide that developed 6 months to several years after patients received treatment with cladribine for haematological conditions
- an association between cladribine and prolonged lymphopenia has been reported
- consider PML in the differential diagnosis for patients with new or worsening neurological signs or symptoms
- if PML is suspected, stop cladribine treatment immediately and ensure the patient receives specialist investigation
- patients should be monitored for signs and symptoms or appearance of new neurological dysfunction (eg, motor, cognitive, or psychiatric symptoms)
- although reports are very infrequent, PML is a life-threatening neurological disorder; advise patients of symptoms of PML and the need to get medical help immediately if these occur

Background

The following cladribine medicines are licenced in the UK:

- Litak, indicated for hairy cell leukaemia
- Leustat, indicated for hairy cell leukaemia and B-cell chronic lymphocytic leukaemia
- Mavenclad, recently authorised for highly active relapsing-remitting multiple sclerosis

Reports of PML in oncology indications

A recent European review was triggered by post-marketing reports of progressive multifocal encephalopathy (PML) in patients given cladribine for haematological cancer. As of March 2017, 3 confirmed reports of PML (including at least 1 fatal case) have been reported in patients worldwide taking cladribine for various haematological conditions. None of these reports were from patients in the UK.

Since cladribine can induce myelosuppression and immunosuppression, as well as lymphopenia that can last several months, it is thought to be biologically plausible that it could increase the risk of PML. An association between cladribine and prolonged lymphopenia has been reported.

Direct Healthcare Professional Communication. Cladribine. 1 December 2017.

For cladribine medicines with oncology indications (Litak and Leustat), the product information for healthcare professionals and patients is being updated and a letter has been sent to haematologists and oncologists about the risk.

PML in multiple sclerosis indication

The product information for cladribine for the multiple sclerosis indication already includes a warning about the risk of PML. A Prescriber's Guide is available.

About PML

PML is a rare, progressive, and demyelinating disease of the central nervous system that can be fatal. It is caused by activation of JC virus, which usually remains latent and typically only causes PML in immunocompromised patients. The factors leading to activation of the latent infection are not fully understood. If PML is suspected, investigations may include magnetic resonance imaging, ultrasensitive polymerase chain reaction (PCR) assay for JC virus DNA, or brain biopsy for JC virus.

Reporting of suspected adverse reactions

Suspected adverse reactions should be reported to us on a Yellow Card, even if some time has passed since administration.

Article citation: Drug Safety Update volume 11, issue 5; November 2017: 2.

Radium-223 dichloride (Xofigo▼): do not use in combination with abiraterone and prednisone/prednisolone, following clinical trial signal of increased risk of death and fractures

A European review has begun into the safety of radium-223 dichloride following an observed increase in the incidence of deaths and fractures in patients with chemotherapy-naive metastatic castration-resistant prostate cancer receiving radium-223 dichloride in combination with abiraterone acetate (Zytiga) and prednisone/prednisolone as part of a clinical trial. Until full analysis of the results is completed, do not treat patients with radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone.

Xofigo▼ is licenced for the treatment of men with castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral metastatic disease.

Preliminary data from a randomised, double-blind, placebo-controlled study showed an increased incidence of deaths (27% versus 20%) and fractures (24% versus 7%) among patients receiving Xofigo in combination with abiraterone acetate and prednisone/prednisolone (n=401) compared to patients receiving placebo in combination with abiraterone acetate and prednisone/prednisolone (n=405). This study in asymptomatic or mildly symptomatic chemotherapy-naive patients with bone-predominant metastatic castration-resistant prostate cancer was unblinded early based on an Independent Data Monitoring Committee recommendation.

Direct Healthcare Professional Communication. Xofigo. 11 December 2017.

EMA starts referral procedure for Xofigo. 1 December 2017.

Until full analysis of the results is completed, do not use radium-223 dichloride in combination with abiraterone acetate and prednisone/prednisolone to treat metastatic castration-resistant prostate cancer (see letter to healthcare professionals). Further advice will be communicated as appropriate at the end of the review.

Article citation: Drug Safety Update volume 11 issue 5; December 2017: 3.

Eluxadoline (Truberzi▼): risk of pancreatitis; do not use in patients who have undergone cholecystectomy or in those with biliary disorders

Cases of pancreatitis, with or without sphincter of Oddi spasm, have been reported in patients taking eluxadoline. Some cases have resulted in hospitalisation and death, primarily in patients who have undergone cholecystectomy.

Advice for healthcare professionals:

- eluxadoline (Truberzi▼), licenced for irritable bowel syndrome with diarrhoea, should be initiated and supervised by a specialist physician experienced in diagnosis and management of gastrointestinal disorders
- do not use in patients without a gallbladder or in patients with known or suspected biliary tree or pancreatic duct obstruction (eg, gallstones, tumour, periampullary duodenal diverticulum) or sphincter of Oddi disease or dysfunction
- tell patients to avoid drinking alcohol during treatment with eluxadoline
- inform patients about symptoms suggestive of pancreatitis—eg, abdominal pain that may radiate to the back or shoulder, nausea, and vomiting
- instruct patients to stop taking eluxadoline and seek immediate medical attention if these symptoms develop
- report all suspected adverse drug reactions to Black Triangle drugs such as Truberzi to the Yellow Card Scheme

Background

Eluxadoline (Truberzi▼) was approved in 2017 for the treatment of irritable bowel syndrome with diarrhoea (IBS-D) in adults.

NICE guidance for prescribing eluxadoline.

On 30 August 2017, the National Institute of Health and Care Excellence (NICE) recommended that eluxadoline could be prescribed on the NHS in England if other pharmacological treatments for IBS-D did not work or were unsuitable and if it was started in secondary care. Use of eluxadoline in the UK is so far extremely low (it is approximated that no more than 20 patients in the UK have started the medicine).

Cases of pancreatitis in patients taking eluxadoline

A routine European review identified 230 cases of, or reactions suggestive of, pancreatitis in patients taking eluxadoline over an estimated exposure of 26,363 patient-years. All cases of pancreatitis came from the USA where, before April 2017, a contraindication in patients without a gallbladder was not in place. Gallbladder status was known in 140 of the cases and of these, most (76%) had undergone cholecystectomy and did not have a gallbladder. Of these, 4 cases were severe: 2 cases in which eluxadoline appears to have contributed to the patient's death, 1 case of necrotising pancreatitis with an unknown outcome, and 1 case involving acute kidney injury due to dehydration and acute respiratory insufficiency due to atelectasis, which were suspected to have been secondary to pancreatitis. Dehydration and pulmonary complications of acute pancreatitis have been reported in the literature.

Most of the reported cases of pancreatitis occurred within 1 week of starting treatment with eluxadoline and some patients developed symptoms even after 1 to 2 doses. However, cases of pancreatitis after longer duration of treatment have also been reported.

In most cases, eluxadoline treatment was withdrawn. At the time of review, out of the reports with an outcome reported (123 reports), most patients (107) had recovered from the pancreatitis or their condition was improving.

Actions taken following review

Direct Healthcare Professional Communication. Eluxadoline. 2 November 2017.

A letter has been sent to healthcare professionals on this issue and the product information (Summary of Product Characteristics and Patient Information Leaflet) has been updated to include the above warnings and new contraindications, as well as to add a restriction that therapy with eluxadoline should be initiated and supervised by a physician experienced in diagnosis and management of gastrointestinal disorders.

Consult the full list of contraindications in the Summary of Product Characteristics before prescribing eluxadoline.

Article citation: Drug Safety Update volume 11 issue 5; December 2017: 4.

Fingolimod (Gilenya▼): new contraindications in relation to cardiac risk

Fingolimod can cause persistent bradycardia, which can increase the risk of serious cardiac arrhythmias. New contraindications have been introduced for patients with pre-existing cardiac disorders.

Advice for healthcare professionals:

- fingolimod can cause serious ventricular arrhythmias, particularly in the first year of use
- fingolimod is now contraindicated in patients with:
  - myocardial infarction or unstable angina
  - cerebrovascular disease (transient ischaemic attacks, stroke)
  - decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure in the previous 6 months
  - severe cardiac arrhythmias requiring treatment with class Ia (eg, quinidine, procainamide, disopyramide) and class III (potassium-channel blockers—eg, amiodarone, sotalol, ibutilide, dofetilide) antiarrhythmic drugs
  - second-degree Mobitz type II atrioventricular (AV) block or third-degree AV block, or sick-sinus syndrome, if they do not have a pacemaker
  - pre-treatment QT intervals ≥500 milliseconds
- report all suspected adverse drug reactions with fingolimod on a Yellow Card

Summary of Product Characteristics. Gilenya▼.

Fingolimod is authorised to treat relapsing-remitting multiple sclerosis in patients whose disease has failed to respond to at least 1 disease-modifying therapy or which is severe and rapidly progressive.

Fingolimod can cause transient bradycardia and second-degree or third-degree atrioventricular (AV) block in early treatment. In January 2013, we highlighted the need for cardiac monitoring after the first dose of fingolimod. However, some patients can have persistent bradycardia, which can increase the risk of serious cardiac arrhythmias.

A recent routine EU review identified 44 post-marketing reports of serious ventricular tachyarrhythmia and 6 reports of sudden death worldwide in patients taking fingolimod up to the end of February 2017. To this date, cumulative exposure to fingolimod post-marketing was estimated to be 397,764 patient-years. The routine EU review recommended that warnings against the use of fingolimod in patients with underlying cardiac disorders should be strengthened to contraindications.

Further information

Direct Healthcare Professional Communication. Fingolimod. November 2017.

Fingolimod (Gilenya▼): not recommended for patients at known risk of cardiovascular adverse events. Drug Safety Update. May 2012.

Fingolimod (Gilenya▼): bradycardia and heart block. Drug Safety Update. January 2013.

Article citation: Drug Safety Update volume 11 issue 5; December 2017: 5.

Fingolimod (Gilenya▼): updated advice about risk of cancers and serious infections

Monitor patients closely for skin cancers. Advise patients to seek urgent attention if they develop signs or symptoms of serious infections.

Advice for healthcare professionals:

- fingolimod has an immunosuppressive effect and can increase the risk of skin cancers and lymphoma and serious opportunistic infections
- re-assess the benefit-risk balance of fingolimod therapy in individual patients, particularly those with additional risk factors for malignancy
- examine all patients for skin lesions before starting fingolimod and closely monitor for skin cancers at least every 6 to 12 months
- advise patients to avoid exposure to UV radiation (including sunlight and phototherapy) and seek urgent medical advice if they notice any skin lesions
- advise patients to seek urgent medical attention if they develop any symptoms or signs consistent with an infection, including up to 2 months after the end of fingolimod therapy
- report all suspected adverse drug reactions with fingolimod, including after discontinuation, on a Yellow Card

Risk of malignancy

Fingolimod has an immunosuppressive effect. A recent routine EU review recommended strengthened warnings for malignancies including skin cancers and lymphoma and serious opportunistic infections.

Basal cell carcinoma and lymphoma were already known to occur in patients taking fingolimod and annual skin screening was advised. The review identified post-marketing reports of T-cell lymphoma (mostly cutaneous) and other types of skin cancer, including malignant melanoma (uncommon; post-marketing frequency less than 1 in 100 patients), squamous cell carcinoma (rare; less than 1 in 1,000), Kaposi sarcoma (very rare; less than 1 in 10,000), and Merkel cell carcinoma (unknown frequency).

For patients taking fingolimod:

- re-assess the benefit-risk balance of fingolimod therapy in individual patients, particularly those with additional risk factors for malignancy (such as previous immunosuppressive treatment and previous malignancy), and either closely monitor for skin cancers or consider discontinuation on a case-by-case basis
- examine all patients for skin lesions before they start fingolimod and then re-examine every 6 to 12 months or more frequently if indicated
- tell patients to protect themselves against UV radiation exposure (including sunlight, sunbeds, phototherapy, and PUVA/photochemotherapy) and seek urgent medical advice if they notice any skin lesions
- refer patients with suspicious lesions to a dermatologist

Risk of fatal fungal infections and reports of progressive multifocal leukoencephalopathy

Analysis of post-marketing reports suggest a higher risk of serious infections, including fatal fungal infections, than clinical trial data predicted. Although the exact frequency of these infections is not known, vigilance for serious opportunistic infections is recommended. The routine review identified 54 reports of opportunistic systemic fungal infections, including 9 fatal cases of cryptococcal meningitis, over 397,764 patient-years of exposure since marketing.

Advise patients to seek urgent medical advice if they develop symptoms or signs consistent with an infection for up to 2 months after discontinuation of fingolimod. Refer any patients with a potentially serious infection to a physician experienced in the investigation and management of infectious diseases.

In April 2016, we informed you about reports of progressive multifocal leukoencephalopathy (PML) in patients taking fingolimod. Worldwide, PML has now been reported in 79 patients taking fingolimod post-marketing, including 22 cases attributable to fingolimod. Monitor patients for signs and symptoms or appearance of new neurological dysfunction and, if PML is suspected, stop fingolimod treatment immediately and investigate appropriately.

Further information

Fingolimod (Gilenya▼): risks of progressive multifocal leukoencephalopathy, basal-cell carcinoma, and opportunistic infections. Drug Safety Update. April 2016.

BNF. Multiple sclerosis.

Article citation: Drug Safety Update volume 11 issue 5; December 2017: 6.

Letters sent to healthcare professionals in November 2017

In November 2017, the following letters were sent to relevant healthcare professionals to inform them of updated safety information:

- Eluxadoline (Truberzi ▼): risk of pancreatitis and sphincter of Oddi spasm
- Fingolimod (Gilenya▼): contraindications in patients with cardiac conditions
- Bleo-Kyowa (bleomycin sulphate), powder for solution for injection – use 5-micron filter during IV infusion or pre-injection – see Caution in Use alert
- Buccolam (midazolam) prefilled plastic syringes: potential product defect – see Caution in Use alert
- ERWINASE: notice of special handling instructions—vials of ERWINASE from batch 185G* should be used with a 5-micron filter needle

Article citation: Drug Safety Update volume 11, issue 5; December 2017: 7.

Medical Device Alert issued in November 2017

For all Medical Device Alerts from MHRA, see Alerts and recalls for drugs and medical devices.

An alert was recently issued by MHRA about:

- ThermoScientific Oxoid CAZ10 ceftazidime, CT1629B antimicrobial susceptibility test disc – potential for false resistance results if stored at the wrong temperature

Article citation: Drug Safety Update volume 11 issue 5; December 2017: 8.
