

# Drug Safety Update



# MHRA

## 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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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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First, check that you are acting within your responsibilities to prevent the serious harms of valproate in pregnancy. Valproate medicines must not be used in women of childbearing potential unless the Pregnancy Prevention Programme is in place. See page 2 for a reminder of actions needed from GPs, specialists, and dispensers who are involved in the care of female patients with valproate and for information on how to order more packs of information materials. Evidence is emerging that some women on valproate are still not receiving the patient information leaflet and alert card and are not being referred for annual specialist review.

Second, act on new restrictions and recommendations on page 4 following a safety review of radium-223 (Xofigo ▼) indicated for castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastases. Use of radium-223 has been restricted to men who have had 2 previous systemic treatments for metastatic castration-resistant prostate cancer or who cannot receive other systemic treatments. Combination treatment with abiraterone acetate and prednisone/prednisolone is contraindicated due to an increased risk of fractures and a trend for increase mortality seen in a clinical trial.

On page 7, see updated monitoring recommendations for patients who have previously been treated for multiple sclerosis with daclizumab beta (Zinbryta ▼), which is no longer available. Following cases of immune-mediated encephalitis, including anti-NMDA receptor encephalitis and GFAP $\alpha$  IgG-associated encephalitis, some of which occurred several months after discontinuation, new advice is given.

Finally, cases of communicating hydrocephalus have been reported during nusinersen (Spinraza ▼) therapy for 5q spinal muscular atrophy (page 11). Advise patients and their caregivers to seek urgent medical attention if any signs or symptoms develop, including persistent vomiting or headache, and treat urgently.

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## **Valproate Pregnancy Prevention Programme: actions required now from GPs, specialists, and dispensers**

Valproate medicines must not be used in women of childbearing potential unless the Pregnancy Prevention Programme is in place. If you are involved in the care of female patients on valproate in the UK, see a reminder of actions required for this medicine. You should have received a pack of information materials for patients—if you have not yet received a pack, or if you are near to running out of any materials, you should order more using the details provided in the article.

### **Reminder of actions for healthcare professionals:**

#### **Actions for GPs**

- identify and recall all women and girls on valproate who may be of childbearing potential
- provide the Patient Guide to the patient (or her parents or responsible person as necessary)
- check they have been reviewed by a specialist in the last year (ie, they have an in-date Risk Acknowledgement Form) and are on highly effective contraception

#### **Actions for specialists**

- book in review appointments at least annually with women and girls under the Pregnancy Prevention Programme and re-evaluate treatment as necessary
- explain clearly the conditions as outlined in the supporting materials
- complete and sign with the patient or their responsible person the Risk Acknowledgement Form—copies of the form must be given to the patient or responsible person and sent to their GP

#### **Actions for dispensers**

- valproate medicines must always be dispensed with the accompanying patient information leaflet
- dispense whole packs whenever possible, and ensure there is a warning label either on the carton or added via a sticker
- discuss risks in pregnancy with female patients each time you dispense valproate medicines and ensure they have the Patient Guide and have seen their GP or specialist to discuss their treatment and the need for contraception
- ensure new packs of valproate information materials are placed in a designated place accessible to all dispensing staff and dispose of any old materials related to valproate medicines

### **How to order more packs**

Packs of information materials to support informing women on valproate of the risks in pregnancy and the need to be enrolled in the Pregnancy Prevention Programme have been sent to prescribers, dispensers, and healthcare professionals. A reminder of the key valproate materials and how to access them online is available in the [May 2018 Drug Safety Update](#). Despite this we are hearing that women on valproate are still not receiving the information they are entitled to, including the patient information leaflet, and some women on valproate are unaware of the serious risks in pregnancy.

If you require more copies or if you have not received a pack, please contact the Sanofi medical information department without delay on 0845 372 7101 or email [UK-Medicalinformation@sanofi.com](mailto:UK-Medicalinformation@sanofi.com).

### **Responsibilities of healthcare professionals**

[Valproate medicines must not be used in women of childbearing potential unless the Pregnancy Prevention Programme is in place](#). As stated in the risk minimisation materials, the requirement for a Pregnancy Prevention Programme is applicable to all premenopausal female patients unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy. As for any medicine, use that does not comply with the conditions of the licence would be off-label and carry the [accompanying responsibilities](#).

### **Report any suspected adverse drug reactions**

Continue to report any suspected adverse drug reactions, including any case of a pregnancy exposed to valproate medicines, to the [Yellow Card Scheme](#) (see [advice on reporting suspected adverse drug reactions from medicines taken during pregnancy](#)). Should exposure occur, pregnancy outcomes should be monitored and reported.

### **Information resources available for those who dispense valproate**

Below is a list of further information resources created for healthcare professionals:

- [Royal Pharmacology Society – Quick Reference Guide for dispensing valproate for girls and women \(updated 13 August 2018\)](#).
- [Company Chemists' Association \(CCA\) audit tool for community pharmacy teams to use in reviewing their support for girls and women taking valproate medicines](#)

### **New video available**

A [new video is available](#) to support healthcare professionals in implementing the new 2018 regulatory measures, including the Pregnancy Prevention Programme and regular patient reviews.

*Article citation: Drug Safety Update volume 12, issue 2; September 2018: 1.*

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## **Xofigo ▼ (radium-223-dichloride): new restrictions on use due to increased risk of fracture and trend for increased mortality seen in clinical trial**

Now only authorised for use in patients with symptomatic bone metastases and no known visceral metastases who have had 2 previous systemic treatments for metastatic castration-resistant prostate cancer or who cannot receive other systemic treatments. Do not use in combination with abiraterone acetate and prednisone/prednisolone.

### **Advice for healthcare professionals:**

- radium-223 should only be used as monotherapy, or in combination with luteinising hormone releasing hormone (LHRH) analogues, for the treatment of men with metastatic castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral metastases, and who are in progression after at least 2 prior lines of systemic therapy (other than LHRH analogues) or who are ineligible for any available systemic treatment
- radium-223 dichloride is not recommended in patients with a low level of osteoblastic bone metastases or in patients with asymptomatic bone metastases only
- carefully assess the benefits and risks of treatment before deciding whether to use radium-223 in patients with mildly symptomatic bone metastases (see below)
- do not use radium-223 in combination with, or within 5 days of discontinuation of, abiraterone acetate and prednisone/prednisolone
- the combination of radium-223 with other systemic cancer therapies other than LHRH analogues is not recommended; subsequent systemic cancer treatment should not be initiated for at least 30 days after the last administration of radium-223 dichloride
- radium-223 dichloride can cause fractures — assess bone health status and risk of fractures before and during treatment and closely monitor bone health for at least 24 months after discontinuation; consider the use of bisphosphonates or denosumab to reduce fracture risk
- report any suspected adverse drug reactions to Xofigo on a [Yellow Card](#)

### **Background and previous communications**

Xofigo ▼ was authorised in the EU in 2013 for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral metastases.

In December 2017, following preliminary data from the ERA-223 study, we advised that radium-223 dichloride should not be used in combination with abiraterone acetate and prednisone/prednisolone until a full review was completed of the study results and the benefit and risk of the medicine (see [Drug Safety Update, December 2017](#)). In March 2018, this recommendation became a contraindication against the use of Xofigo with abiraterone acetate (Zytiga) and prednisone/prednisolone until the completion of the review (see [letter sent to healthcare professionals](#)).

The [EU review has now concluded](#) and new restrictions and recommendations have been added to the [Summary of Product Characteristics](#) and a [letter sent to healthcare professionals](#). The reasons for these changes are outlined in the following sections.

### **Restricted indication**

Data from the randomised, double-blind, placebo-controlled [ERA-223 trial](#) show an increased incidence of fractures (29% versus 11%); a reduction in overall median survival (30.7 months versus 33.3 months; HR 1.195, 95% CI 0.950–1.505; p=0.13); and an increased risk of radiological non-bone progression (HR 1.376, 95% CI 0.972–1.948; p=0.07) among men receiving radium-223 in combination with abiraterone acetate plus prednisone/prednisolone (n=401) compared with men receiving placebo plus abiraterone acetate and prednisone/prednisolone (n=405), respectively. The population assessed in the ERA-223 trial were chemotherapy-naive with asymptomatic or mildly symptomatic, metastatic, castration-resistant prostate cancer.

In view of these risks, the indication for radium-223 has been restricted to men with symptomatic bone metastases and no known visceral metastases, who have received 2 previous systemic treatments for metastatic prostate cancer (other than LHRH analogues) or who cannot receive other systemic treatments.

### **Not recommended in men with a low level of osteoblastic bone metastases**

In a subgroup analysis of another randomised, double-blind, placebo-controlled phase 3 trial ([ALSYMPCA](#)), radium-223 treatment showed no significant improvement on overall survival (versus standard of care) in men with fewer than 6 metastases (HR for radium-223 vs placebo 0.901, 95% CI 0.553–1.466; p=0.674) or with a baseline total alkaline phosphatase lower than 220 U/L (HR 0.823, 95% CI 0.633–1.068; p=0.142). The use of radium-223 is therefore not recommended in men with a low level of osteoblastic bone metastases.

In mildly symptomatic patients, carefully assess the benefit and risks of treatment, considering that high osteoblastic activity is likely to be required for treatment benefit.

### **New restrictions for the use of radium-223 with other systemic anti-cancer therapies**

In addition to the contraindication for concomitant use of radium-223 with abiraterone and prednisone/prednisolone, radium-223 is not recommended to be initiated in the first 5 days following the last dose of abiraterone and prednisone/prednisolone. This allows for an adequate washout period for abiraterone acetate, based on its elimination half-life.

Also, it is possible that there is an increased risk of fracture and death when radium-223 is combined with other systemic cancer therapies. Therefore, combination of radium-223 with other systemic cancer therapies other than LHRH analogues is not recommended.

Data on a safe period after which systemic cancer treatment can be started following the final dose of radium-223 are limited. Based on the estimated biological half-life of radium-223 (6 days in bone and 5 days in whole body), subsequent systemic cancer treatment (including abiraterone acetate) should not be initiated for at least 30 days after the last administration of radium-223 dichloride.

### **New recommendations to minimise the risk of fractures**

The European review concluded that radium-223, either as monotherapy or in combination with an LHRH analogue, increases the risk of fractures, especially in patients with a history of osteoporosis or in patients with fewer than 6 bone metastases.

Before, during, and after treatment, in all patients, carefully assess and monitor bone status (for example, by scintigraphy, bone mineral density) and risk of fractures (for example, presence of osteoporosis, less than 6 bone metastases, medication increasing fracture risk, low body-mass index). In men with a high baseline risk of fracture, carefully consider the benefit of treatment against the risks.

Fractures have occurred for up to 24 months after the first dose of radium-223, therefore closely monitor bone health for at least 24 months after discontinuation.

Use of bisphosphonates or denosumab has been shown to reduce the incidence of fractures in patients treated with radium-223. Therefore, consider use of these medicines before starting or resuming treatment with radium-223.

### **Next steps**

Further studies will be conducted to characterise the efficacy and safety of radium-223. The results of an observational study are expected in 2020 and those of a Phase IV randomised double-blind study are due in 2024. Studies will look closely at the mechanisms responsible for the increased risk of fractures and possible increased mortality reported in the ERA-223 study.

### **Report any suspected adverse drug reactions**

Please continue to report any suspected adverse drug reactions associated with Xofigo to the MHRA through the [Yellow Card Scheme](#). When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, product brand name, and batch number.

*Article citation: Drug Safety Update volume 12, issue 2; September 2018: 2.*

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## **Daclizumab beta (Zinbryta ▼): risk of immune-mediated encephalitis – some cases several months after stopping treatment**

Monitoring for encephalitis should continue for 12 months following discontinuation of daclizumab. Inform all patients who have discontinued daclizumab and their caregivers of the common symptoms of encephalitis and the need to contact their doctor immediately if they occur.

### **Advice for healthcare professionals:**

- cases of immune-mediated encephalitis, including anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, have occurred several months after discontinuation of daclizumab
- prescribers should contact patients who have discontinued daclizumab and their caregivers and advise them to make contact immediately if any of the common prodromal symptoms or early common neuropsychiatric, behavioural, neurological, cognitive, or movement-related symptoms develop (see description below and in publications<sup>1-4</sup>)
- in patients presenting with atypical neuropsychiatric symptoms, a high index of clinical suspicion should be given for autoimmune encephalitis
- clinicians are advised to be vigilant for any symptoms suggestive of autoimmune encephalitis; monitoring for encephalitis should continue for 12 months following discontinuation of daclizumab
- be aware of a case of Glial fibrillary acidic protein (GFAP) $\alpha$  immunoglobulin G (IgG)-associated encephalitis in a patient being treated with daclizumab recently reported in the literature<sup>4</sup>
- if you suspect encephalitis in a patient who has discontinued daclizumab, consider testing for a broad panel of autoantibodies (eg, antigens for neuronal cell surface and synaptic proteins), including anti-NMDA receptor antibody in cerebrospinal fluid (CSF) and serum as early as possible
- ensure review of all suspected cases by a specialist in diagnosis and management of autoimmune encephalitis
- report suspected adverse drug reactions, including those which occur after the withdrawal of a medicine, to the [Yellow Card Scheme](#) without delay

### **Background**

In March 2018 the marketing authorisation for Zinbryta (daclizumab beta) was suspended and the medicine recalled from the EU market following reports of serious and potentially fatal immune reactions affecting the brain (including encephalitis and meningoencephalitis), liver, and other organs (see [Drug Safety Update, March 2018](#)). Physicians were advised to monitor patients at least monthly and more frequently as clinically indicated, for up to 6 months after the last dose.

In August 2018, the EMA was informed by the marketing authorisation holder of cases of immune-related encephalitis occurring following discontinuation of Zinbryta (see description below). In August 2018, [a letter was issued by the marketing authorisation holder to healthcare professionals](#) to inform them of this risk and of the updated recommendations. MHRA is issuing further advice in this article, following the recommendations of the UK's [Pharmacovigilance Expert Advisory Group](#).

## Cases of anti-NMDA receptor encephalitis, including presenting symptoms

As of 10 July 2018, 7 cases of encephalitis have been reported after discontinuation of daclizumab; 2 of them were confirmed as anti-NMDA receptor encephalitis (including 1 patient from the UK). Some of the other encephalitis cases were reported to have involved widespread rash, eczema, elevated liver enzymes, skin involvement, eosinophilia, and/or eosinophilic infiltrates.

The reported cases of anti-NMDA receptor encephalitis occurred around 3–4 months after discontinuation of Zinbryta. The patients with anti-NMDA receptor encephalitis presented with headache, fever, vomiting, confusion, tremor, visual disturbances, and seizures.

1. Graus F, et al.  
[A clinical approach to diagnosis of autoimmune encephalitis.](#)  
*Lancet Neurol*  
2016; 15: 391–404.

Autoimmune encephalitis can be a severe and persistently debilitating disorder. It can be fatal but is treatable with full or substantial recovery especially if diagnosed early and with prompt multidisciplinary management.<sup>1–3</sup> Where the outcome was reported, most patients in these cases have not fully recovered. The frequency of autoimmune encephalitis in association with daclizumab is unknown.

2. Liu H, et al.  
[Anti-N-methyl-D-aspartate receptor encephalitis associated with an ovarian teratoma: two cases report and anaesthesia considerations.](#)  
*BMC Anesthesiol*  
2015; 15: 150.

### Case of GFAP $\alpha$ IgG-associated encephalitis

On 15 July 2018, a [publication](#)<sup>4</sup> described a case of steroid-responsive GFAP $\alpha$  IgG-associated encephalitis in a patient on treatment with daclizumab. The patient demonstrated aggressive behaviour and occasionally expressed suicidal thoughts, then 4 months later was admitted to hospital due to fluctuating dysarthria, progressive memory loss, fatigue, and depression. The patient was treated with methylprednisolone and plasma exchange and partially improved.

3. Newman MP, et al.  
[Autoimmune encephalitis.](#)  
*Intern Med J*  
2016; 46: 148–57.

### Diagnosis of autoimmune encephalitis

Clinicians are advised to be vigilant for any symptoms suggestive of autoimmune encephalitis and to inform all patients previously treated with daclizumab and their caregivers about the possible presenting symptoms and what to do if they occur.

4. Luessi F, et al.  
[GFAP \$\alpha\$  IgG-associated encephalitis upon daclizumab treatment of MS.](#)  
*Neurol Neuroimmunol Neuroinflamm*  
2018; 5: e481.

If patients with multiple sclerosis present with atypical symptoms, especially neuropsychiatric symptoms, a full drug history should be taken and if found to be previously exposed to daclizumab, a high index of clinical suspicion should be given to autoimmune encephalitis.

If a case of encephalitis is suspected in a patient who has discontinued daclizumab, physicians should perform NMDA receptor antibody tests in cerebrospinal fluid and serum. Since a recent case of anti-GFAP encephalitis has also been reported,<sup>4</sup> testing for a broad panel of autoantibodies should also be conducted (eg, antigens for neuronal cell surface and synaptic proteins).

Ensure review of all suspected cases by a specialist in the diagnosis and management of autoimmune encephalitis. It is important to be aware that many patients may not have typical autoimmune encephalitis antibodies, thus a clinical diagnosis may be necessary and not consistently supported by investigations.

### Call for reporting

Report suspected adverse drug reactions, including those occurring after cessation of treatment, to the [Yellow Card Scheme](#) without delay.

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## **Nusinersen (Spinraza ▼): reports of communicating hydrocephalus; discuss symptoms with patients and carers and investigate urgently**

Advise patients and their caregivers to seek urgent medical attention if any signs or symptoms of communicating hydrocephalus develop during nusinersen therapy for spinal muscular atrophy. Patients with communicating hydrocephalus may require treatment with a cerebrospinal fluid (CSF) shunt.

### **Advice for healthcare professionals:**

- communicating hydrocephalus has been rarely reported during treatment with nusinersen; most cases developed after 2 to 4 loading doses
- discuss the risk of communicating hydrocephalus and its clinical features with patients and their caregivers
- advise them to seek urgent medical attention if any possible symptoms or signs develop including: persistent vomiting or headache, decreased consciousness, or a rapid increase in head size in children
- consider communicating hydrocephalus in the differential diagnosis of any patient with suggestive symptoms and signs and investigate them urgently
- refer patients with hydrocephalus to a neurosurgeon as soon as possible as they may require treatment with a CSF shunt
- if a CSF shunt is considered necessary, prescribers should inform patients and their carers that the benefits and risks of continued nusinersen treatment in patients with CSF shunts are not known (see below)
- report any suspected adverse drug reactions to nusinersen on a [Yellow Card](#), including hydrocephalus or any problems after insertion of a CSF shunt

### **Background**

Nusinersen (Spinraza ▼) is an antisense oligonucleotide indicated for the treatment of 5q spinal muscular atrophy that was first authorised in December 2016. Nusinersen is given intrathecally by lumbar puncture as 4 loading doses on days 0, 14, 28, and 63 of therapy, followed by maintenance doses every 4 months.

### **Reports of communicating hydrocephalus**

Worldwide, 5 cases of communicating hydrocephalus have been reported up to 6 July 2018 during routine clinical use of nusinersen. Of the 5 cases, 4 were children with spinal muscular atrophy type 1 who presented with signs of hydrocephalus after receiving 2 to 4 loading doses and one was an adult with scoliosis. Three of the children required cerebrospinal fluid (CSF) drainage procedures and continued nusinersen treatment (2 had ventriculoperitoneal shunts). One child did not require a CSF shunt and is being monitored after nusinersen was discontinued.

There is no known association between spinal muscular atrophy and communicating hydrocephalus and investigations did not reveal an underlying cause such as intracranial haemorrhage or infection.

Worldwide, up to 30 September 2017, approximately 1,437 patients have received nusinersen in routine clinical practice (439 patient-years). We have not received any reports of hydrocephalus associated with nusinersen treatment in the UK, although usage is currently very limited.

Discuss with patients, and their caregivers if necessary, the risk of hydrocephalus and advise them to seek urgent medical attention if any signs or symptoms of hydrocephalus develop including persistent vomiting or headache, seizures, decreased consciousness, or a rapid increase in head size in children.

Hydrocephalus should be considered in any patient with suggestive clinical features and confirmed cases should be referred urgently to a neurosurgeon for advice on further management.

The effectiveness and safety of nusinersen in patients with CSF shunts has not been determined. If nusinersen is continued, prescribers should continue to monitor the response to therapy. There are no data on the complication rate of CSF shunts with continued nusinersen treatment and the elimination rate of nusinersen from the central nervous system following CSF shunt insertion has not been determined. If a CSF shunt is required, patients and their carers should be informed that the risks and benefits of nusinersen in patients with CSF shunts are not known.

### **Next steps and continued monitoring**

The risk of hydrocephalus has been added to the [product information for nusinersen](#) and prescribing clinicians were informed of this risk by [letter in August 2018](#). As a new medicine, the benefits and risks of this medicine are being reviewed regularly, including any further data about the risk of hydrocephalus and the effectiveness and safety of nusinersen in patients with CSF shunts. The marketing authorisation holder is also conducting additional studies into the safety of nusinersen.

### **Report any suspected adverse drug reactions**

As for all medicines, MHRA will continue to closely monitor the safety of nusinersen. As a black triangle drug under the additional monitoring scheme, any suspected adverse drug reactions associated with nusinersen should be reported on a [Yellow Card](#), including signs or symptoms of hydrocephalus or any problems developing after insertion of a CSF shunt such as lack of efficacy or shunt dysfunction.

*Article citation: Drug Safety Update volume 12, issue 2; September 2018: 4.*

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## Letters and drug alerts sent to healthcare professionals in August 2018

In August 2018, the following letters were sent from marketing authorisation holders to healthcare professionals about the safety of medicines:

- Daclizumab beta (Zinbryta ▼): [Cases of immune-mediated encephalitis, including anti-NMDA receptor encephalitis, reported several months after discontinuation of treatment](#)
- Actilyse (Alteplase) in acute ischaemic stroke: [Important information on extension to use in adolescents \(≥16 years\) and request for data collection](#)
- Esmya (ulipristal acetate): [new contraindication, requirements for liver monitoring, and restricted indication](#)
- Xofigo ▼ (radium-223-dichloride): [new restrictions on use due to increased risk of fracture and trend for increased mortality](#)

In August 2018, MHRA issued the following [Alerts and recalls for drugs](#):

- [Nutriflex Omega Special 2500ml: Company-led recall](#)  
20 August 2018 - B. Braun Medical Ltd are recalling specific batches of Nutriflex Omega Special 2500ml as it has been identified that these may have an out of specification result in the glucose chamber at the end of their shelf life.
- [Nutriflex Lipid Special without Electrolytes 2500ml: Company-led recall](#)  
23 August 2018 – B. Braun Medical Ltd are recalling specific batches of Nutriflex Lipid Special without Electrolytes 2500ml as it has been identified that these may have an out of specification result in the glucose chamber at the end of their shelf life

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