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In this Edition

High-Strength Insulin Preparations

Several new high-strength insulin products have been approved for use throughout the EU since 2013*. High-strength insulin products contain a concentration of insulin which exceeds the standard 100 units/ml (e.g. they may contain 200 units/ml or 300 units/ml) and provides for a better dissolution profile over the duration of action, helping to meet an increasing need for higher doses while reducing the number and volume of injections. However, there are important differences in the way that high-strength insulin products are used compared with existing standard-strength insulin formulations. There is therefore a risk of medication error and accidental mix-up. Information and recommendations for use can be found in the product information (Summary of Product Characteristics (SmPC) and Package Leaflets (PLs)) for the individual insulin preparations.

The packaging and pre-filled syringes or pre-filled pens for high-strength insulins have been designed to mitigate the risk of medication error and mix-ups, with devices calibrated to ensure the correct dose of insulin is delivered. It is essential that insulins are not extracted from these devices for delivery by an insulin syringe. In addition, educational materials are available for the various high-strength insulin products which provide information on dosing, dose adjustment, and the need for dose conversion when switching between standard and high-strength products (if necessary), interchangability and monitoring as appropriate to the individual product.

Healthcare professionals and patients therefore need to understand the insulin strength of these products and how to use them correctly in order to minimise the risk of medication errors such as administering the wrong insulin dose. Prescribers should specify the strength in the prescription and ensure it is differentiated from the dose, for any products where both strengths are available. When dispensing products where there are two strengths available, pharmacists should confirm the strength, liaise with patients to reinforce advice as necessary. Patients should be reminded that the dose is in units on the pen and no calculations need to be made. Patients should also be advised to carefully check the units on the pen and use them to dial up their dose in units, seeking assistance if needed.

The European Medicines Agency (EMA) has published guidance on prevention of medication errors with high-strength insulins which provides further important information and guidance on the safe and effective use of these medicines. This was recommended as part of the *risk minimisation strategy for high-strength and fixed-combination insulin products* which is also available on the EMA website.

Electronic versions of educational materials approved by the HPRA for specific medicinal products on the Irish market are available on the HPRA website under *Educational Materials for Medicines*. Hard copy versions of these materials are available directly from the marketing authorisation holder of the specific product.

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Key Message

- Healthcare professionals and patients should be aware of the availability of high-strength insulin products coming onto the Irish market and that some product ranges may include both standard- strength and high-strength insulin preparations.
- Prior to starting treatment with any of these products or when switching from a standard-strength insulin to a high-strength insulin, prescribers should consult the product information (SmPC and PL) and any educational materials provided with these medicinal products.
- Healthcare professionals should ensure that patients and/or carers read and understand the package leaflet and any patient educational material provided with the product and receive appropriate training on the correct use of the product prior to use.
- Any reports of suspected adverse reactions associated with use of these products should be notified in the usual way.

**High-Strength insulin products include Tresiba, Humalog, and Toujeo. Further details on these products are available on www.hpra.ie and www.ema.europa.eu*

Antiretroviral medicines - updated advice on lipodystrophy and lactic acidosis

Product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for antiretrovirals, which are used for the treatment of HIV, has contained warnings in relation to lipodystrophy and lactic acidosis since early 2000 in line with clinical findings. Class Warnings for lactic acidosis applied only to nucleoside and nucleotide analogue medicines, whereas lipodystrophy warnings applied to all antiretroviral agents.

The European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) recently completed a review of the appropriateness and applicability of these warnings as they were being routinely applied to antiretroviral agents, but which may not now accurately reflect current scientific understanding.

Lipodystrophy

The review of the risk of lipodystrophy included lipoatrophy, lipoaccumulation and changes in blood-lipid levels:

Lipoatrophy

Previously lipoatrophy was considered to be associated with nucleoside reverse transcriptase inhibitors (NRTIs). The EU review noted that lipoatrophy was associated with reduced mitochondria levels in fat cells and therefore only related to substances with a high risk of mitochondrial toxicity i.e. zidovudine, stavudine and possibly didanosine. However lipoatrophy was not seen in regimens with other NRTI products. Instead treatment was associated with fat gain from improved HIV infection control.

Lipoaccumulation

There was no clear evidence that disproportional body-fat distribution was related to antiretroviral treatment.

Blood-lipid level changes

Warnings for increased blood-lipid levels were previously included in the product information (SmPC and PL) for protease inhibitors and for nucleoside and nucleotide analogues. Hyperglycaemia was also thought to be associated with protease inhibitors. Consistent with current HIV treatment guidelines (European AIDS Clinical Society. *Guidelines, version 8.0* October 2015.), product information will be amended to advise that weight gain and metabolic changes (such as lipid and glucose increases) may occur during treatment with any HIV medicine.

Lactic Acidosis

Warnings about the risk of lactic acidosis in association with antiretrovirals were previously only considered applicable to nucleoside and nucleotide analogues. The EU review looked at evidence from a range of sources including observational studies and case reports and the risk of lactic acidosis was considered to differ across the class, being most strongly associated with zidovudine, stavudine and didanosine. Therefore, in line with current evidence, warnings about lactic acidosis will be removed for nucleoside and nucleotide analogues, with the exception of products that contain zidovudine, stavudine or didanosine. For combination medicines, warnings relevant to any of the active substances will remain in the product information (SmPC and PL).

Key Message

- Product information for antiretrovirals will be updated to reflect current knowledge about lipodystrophy (including lipoatrophy) and lactic acidosis, so that patients and healthcare professionals can decide on treatment based on the most up-to-date advice.

** Further details on antiretrovirals are available on www.hpra.ie and www.ema.europa.eu*

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Natalizumab (Tysabri) - Updates to progressive multifocal leukoencephalopathy (PML) risk minimisation measures

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) recently completed a review of the known risk of progressive multifocal leukoencephalopathy (PML) with natalizumab (Tysabri) and has recommended new measures to minimise this risk. Following this review, healthcare professionals are reminded of the key measures to minimise the risk of PML and advised of important, new measures that may aid in earlier identification of PML, with the goal of further improving outcomes in those patients that develop PML.

Information for Healthcare Professionals

- Recent analyses suggest that:

- Early detection of PML is associated with improved outcomes and

- PML, which is clinically asymptomatic at diagnosis, can represent unilobar disease on MRI more often than symptomatic PML, with a higher survival rate and better clinical outcome.

- More frequent MRIs (e.g. every 3-6 months) using an abbreviated MRI protocol (FLAIR, T2-weighted and DW imaging) should be considered for patients at higher risk of PML.

`- In patients who have not received prior immunosuppressant therapy and are anti-JCV antibody positive, the level of anti-JCV antibody response (index) is associated with the level of risk for PML. Evidence suggests that the risk of PML is low at index value ≤0.9 and increases substantially at values above 1.5 in patients treated with natalizumab for more than two years.

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

- Are anti-JCV antibody positive, have received more than 2 years of natalizumab therapy and have received prior immunosuppressant therapy or,

- Have high anti-JCV antibody response (index), have received more than two years of natalizumab therapy and no prior history of immunosuppressant therapy.

- Patients with low anti-JCV antibody index values and no history of prior immunosuppressant use should be retested every six months once they reach the 2-year treatment point.

- Educational materials containing these new important measures are currently being prepared by the Marketing Authorisation Holder (MAH) and will be available for relevant healthcare professionals shortly.

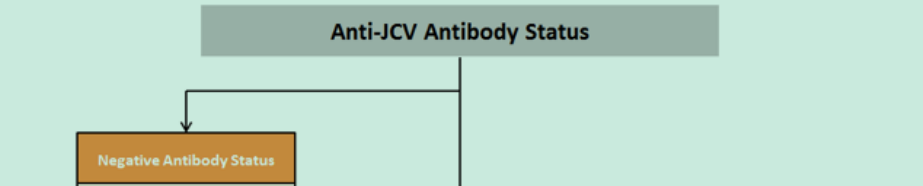
- A Direct Healthcare Professional Communication (DHPC) has been circulated by the Marketing Authorisation Holder (MAH-please see below) and the approved product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) will be updated appropriately.

Background Information

The risk of PML in patients receiving natilizumab is known to be higher in patients who are serum anti-JCV antibody positive, who have prior exposure to immunosuppressant therapy, and with increasing duration of natilizumab exposure (especially after two years).

Updated risk estimates for PML in natilizumab treated patients are available from several large clinical studies (see below). For patients with no prior immunosuppressant use, the table now includes information on the association between anti-JCV antibody response (index) and risk of developing PML.

Updated risk estimates for PML in natalizumab treated patients



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

'IS use' denotes immunosuppressant use

PML risk estimates in 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 clinical studies. Further stratification of PML risk by anti-JCV antibody index interval for patients with no prior history of immunosuppressant use was derived from combining the overall yearly risk with the antibody index distribution. The risk of PML in anti-JCV antibody negative patients was estimated based on post-marketing data from approximately 125,000 exposed patients.

The Physician Information and Management Guideline includes comprehensive information on the diagnosis, risk stratification and treatment of PML. This is being updated with the estimation of PML risk in the different patient subgroups. Treatment initiation and continuation forms along with the Patient Alert Card are also being updated, and a treatment discontinuation form is being introduced.

Key Message

- The risk of PML in patients receiving natalizumab is already known to be higher in patients who:
- Are anti-JCV antibody positive, have received more than two years of natalizumab therapy and have received prior immunosuppressant therapy or,
- Have high anti-JCV antibody response (index); have received more than two years of natalizumab therapy and no prior history of immunosuppressant therapy.
- During treatment with natalizumab, patients should be monitored at regular intervals for signs and symptoms of new neurological dysfunction. A full brain MRI should be performed at least once a year during treatment.
- For patients at higher risk of PML, more frequent MRIs (every 3-6 months) using an abbreviated protocol (e.g. FLAIR, T-weighted and DW imaging) should be considered.
- PML should be considered in the differential diagnosis of any patient treated with natalizumab, presenting with neurological symptoms and/or new brain lesions on an MRI.
- Treatment with natalizumab must be stopped if PML is suspected and until it has been excluded.
- Patients/carers should be advised to continue to be vigilant about the risk of PML for up to six months following discontinuation of natalizumab.
- Any suspected cases of PML should be reported to the HPRA (www.hpra.ie) using the usual reporting methods.

Further information on Tysabri is available at www.hpra.ie and www.ema.europa.eu

Fingolimod (Gilenya) - Risks related to its immunosuppressive effects

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) recently advised that healthcare professionals and patients be informed of recent product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) changes in relation to the immunosuppressive effect of fingolimod and to reiterate some important recommendations for use.

Fingolimod is a sphingosine-1-phosphate receptor modulator, metabolised by sphingosine kinase to the active metabolite fingolimod-phosphate. It is indicated as single disease modifying therapy in adult patients with highly active relapsing remitting multiple sclerosis despite a full and adequate course of treatment with at least one disease-modifying therapy. It has been approved in the US since September 2010 and for use across the EU since March 2011.

Due to its potent immunosuppressive effects, patients are at risk of serious adverse reactions and healthcare professionals are advised as follows:

Advice to Healthcare Professionals

Basal Cell Carcinoma (BCC)

- Cases of BCC have been reported in patients receiving fingolimod from both the clinical trial setting and post-marketing surveillance.
- Healthcare professionals and patients should be aware that vigilance for skin lesions is warranted.
- Medical evaluation of the skin is recommended at initiation, after at least one year and then at least yearly taking into consideration clinical judgement.
- Patients should be referred to a dermatologist if suspicious lesions are detected.
- Patients with active malignancies (including BCC) should not be treated with fingolimod.

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Opportunistic Infections

The immunosuppressive effects of fingolimod may increase the risk of CNS infections including opportunistic infections such as viral (e.g. herpes simplex virus, varicella zoster virus), fungal infections (e.g. cryptococcal meningitis) or bacterial infections (e.g. atypical mycobacterium). Prescribers are therefore reminded that:

- Initiation of treatment with fingolimod should be delayed in patients with severe active infection until the infection is completely resolved.
- The benefit-risk balance of using fingolimod should be considered for each individual patient prior to initiation of treatment and also prior to re-initiation of treatment.
- Suspension of treatment should be considered if a patient develops a serious infection.
- Following discontinuation of treatment, fingolimod may take up to two months to be eliminated from the body and healthcare professionals and patients should be alert for symptoms of infection during this period.

Lymphoma

- Cases of lymphoma have been reported in patients treated with fingolimod.

Progressive Multifocal Leukoencephalopathy (PML)

- PML is an opportunistic infection which may be fatal or result in severe disability and cases of PML have been reported in association with fingolimod.
- Before initiating treatment with fingolimod, a baseline MRI should be available (usually within 3 months as a reference).
- During routine MRI scans, healthcare professionals should pay attention to PML suggestive lesions.
- Patients and carers should be informed of the early symptoms suggestive of PML (e.g. change in behaviour/mood, memory lapses, speech difficulties) and recommended to seek immediate medical attention if any of these symptoms are experienced.
- If PML is suspected, treatment with fingolimod should be suspended until PML has been excluded.
- PML only occurs in the presence of a JCV infection. If JCV testing is undertaken however, it should be considered that the influence of lymphopenia on the accuracy of the anti-JCV antibody test has not been studied in fingolimod treated patients. Therefore a negative JCV antibody test does not preclude the possibility of subsequent JCV infection.

Complete Blood Count (CBC) Monitoring

- A recent (i.e. within the last six months or after discontinuation of prior therapy) complete blood count (CBC) should be available to healthcare professionals prior to initiating treatment with fingolimod to ensure that immune effects of previous therapy have resolved.
- Assessment of CBC is also recommended periodically during treatment i.e. three months after starting treatment and at least annually thereafter. CBC should also be measured in case of signs of infection.

Key Message

- In patients receiving fingolimod, medical evaluation of the skin before treatment initiation and during treatment is recommended due to a risk of BCC.
- Healthcare professionals/carers should be alert to the risk of PML and should inform patients/carers of early symptoms suggestive of PML recommending they seek medical advice if any experienced. During routine MRI scans, healthcare professionals should pay close attention to lesions suggestive of PML.
- Treatment with fingolimod should not be initiated in patients with severe active infection and suspension of treatment should be considered if a patient develops a serious infection.
- A complete blood count (CBC) should be available prior to initiating treatment and regular CBC is recommended (i.e. 3 months after commencing treatment and at least annually thereafter).
- A Direct Healthcare Professional Communication (DHPC) was circulated to relevant healthcare professionals in January and is available from the HPRA website.
- The product information for fingolimod (SmPC and PL) will be updated with this information.

Further information on Gilenya is available at www.hpra.ie and www.ema.europa.eu

Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter

PRODUCT	SAFETY ISSUE
SGLT2 inhibitors (Invokana, vokanamet, forxiga	Updated advice on the risk of diabetic ketoacidosis during treatment with SGLT2 inhibitors.
Zaltrap (aflibercept)	Information on the risk of osteonecrosis of the jaw.
Natalizumab (Tysabri)	Updates to PML risk minimisation measures.
Levonorgestrel Intrauterine Delivery Systems (Mirena and Jaydess)	Update on risk of perforation

Correspondence/Comments should be sent to the Pharmacovigilance Section, Health Products Regulatory Authority, contact details below.

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