



Topical tacrolimus (Protopic) – Important recommendations for appropriate use to minimise risks

Topical tacrolimus (Protopic) is a macrolide immunosuppressant authorised for use across the EU since 2002. It is available in two strengths (0.03% and 0.1%) and is indicated for use in patients with moderate to severe atopic dermatitis who failed to respond adequately, or were intolerant to conventional therapies such as topical corticosteroids.

Protopic should not be prescribed to patients under 2 years of age. The effect of treatment with Protopic on the developing immune system of children less than 2 years of age has not been established. Use of Protopic in children aged 2 to 16 years of age is restricted to the lower strength only i.e. Protopic 0.03% ointment. Protopic treatment should only be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis. For full details of the authorised indications see the [Summary of Product Characteristics \(SPC\)](#) on www.ema.europa.eu.

Prolonged systemic exposure to intensive immunosuppression following systemic administration of calcineurin inhibitors (in combination with other systemic immunosuppressants) has been associated with an increased risk of developing lymphomas and skin malignancies. There have been case reports of malignancies, including lymphomas and skin cancers in patients using tacrolimus ointment. Additionally, some published epidemiological studies have suggested a potentially increased risk for cutaneous T-cell lymphoma in patients treated with topical calcineurin inhibitors, including tacrolimus ointment.¹⁻³ As part of a Risk Management Plan agreed with regulatory authorities, further studies are ongoing or planned by the Marketing Authorisation Holder to investigate these risks.

This **information** was recently communicated to Healthcare Professionals and is available on www.imb.ie.

Advice for Healthcare Professionals

Prescribers are advised to strictly adhere to the authorised indications, patient populations and prescribing recommendations as outlined above and as follows:

- When used to treat active flares (twice daily), treatment should not be continuous on a long-term basis. If no signs of improvement are seen after two weeks of treatment, alternative treatment options should be considered.
- During maintenance use (twice weekly), patients should be monitored for response to therapy and the need for continued treatment should be evaluated. After 12 months treatment, a review of the patient's condition should be conducted and a decision taken whether to continue maintenance treatment based on an individual benefit-risk assessment. In children 2 to 16 years old, Protopic therapy should be stopped after 12 months to assess the need to continue this regimen and to evaluate the course of the disease.
- Protopic ointment should not be applied to lesions that are considered to be potentially malignant or pre-malignant.
- Lymphadenopathy present at initiation of therapy should be investigated and kept under review. Patients who receive Protopic and who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves.
- In case of persistent lymphadenopathy, the aetiology of the lymphadenopathy needs to be investigated. In the absence of a clear aetiology for the lymphadenopathy or in the presence of acute infectious mononucleosis, discontinuation of Protopic should be considered.
- Protopic should not be used in patients with

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congenital or acquired immunodeficiencies or in patients on therapy that cause immunosuppression.

- Exposure of the skin to sunlight should be minimised and the use of ultraviolet (UV) light (solarium, therapy with UVB or PUVA) should be avoided.
- Patients should be counselled on appropriate sun protection methods while undergoing treatment with Protopic, such as minimisation of the time in the sun, use of sunscreen and covering of the skin with appropriate clothing.
- When prescribing or dispensing Protopic, both at the time of first prescription and each time a prescription is refilled, patients should be advised to read the package leaflet and to discuss any concerns or uncertainties with a healthcare professional.
- Any suspected adverse reactions associated with the use of Protopic should be reported to the IMB.

Key Message

Some published epidemiological studies have suggested a potentially increased risk for cutaneous T-cell lymphoma in patients treated with topical calcineurin inhibitors, including tacrolimus ointment.

Healthcare Professionals should be aware of and adhere to the risk minimisation measures recommended in the SPC in relation to patient selection and on treatment monitoring including periodic review of response.

References available upon request from the Irish Medicines Board

Strontium (Protelos and Osseor) – Updates to product information on risks of venous thromboembolism and severe allergic skin reactions

Strontium has been authorised for use across the EU since 2004 for the treatment of osteoporosis in postmenopausal women to reduce the risk of vertebral and hip fractures.

A risk of venous thromboembolism (VTE) was identified from clinical studies at the time of first authorisation of strontium and cases of severe allergic skin reactions, such as DRESS (drug rash with eosinophilia and systemic symptoms), SJS (Stevens-Johnson syndrome) and TEN (toxic epidermal necrolysis) were reported post marketing. Information on both safety issues was included in the **product information** and was closely monitored at EU level.

A study analysing the side effects associated with strontium ranelate spontaneously reported in France from January 2006 to March 2009 noted 199 severe adverse reactions, of which 52% were cardiovascular

(most frequently VTE events) and 26% were cutaneous. In light of these new data, a review of the benefits and risks of strontium-containing medicines was undertaken at EU level.

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency reviewed all available data on these risks including data from clinical and non-clinical studies, population-based studies and post-marketing surveillance. Results from population-based studies and post-marketing surveillance showed that the risk of VTE is higher in patients with a history of VTE, as well as in patients who are temporarily or permanently immobilised. The CHMP recommended that strontium must not be used in these patients. As the number of cases of VTE in elderly patients (over 80 years of age) was shown to be higher with strontium in comparison with placebo, the CHMP also recommended that doctors re-evaluate the need for continued treatment in patients over 80 years of age at risk of VTE.

Regarding the risk of severe allergic skin reactions, the CHMP concluded that these serious side effects should continue to be kept under close surveillance, and that the warnings in the product information should be updated to include the signs and symptoms of DRESS, SJS and TEN, as well as their time to onset. The best results in managing these adverse reactions is associated with early diagnosis and discontinuation of treatment, patients should be advised to immediately stop treatment if they develop allergic reactions, and those who stop treatment should not re-start it at any time.

Advice to Healthcare Professionals

- Strontium containing medicines are now contraindicated in patients with VTE or a history of VTE, as well as in patients who are temporarily or permanently immobilised.
- When treating patients over 80 years of age at risk of VTE, prescribers should carefully re-evaluate the need to continue treatment with strontium.
- Patients should be informed of the likely signs and symptoms of severe skin reactions such as DRESS, SJS or TEN and advised to stop treatment immediately and permanently if symptoms of severe allergic skin reactions occur. These include extensive skin rashes, blisters, sores and flu-like symptoms.
- Strontium should be immediately discontinued in patients who develop DRESS, SJS or TEN, and treatment should not be re-started at any time in these patients.

Key Message

Strontium is now contraindicated in patients with VTE or a history of VTE, as well as in patients who are temporarily or permanently immobilised.

Strontium should be immediately discontinued in patients who develop DRESS, SJS or TEN, and not re-started at any time in these patients.



Vernakalant (Brinavess) – Risk of severe hypotension and bradycardia

Brinavess (vernakalant) is an intravenously administered anti-arrhythmic drug which was authorised for use across the EU in 2010 for rapid conversion of recent onset atrial fibrillation to sinus rhythm in adults:

- For non-surgery patients: atrial fibrillation ≤ 7 days duration
- For post-cardiac surgery patients: atrial fibrillation ≤ 3 days duration

Since authorisation, severe hypotension and bradycardia with Brinavess have been reported, including a case of cardiogenic shock with a fatal outcome that occurred in a clinical study (ACT V). Because of these safety concerns, the product information for Brinavess is being updated with strengthened recommendations for monitoring blood pressure and heart rate. Prescribers are reminded that it is important to use Brinavess according to the approved indications within the respective patient populations, as described in the [product information](#) (available on www.ema.europa.eu) and as outlined below.

Advice to Healthcare Professionals

Only well-qualified and experienced healthcare professionals should administer Brinavess I.V. infusion.

Before giving Brinavess

- As above, Brinavess should only be used in accordance with the requirements described in the product information.
- Patients must not be given any I.V. anti-arrhythmic drugs (class 1 or class 3) within 4 hours prior to, during or up to 4 hours after Brinavess administration.
- Patients should be assessed for signs and symptoms of cardiac failure before administration of vernakalant.
- Patients should be adequately anticoagulated, if necessary (*Please consult your local treatment guidelines on anticoagulation in AF*).
- Patients should be adequately hydrated and haemodynamically stabilised.
- Hypokalaemia (serum potassium < 3.5 mmol/L) should be corrected.

Monitoring advice

- Patients should be monitored for adverse events, which may occur after Brinavess administration, including hypotension, bradycardia, atrial flutter or ventricular arrhythmia. In clinical trials, patients with heart failure had a higher incidence of hypotensive adverse reactions than patients without heart failure. In heart failure patients, ventricular arrhythmia occurred more frequently with vernakalant than with placebo. Cases of severe hypotension have also been observed.
- During the entire duration of the infusion, and for at least 15 minutes after completion, patients should be monitored frequently for any signs or symptoms of a sudden decrease in blood pressure or heart rate. Patients should be further monitored for 2 hrs after the start of infusion and until clinical and ECG parameters have stabilised.
- If a patient develops any signs or symptoms indicating clinically meaningful bradycardia, has a clinically unintended drop in blood pressure, becomes hypotensive, or develops ECG changes (such as a clinically meaningful sinus pause, complete heart block, new bundle branch block, significant prolongation of the QRS or QT interval, changes consistent with ischaemia or infarction and ventricular arrhythmia), administration of Brinavess should be discontinued and appropriate medical management provided.
- Any suspected adverse reactions associated with the use of Brinavess should be reported to the IMB

Key Message

Cases of severe hypotension and bradycardia occurring with Brinavess have been reported, including a case of cardiogenic shock with a fatal outcome. Therefore, the recommendations for monitoring blood pressure and heart rate during and after Brinavess infusion have been strengthened.

Only a well-qualified healthcare professional should administer Brinavess.

During the entire duration of the infusion, and for at least 15 minutes after completion of the infusion, patients should be frequently monitored for any signs or symptoms of a sudden decrease in blood pressure or heart rate. If signs of a sudden decrease in blood pressure or heart rate develop, with or without symptomatic hypotension or bradycardia, the infusion must be stopped immediately.



Fingolimod (Gilenya) – Updated recommendations on cardiovascular monitoring during treatment initiation

Fingolimod (Gilenya) is a sphingosine-1-phosphate receptor modulator, metabolized by sphingosine kinase to the active metabolite fingolimod-phosphate which is indicated as single disease modifying therapy in patients with highly active relapsing remitting multiple sclerosis where patients have failed to respond to beta-interferon or in those with rapidly evolving severe relapsing remitting MS. It has been approved in the US since September 2010 and for use across the EU since March 2011.

From clinical trials, it was known that Gilenya causes transient bradycardia and might be associated with atrioventricular (AV) block. Warnings on these important cardiovascular effects were included in the **product information** and it was recommended that patients should be observed for signs and symptoms of bradycardia for at least six hours after the first dose (or when two weeks had elapsed since the last dose).

Following the death of a patient in the US within 24 hours of taking the medicine for the first time and other reported adverse events, a review of the cardiovascular safety of Gilenya was undertaken at EU level. The CHMP reviewed the available safety data from clinical studies and post-marketing surveillance and also considered the circumstances surrounding the reported cases of sudden or unexplained death in patients treated with Gilenya. Most of the deaths and cardiovascular disorders occurred in those patients with a history of cardiovascular disease and/or taking other medicines. However, the data reviewed were not conclusive as regards a causal relationship between Gilenya and the deaths.

The CHMP considered that there is clear evidence of the benefit of Gilenya in relapsing-remitting multiple sclerosis. However, considering that certain patients have an increased risk of cardiovascular disorders, particularly those with a history of cardiovascular or cerebrovascular disease and those who are taking other medicines that induce bradycardia (see below), the CHMP concluded that Gilenya cannot be recommended in these patients. However, if treatment is nonetheless considered necessary, advice from a cardiologist should be sought and patients should be monitored and managed as outlined below.

The CHMP also noted that the maximum effect of Gilenya on decreasing the heart rate occurred within six hours after the first dose in most patients. Therefore, it was recommended that the product information be amended to further strengthen the warnings on the cardiovascular effects of the medicine and to ensure

close monitoring of all patients, particularly during the six hours after the first dose. Blood pressure, heart rate and ECG should be checked pre-administration and at least hourly following the first dose. Continuous ECG monitoring for the first six hours is also recommended. If the heart rate is at its lowest at the six hour time point, monitoring should be extended by a further two hours and until the heart rate increases again. In addition, if patients develop any relevant cardiac disorders during this six hour period i.e. presence of HR < 45 beats per min, QTc \geq 500 msec, persistent new-onset 2nd degree AV block, Mobitz Type I block or higher degree AV block at the six hour time point or occurrence at any time during the initial six-hour monitoring period of new onset 3rd degree AV block, then monitoring should be extended at least overnight and until resolution.

Advice to Healthcare Professionals

Patient Selection

Gilenya is not recommended in patients:

- a) With the following conditions:
 - 2nd degree Mobitz Type II or higher degree AV block, Sick-sinus syndrome, or Sino-atrial heart block
 - Significant QT prolongation (QTc > 470 msec (female) or > 450 msec (males))
 - History of symptomatic bradycardia or recurrent syncope, known ischaemic heart disease, cerebrovascular disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, uncontrolled hypertension, or severe sleep apnoea.
- b) Receiving the following antiarrhythmic or heart-rate-lowering drugs:
 - Class Ia (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol) antiarrhythmics.
 - Beta blockers
 - Heart rate lowering calcium channel blockers (e.g. verapamil, diltiazem or ivabradine)
 - Other substances which may decrease heart rate (e.g. digoxin, anticholinesterase agents or pilocarpine).

In such patients, treatment with Gilenya should be considered only if the anticipated benefits outweigh the potential risks and advice from a cardiologist should be sought prior to initiation of treatment including, if appropriate, the possibility to switch to non heart rate lowering drugs. If treatment with Gilenya is considered for these patients, monitoring at least overnight should be initiated.



Monitoring Advice

For all patients, monitoring should include:

- A 12-lead ECG and blood pressure measurement before starting the first dose and after six hours
- Blood pressure and heart rate measurement every hour after the first dose for six hours
- During the first six hours of treatment, continuous ECG monitoring is recommended
- If the patient's heart rate at the end of the six-hour period is the lowest following first dose administration, monitoring should be extended by at least two hours and until the heart rate increases

Criteria for extended monitoring:

In those patients with evidence of clinically important cardiac effects during the first six hours of treatment, monitoring should be extended, including at least overnight monitoring, until resolution. Recommended criteria for extending monitoring include:

- The occurrence at **anytime** during the monitoring period after first dose of
 - New onset 3rd degree atrioventricular block
- The presence **at the end** of the monitoring period after first dose of

- Heart rate less than 45 beats per minute
- QTc interval ≥ 500 msec.
- Persistent new-onset 2nd degree atrioventricular block, Mobitz Type I (Wenckebach) or higher degree atrioventricular block

Any suspected adverse reactions associated with use of Gilenya should be reported to the IMB

Key Message

Gilenya is not recommended in patient groups at high risk of cardiovascular adverse events, such as those with significant QT prolongation or history of bradycardia, ischaemic heart disease, cardiac failure, cerebrovascular disease, uncontrolled hypertension, and those receiving antiarrhythmic or heart-rate lowering drugs.

Monitoring advice after the first dose has been updated. All patients should be monitored before, during, and immediately after the first six hours of treatment. If the patient's heart rate decreases to its lowest point at the end of the six-hour treatment period, monitoring should be extended at least overnight and until resolution.

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

Product	Safety Issue
Adenuric (febuxostat)	Risk of serious hypersensitivity reactions.
Fastum Gel (ketoprofen)	Reminder of contraindications and photosensitivity preventative measures.
Gilenya (fingolimod)	Recommendations for cardiovascular monitoring during treatment initiation.
Perfalgan (intravenous paracetamol)	Risk of accidental overdose in neonates and infants.
Protelos/Osseor (strontium)	New contraindications and warnings.
Protopic (tacrolimus)	Recommendations for appropriate use and risk minimisation measures.
Saizen Solution for Injection (Somatropin)	Risk of unintentional overdose when switching patients on Saizen powder to Saizen Solution for Injection.
Somavert (pegvisomant)	Reminder for enhance vigilance following change to manufacturing process.
Tolvaptan (Samsca)	Close monitoring of serum sodium recommended during treatment.
ViaSpan Solution for Organ Preservation	Potential for product contamination.



Blue dye* – containing products – Risk of serious allergic reactions with off-label use

(*Patent Blue V, Sulphan blue and Methylene blue)

The Pharmacovigilance Working Party (PhVWP) of the European Medicines Agency recently conducted a review of all relevant data relating to the risk of allergic reactions with the use of blue dyes in sentinel lymph node biopsy following concerns raised in some EU member states. In Ireland, blue dyes are not authorised for use for lymphatic mapping during breast tumour surgery. The PhVWP evaluation concluded that blue dyes, used for lymphatic mapping during breast tumour surgery, may cause serious allergic reactions, including anaphylaxis, and recommended that emergency facilities are available for at least 1 hour after their administration.

Sulphan Blue (Isosulphan Blue) and Patent Blue V-containing products are not authorised in Ireland. Methylthioninium Chloride Proveblue was recently authorised for use across the EU for acute symptomatic treatment of medicinal and chemical products-induced methaemoglobinaemia in adults, children and adolescents (aged 0 to 17 years old). It is not indicated for use in sentinel lymph node biopsy.

Further details of the review are available in the **PhVMP monthly report for April**, available under 'publications' on the IMB website.

Any suspected adverse reactions with blue-dye-containing products should be reported to the IMB.

Key Message

Healthcare professionals should be aware of the outcome of an EU review which concluded that blue dyes, used for lymphatic mapping during breast tumour surgery, may cause serious allergic reactions (including anaphylaxis).

Antipsychotics* – Risk of extra- pyramidal effects and withdrawal symptoms in newborns following exposure during pregnancy

The PhVWP recently reviewed data from worldwide spontaneous reporting and information made available by the US Food and Drug Administration (FDA)¹ on neonatal withdrawal syndrome and extrapyramidal effects in newborns, associated with antipsychotics. Reports included cases of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder. The review concluded that the available data indicate a risk of extrapyramidal effects and of withdrawal symptoms in newborns following maternal use of antipsychotics during the third trimester of pregnancy and therefore neonates should be monitored carefully. Although the data was limited for some antipsychotics, the PhVWP agreed that these effects are likely to be a class effect and recommended that the available information be reflected in the product information for all antipsychotics in the EU.

Key message

Neonates exposed to antipsychotics during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. Consequently, newborns should be monitored carefully.

1. U.S. Food and Drug Administration Drug Safety Communication: antipsychotic drug labels updated on use during pregnancy and risk of abnormal muscle movements and withdrawal symptoms in newborns. Silver Spring, MD: US FDA; 22 February 2011.

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Drug Safety – June 2012 – Issue Number 48

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