



### Tredaptive (Nicotinic Acid/Laropiprant) – Suspension of Marketing Authorisation

Tredaptive, a fixed dose combination product containing extended release nicotinic acid (1000 mg) and laropiprant (20mg), was authorised for use across the EU in 2008 for the treatment of dyslipidaemia in adults, particularly in patients with combined mixed dyslipidaemia and primary hypercholesterolaemia. It was used in combination with a statin, when the cholesterol lowering effect of statin treatment alone was not sufficient or in patients unable to take statins.

An EU wide **review** of Tredaptive was started in December 2012 after new data from a large, long-term study (HPS2-THRIVE) involving approximately 25,000 patients suggested that the benefits of these medicines did not outweigh the risks.

The preliminary results of the study indicated that adding Tredaptive to statin therapy did not provide significant additional benefit in reducing the risk of major vascular events such as heart attack and stroke, compared with statin therapy alone. In addition, a higher frequency of non-fatal but serious adverse events were seen in patients taking Tredaptive with statin therapy compared with patients taking statin therapy alone. These events included bleeding, myopathy, infections and new-onset diabetes. Following initiation of the review, a **letter** was sent to healthcare professionals highlighting the new information and advising that new patients should not be started on Tredaptive. The review was completed in January 2013, which concluded that the benefit-risk balance for Tredaptive was considered negative, and the medicine has now been recalled.

#### Advice for Healthcare Professionals

- The recall of Tredaptive commenced on 21st January 2013.
- Pharmacists should refer any patients presenting with prescriptions for Tredaptive to the treating doctor.
- Patients who have been treated should be reviewed to facilitate discontinuation of Tredaptive
- Any patients currently taking Tredaptive should make a non-urgent appointment with their doctor to discuss their treatment.

#### Key Message

- **The supply of Tredaptive has been suspended after the results of the HPS2-THRIVE trial suggested that the benefits of this medicine do not exceed the risks**

#### Contact Details

Have we got the correct contact details for you to ensure that you are receiving this Drug Safety Newsletter (DSN) promptly and in the most convenient way to support your review and use of it?

If there are any errors in the contact information used to provide the DSN to you, then please do not hesitate to let us know, by contacting [imbpharmacovigilance@imb.ie](mailto:imbpharmacovigilance@imb.ie)

Please also see the back page of this publication regarding email access to the Drug Safety Newsletter and also IMB alerts.

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## Restriction of indications for trimetazidine (Vastarel)

Trimetazidine (Vastarel)\* is an anti-anginal medicine which is now indicated only for use in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line anti-anginal therapies. This followed an EU review of all available data on the benefits and risks of these medicines. For all other indications, the review concluded that the efficacy of treatment in the context of current guidance was not sufficiently documented and as such, the benefits of trimetazidine no longer outweigh the risks. It was therefore recommended that these indications should be withdrawn from the marketing authorisation. Accordingly, trimetazidine-containing products should no longer be prescribed for the treatment of patients with tinnitus, vertigo or disturbances in vision.

The review of trimetazidine-containing products was initiated because of concerns that the efficacy of these products was not sufficiently demonstrated. There were also reports regarding the occurrence of movement disorders such as Parkinsonian symptoms, restless leg syndrome, tremors and gait instability associated with the medicines. Although cases which have been reported were usually reversible on discontinuation of treatment, use of trimetazidine is now contraindicated in patients with Parkinsons disease, parkinsonian symptoms, tremors, restless leg syndrome or other related movement disorders. Trimetazidine should be discontinued permanently in patients who develop movement disorders such as Parkinsonian symptoms. If Parkinsonian symptoms persist for more than four months after discontinuation, a neurologist's opinion should be sought.

Use of trimetazidine is now also contraindicated in patients with severe renal impairment and caution is advised in elderly patients older than 75 years old and in patients with moderate renal impairment. A dose reduction is recommended in patients with moderate impairment and in elderly patients that may have increased trimetazidine exposure due to age-related decrease in renal function.

## Advice for Healthcare Professionals

- Trimetazidine-containing products should only be prescribed in adult patients as add-on therapy for the symptomatic treatment of stable angina pectoris inadequately controlled by first-line anti-anginal therapies or to patients intolerant to such therapy.
- Trimetazidine is no longer indicated in the symptomatic treatment of vertigo, tinnitus or disturbances in vision.
- Trimetazidine should not be used in patients with Parkinsons disease, parkinsonian symptoms, tremors, restless leg syndrome and other related movement disorders.
- Trimetazidine should not be used in patients with severe renal impairment. For patients with moderate renal impairment and the elderly that may have increased trimetazidine exposure due to age-related decrease in renal function, the dose should be reduced.

### Key Message

- **The indication for use of trimetazidine-containing products has been restricted to use in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first line anti-anginal therapies.**
- **Treatment with trimetazidine should be discontinued permanently in patients who develop movement disorders such as Parkinsonian symptoms and neurological advice should be sought if symptoms persist for more than four months following discontinuation.**

\* The product information is currently being updated and should be consulted for full details of all the changes.



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## Adverse Reaction Reporting

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The IMB greatly appreciates the contribution of busy healthcare professionals in reporting suspected adverse reactions, facilitating the continued surveillance of the safety of medicines. While the time-consuming nature of form-filling and the provision of follow-up information to the IMB is recognised, the collection and evaluation of comprehensive reports is essential to ensure that appropriately detailed case information is available for the continuous surveillance of the safety of medicines. Such reports are essential for the IMB to ensure that regulatory action/proposals take account of all available data. There are several options in place for reporting suspected adverse reactions to the IMB. These are as follows:

- By following the links to the online reporting options accessible from the [IMB homepage](#),
- Using the downloadable report form also accessible from the [IMB website](#), which may be completed manually and submitted to the IMB via 'freepost'
- Using the traditional 'yellow card' report, which also utilises a freepost system
- By telephone to the IMB Pharmacovigilance Section (01 – 6764971)

Please note that certain mandatory fields are required to successfully submit an adverse reaction report via the online systems. These include reporter details and a contact address. The latter facilitates return of a unique report identifier number, as a confirmation of a successfully submitted report. Once submitted, a hyperlink is provided, which allows a PDF of the report to be generated as a record. A PDF of the report is also attached to the acknowledgement email.

In addition and in line with international guidance for adverse reaction reporting, the minimum criteria for an adverse reaction report must be provided:

- An identifiable patient (i.e. patient initials/age/sex/record number)
- An identifiable medicinal product (i.e. product name or active substance if brand is unavailable)
- An identifiable reporter
- An identifiable reaction

While these elements reflect the minimum criteria essential for a 'valid' adverse reaction report, additional information regarding the details relating to the reaction and the patient, such as relevant medical history, concomitant treatment(s), action taken with the medicine, patient outcomes and any relevant in-use circumstances are also extremely helpful in the evaluation of a suspected adverse

reaction. Provision of this information also helps in reducing the need for subsequent follow up of individual case reports.

### Key Message

A variety of options exist to facilitate adverse reaction reporting. Please use the one best suited to your practice and provide as much information as possible to facilitate case report evaluation.

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## Use of the IMB online ADR report forms and Drug Safety Newsletter (DSN) for CPD purposes

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The Irish Academy of Continuing Medical Education (*iaCME*) is an independent, provider of accredited CPD for healthcare professionals using e-learning and web based technologies. It was established and developed to meet current CPD requirements and is operated by Irish healthcare professionals (including pharmacists and a GP) who have extensive experience in the area of medicines regulation and quality management, as well as CPD. Their mission is "To enhance professional competence and patient care by providing a world class on-line CPD resource".

As part of the CPD services provided by *iaCME*, they have developed a module on ADR reporting, which includes a screencast in the training materials that follows the entry of details in the IMB online ADR report form.

*iaCME* has also developed a series of CPD modules based on the information and advice for Healthcare Professionals included in the IMB's Drug Safety Newsletter (DSN). The DSN can be used for practice-based CPD to enhance knowledge in relation to the safety of medicines and to support healthcare professionals in applying learnings from the newsletter to their individual practices. This resource is offered free of charge to healthcare professionals and may be accessed via a [dedicated link](#) on the IMB website under 'Human Medicines-Resources for Healthcare Professionals'.

On successful completion of a module, a downloadable personalised certificate is provided to users reflecting the CPD activity and acting as a record, customised for each specific edition of the newsletter.

The e-learning activities available via *iaCME* have up to now been accredited under the RCGP's EPASS scheme. An application for national accreditation for the 2013 editions of the DSN is now underway with professional training bodies in Ireland.

Further information is available from the *iaCME* website (<http://www.iacme.ie/>)



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

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Product	Safety Issue
<b>Tisseel Lyo</b> , Tisseel Ready to use and Artiss Solutions for Sealant fibrin (Human Fibrinogen)	Risk of air or gas embolism with inappropriate use (too high pressure, too short distance) of spray devices administering sealant products
<b>Gilenya</b> (fingolimod)	Guidance on repeat “first dose cardiovascular monitoring” in case of treatment interruption
<b>Tredaptive</b> (nicotinic acid/laropiprant)	Recommendation not to start new patients on Tredaptive in light of results of HPS2-THRIVE cardiovascular outcomes study, which did not achieve primary endpoint.
<b>Tredaptive</b> (nicotinic acid/laropiprant)	Information on suspension of this medicine
<b>Tredaptive</b> (nicotinic acid/laropiprant)	Treatment with Tredaptive should be discontinued
<b>Pradaxa</b> (dabigatran etexilate)	Notification relating to the product being contraindicated in the patients with prosthetic heart valve requiring anticoagulant treatment.
<b>Angiox</b> (bivalirudin)	Communication on approved dosing regimens for Angiox (bivalirudin) undergoing percutaneous coronary intervention (PCI)
<b>Acetylcysteine</b> (Parvolex)	Paracetamol overdose: New guidance on treatment with intravenous acetylcysteine
<b>Revlimid</b> (Lenalidomide)	Communication on the risk of hepatic disorders associated with Revlimid (Lenalidomide) use, in the context of other risk factors.
<b>Xagrid</b> (Anagrelide Hydrochloride)	Communciation on the association of Xagrid with cardiovascular risk in patients with essential thrombocythaemia (ET) whatever the patient’s medical history or medical condition is. Also a reminder that Xagrid is indicated as a second line therapy in at-risk patients.

### View the Drug Safety Newsletter online or via email

The IMB publishes an electronic version of the Drug Safety Newsletter on its website, [www.imb.ie](http://www.imb.ie). Should you wish to receive an email alert notifying you that future editions of the newsletter are available online, please submit your request to [imbpharmacovigilance@imb.ie](mailto:imbpharmacovigilance@imb.ie). Alternatively the electronic version can be emailed directly to you. Signing up to this service will ensure you no longer receive a print version. The online edition is in PDF format, thus allowing you to save the newsletter and/or print specific pages. The online version will also contain hyperlinks to the product information and other documents on the IMB and EMA websites. By signing up to this environmentally friendly online service, you will receive prompt notification of publications and will assist the IMB to reduce postage, production and related costs.



IRISH MEDICINES BOARD

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