



### **Clopidogrel and Proton Pump Inhibitors: Updated recommendations on interaction potential**

#### **Background:**

Clopidogrel is indicated for the prevention of atherothrombotic events in patients who have had a myocardial infarction or ischaemic stroke, or who have established peripheral arterial disease. The combination of clopidogrel (brand name Plavix) and aspirin may be used to prevent atherothrombotic events in patients with acute coronary syndrome.

Proton pump inhibitors (PPIs) are indicated for the treatment of oesophageal reflux disease, dyspepsia, or gastric ulcers, and are frequently co-prescribed with clopidogrel.

#### **Updated recommendation:**

The previous advice on the concomitant use of clopidogrel with proton pump inhibitors has now been modified in the context of additional data. Use of either omeprazole or esomeprazole with clopidogrel should be discouraged. The current evidence does not support extending this advice to other PPIs.

#### **Previous advice regarding interaction potential:**

Following assessment of available data in May 2009, the EU Committee for Medicinal Products

for Human Use (CHMP) concluded that concomitant use of any PPIs with clopidogrel should be avoided unless considered essential. The product information for clopidogrel was consequently updated on the basis of pharmacokinetic, pharmacodynamic, and some clinical outcome data, which demonstrated that omeprazole competitively inhibits the CYP2C19 isoenzyme (which metabolises clopidogrel to its active metabolite)<sup>1</sup> reduces the ability of clopidogrel to inhibit platelet aggregation<sup>2,3</sup> and reduces the beneficial effect of clopidogrel in patients.<sup>4,5</sup> Although evidence for a similar effect on clopidogrel metabolism with the other PPIs was relatively sparse, a precautionary approach for the whole class was adopted in light of the findings of some clinical outcome studies suggesting an attenuation of the cardioprotective effect of clopidogrel by PPIs other than omeprazole.<sup>6</sup>

#### **New evidence supporting updated recommendations:**

Since the 2009 review, new evidence has become available which, although having some methodological limitations, casts some doubt on the clinical relevance of possible interactions between clopidogrel and PPIs as a class effect. However, the evidence supporting an interaction with omeprazole and esomeprazole remains.

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Recent (unpublished) mechanistic studies in healthy volunteers have indicated that the addition of omeprazole to clopidogrel therapy reduces the inhibition of platelet aggregation, whether the two medicines are given simultaneously or 12 hours apart. However, post hoc analyses from the PRINCIPLE-TIMI and TRITON-TIMI trials<sup>7</sup> found that use of PPIs (unspecified) reduced platelet function in patients who were randomly assigned clopidogrel, but did not affect clinical outcome.

The COGENT study,<sup>8</sup> which randomly allocated patients to clopidogrel with or without omeprazole, found no effect of concomitant omeprazole on cardiovascular outcome (this study was terminated early after 133 days).

A retrospective study<sup>9</sup> of cardiovascular and gastrointestinal outcome in patients on clopidogrel and aspirin with and without gastroprotective agents found that although PPI use was associated with an increase in adverse cardiovascular events, it was also associated with a significantly reduced incidence of upper GI bleeding. The available evidence for an interaction between clopidogrel and PPIs is therefore not completely consistent. Nevertheless, pharmacokinetic, pharmacodynamic, and some clinical outcome data suggest a significant interaction for omeprazole, and there is also some evidence in relation to esomeprazole.

It is possible that the findings of clinical studies for the different PPIs are inconsistent because there is true variation in the extent to which they interact with clopidogrel. This inconsistency may also reflect several variables including an individual's pharmacogenetics, medication compliance, and comorbidities; the doses of clopidogrel and the relevant PPI; and the study design.

In light of the most recent evidence, the previous advice (to avoid all PPIs unless absolutely necessary for patients taking clopidogrel) is no longer considered necessary. Nevertheless, as a precaution, concomitant use of clopidogrel with omeprazole or

esomeprazole should be discouraged. Product information will be updated to reflect the latest recommendations.

The current evidence does not support extending this advice to other PPIs. However, because it is not possible to completely exclude a possible interaction with these PPIs on the basis of available data, the potential risk of a slight reduction in efficacy of clopidogrel should be considered in the context of the potential gastrointestinal benefit of the PPI.

**Key message:**

**In light of the most recent evidence, the previous advice on the concomitant use of clopidogrel with proton pump inhibitors has now been modified. Use of either omeprazole or esomeprazole with clopidogrel should be discouraged. The current evidence does not support extending this advice to other PPIs.**

**Advice to Healthcare Professionals:**

- Concomitant use of clopidogrel and omeprazole or esomeprazole is to be discouraged unless considered essential.
- Consider PPIs other than omeprazole or esomeprazole in patients who are taking clopidogrel. Other gastrointestinal therapy such as H2 blockers (except cimetidine) or antacids may be more suitable in some patients.
- Discourage concomitant use of other known CYP2C19-inhibiting medicines with clopidogrel because these are expected to have a similar effect to omeprazole and esomeprazole (CYP2C19 inhibitors include fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine, and chloramphenicol).

*A list of references is available on request from the Irish Medicines Board.*



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## **Exelon (rivastigmine) transdermal patch – Medication errors and risk of overdose**

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### **Indications and posology:**

Exelon transdermal patches contain rivastigmine and are indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia. It is available in two dosage strengths 4.6 mg /24 hours and 9.5 mg /24 hours. Treatment is started with 4.6 mg /24h. After a minimum of four weeks and if well tolerated, as assessed by the treating physicians, the daily dose should be increased to 9.5 mg /24h which is the recommended effective dose. The Summary of Product Characteristics provides guidance on switching from oral rivastigmine to the transdermal patch presentation.

### **Medication errors and risk of overdose:**

Cases of overdose have been reported with Exelon transdermal patches following inappropriate use and medication errors. Serious medical outcomes including death may occur if medication errors and inappropriate use are not detected promptly and not managed appropriately. In some cases of accidental overdose the patient may not display any symptoms. Where symptoms are present, they may include nausea, vomiting, diarrhoea, hypertension and hallucinations. Due to the known vagotonic effect of cholinesterase inhibitors on heart rate, bradycardia and/or syncope may also occur. As rivastigmine has a plasma half-life of about 3.4 hours and a duration of acetyl-cholinesterase inhibition of about 9 hours, it is recommended that in cases of asymptomatic overdose, all Exelon transdermal patches should be removed immediately and no further transdermal patch should be applied for the next 24 hours. In overdose accompanied by severe nausea and vomiting, the use of antiemetics should be considered. Symptomatic treatment for other

adverse reactions should be given as necessary. The product information should be consulted for guidance on managing the patient in the event of a suspected overdose. A letter approved by the IMB was sent to healthcare professionals by the Marketing Authorisation Holder in April 2010, regarding the updated product information for Exelon transdermal patches and is available on the IMB website.

The most frequent causes of overdose are lack of patch removal and application of more than one patch at a time.

#### **Key Messages:**

**Patients and carers need to be instructed on the appropriate use of the transdermal patch and in particular should be advised that:**

- **Only one patch should be applied per day to healthy skin on one of the recommended locations: the upper or lower back, or upper arm or chest.**
- **The patch should be replaced by a new one after 24 hours, and the previous day's patch must be removed before applying a new patch to a different skin location.**
- **To minimize skin irritation, application to the same site location within 14 days should be avoided.**
- **The transdermal patch should not be cut into pieces.**

**Exelon patches should only be used in accordance with the approved administration instructions. Patients and their carers should be comprehensively advised on the appropriate use of the products.**



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## **Intravenous zoledronic acid and updated information on adverse effects on renal function**

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- Zoledronic acid 5 mg for infusion (**Aclasta**) is used for the once-yearly treatment of osteoporosis in patients at increased risk of fracture, and as a single dose for the treatment of Paget's disease of the bone.
- Zoledronic acid 4 mg for infusion (**Zometa**) is given every 3–4 weeks for the reduction of bone damage in advanced malignancies involving bone, and as a single dose for tumour-induced hypercalcaemia.

Zoledronic acid has been associated with reports of renal impairment and renal failure, especially in patients with pre-existing renal dysfunction or other risk factors. The product information for Zometa already contains substantial warnings and precautions regarding renal impairment and renal failure.

Warnings in the product information for Aclasta are now being strengthened following reports of renal failure or renal impairment with its use. Up to August 2009, there have been 139 reports of renal impairment or renal failure worldwide, following the administration of Aclasta. The majority of cases were associated with the first dose, and generally occurred in patients with pre-existing renal dysfunction or other risk factors, including: advanced age; use of concomitant nephrotoxic drugs or diuretic therapy; or dehydration. Renal failure requiring dialysis or resulting in death has occurred in some at-risk patients. A letter approved by the IMB was sent by the Marketing Authorisation Holder to healthcare professionals in March 2010, regarding the updated product information for Aclasta and this letter is available on the IMB website.

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

#### **For all patients receiving zoledronic acid**

- Renal function should be measured before each infusion of zoledronic acid
- Patients, especially elderly patients and those receiving diuretic therapy, should be appropriately hydrated before administration of zoledronic acid
- The duration of infusion of zoledronic acid should be at least 15 minutes
- Monitoring of renal function after zoledronic

acid infusion should be considered, particularly in at-risk patients such as: those with pre-existing renal dysfunction; those of advanced age; those using concomitant nephrotoxic drugs or diuretic therapy; or those who are de-hydrated

- Zoledronic acid should be used with caution when used concomitantly with medicines that could affect renal function

#### **For patients receiving Aclasta**

- A single dose of Aclasta for the treatment of osteoporosis and Paget's disease of the bone should not exceed 5 mg
- Aclasta should not be used in patients with creatinine clearance <35 mL/min

#### **For patients receiving Zometa**

- The recommended dose for Zometa in patients with normal renal function is 4 mg, which should be reduced in patients with mild-to-moderate renal impairment
- Zometa for cancer treatment is not recommended for use in patients with creatinine clearance <30 mL/min, and should only be considered for the treatment of hypercalcaemia in cancer patients with severe renal impairment after evaluating the risk and benefits of treatment
- In patients who show evidence of renal deterioration during the treatment period, Zometa should be withheld and only resumed when serum creatinine returns to within 10% of baseline

#### **Key Message:**

- Zoledronic acid has been associated with reports of renal impairment and renal failure, especially in patients with pre-existing renal dysfunction or other risk factors. Renal function should be measured before each dose, and patients should be adequately hydrated before treatment. Renal function monitoring is recommended after use of zoledronic acid in at-risk patients – especially those with pre-existing renal impairment. Use in patients with severe renal impairment is generally not recommended, but may be considered for tumour-induced hypercalcaemia, if the benefits outweigh the risks.



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## **Yasmin (ethinylestradiol/drospirenone): Update on risk of venous thromboembolism**

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Recently published studies suggest that the risk of venous thromboembolism (VTE) in association with use of the combined oral contraceptive Yasmin may be slightly higher than previously estimated, and somewhere between the risk associated with combined oral contraceptives (COCs) containing levonorgestrel (otherwise known as ‘second generation’) and those containing desogestrel or gestodene (known as ‘third generation’). The incidence of VTE in association with the use of levonorgestrel, desogestrel and gestodene-containing COCs has been studied extensively. Overall, these studies have shown that women who use desogestrel or gestodene-containing COCs have a slightly higher risk of developing VTE than those who use levonorgestrel-containing COCs. The risk of VTE with Yasmin remains very small and, like other oral contraceptives, is less than that associated with pregnancy. Prescribers should be aware of the new evidence when discussing the most suitable type of contraceptive for any woman who wants to start or switch contraception.

It has long been recognised that all combined hormonal contraceptives, including Yasmin, are associated with a small increase in the risk of venous thromboembolism (VTE), including deep venous thrombosis and pulmonary embolism, compared with no use. For a given dose of oestrogen, the absolute incidence of VTE varies according to the type of progestogen but is, for all COCs, very small. With all COCs the risk is greatest in the first year of use.

Yasmin contains drospirenone, a relatively new progestogen, and was first licensed in 2000. In 2006, the results from two large prospective cohort studies (EURAS and Ingenix)<sup>1,2</sup> suggested that the risk of VTE in Yasmin users is comparable with that for other

contraceptives that contain a similar level of oestrogen, including those containing levonorgestrel. More recently, the results from a Danish cohort study<sup>3</sup> and a Dutch case-control study<sup>4</sup> have suggested that this risk may be slightly higher than previously estimated and somewhere between the risk associated with levonorgestrel-containing COCs and with desogestrel or gestodene-containing COCs (relative risks for the comparison of Yasmin with levonorgestrel-containing COCs: 1.64; 95% CI 1.27–2.10 and 1.7; 0.7–3.9, respectively).

Because of some limitations in the methodology of these recent studies, further analyses are needed before any firm conclusions can be drawn. In the meantime, when jointly discussing the choice of contraceptive with an individual woman, prescribers should be aware of the new evidence and take into consideration her medical history and any associated risk factors taking account of contraindications.

All hormonal contraceptives are highly effective, with well characterised safety profiles. The risk of a venous thrombosis in women who use Yasmin, as for all combined oral contraceptive COCs, is smaller than the risk of VTE associated with pregnancy.

Product information for Yasmin, as for all COCs, already contains extensive warnings about the risk of VTE and these will be updated to reflect the new data. [See the European Pharmacovigilance Working Party (PhVWP) monthly report: a link is provided on the IMB website under Publications, PhVWP reports accessible at <http://www.imb.ie> to the report at <http://www.ema.europa.eu/htms/human/phv/reports.htm> ]



#### Key messages:

- Recent evidence suggests that the risk of VTE in association with Yasmin may be slightly higher than previously estimated and somewhere between that for levonorgestrel-containing COCs and that for desogestrel or gestodene-containing COCs. Because of some limitations in the methodology of these recent studies, further analyses are needed before any firm conclusions can be drawn.
- The risk of a venous thrombosis in women who use Yasmin, as for all COCs, is smaller than the risk of VTE associated with pregnancy. As with all COCs, the Package Leaflet for Yasmin already contains extensive warnings about the risk of VTE. These warnings include the information that in healthy women taking any COC, including Yasmin, about 20–40 cases of VTE are expected to occur in every 100,000 women each year, depending on the type of progestogen. The corresponding figure for women not using a contraceptive COC is about 5–10 cases per 100,000 each year. By comparison, about 60 cases of VTE are expected to occur in every 100,000 pregnancies.
- Prescribers should be aware of the new evidence when discussing the most suitable type of contraceptive for a woman who wants to start or switch contraception.
- Prescribing decisions should take into account each woman's relevant history and personal risk factors and any contraindications.
- All COCs, including Yasmin, should be prescribed with caution to obese women (BMI >30), or those with a higher baseline risk of VTE for other reasons.
- When used appropriately, the benefits of COCs outweigh the risk of VTE, which is rare.

#### Adverse Reaction Reporting:

Healthcare professionals are reminded that any suspected adverse reactions should be notified to the IMB Pharmacovigilance Unit. Adverse reactions may be reported to the Irish Medicines Board via the on-line reporting system ([www.imb.ie](http://www.imb.ie)), or using the downloadable or post-paid yellow card system. Medication errors can also be reported using the same options.

Alternatively, completed forms may be submitted by fax (01 -6762517).

Post-paid reports cards are also available from the Pharmacovigilance Unit at the IMB (01 6764971).

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#### Contact Details

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The IMB is anxious to ensure that our mailing lists for healthcare professionals are accurate and up to date. If there are any errors/changes to the address to which this communication was sent, it would be appreciated if you would contact the Pharmacovigilance Section of the IMB (see below). Details of e-mail addresses are particularly welcome to facilitate rapid dissemination of safety-related information.

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IRISH MEDICINES BOARD

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