

Important updates on drug safety from the MHRA/CHM

In the May edition of Drug Safety Update¹ the MHRA and CHM included important drug safety advice on: aliskiren▼ (Rasilez®); ACE inhibitors and angiotensin II receptor antagonists (A2RAs); non-steroidal anti-inflammatory drugs (NSAIDs); orlistat as a non-prescription medicine; and oral topical salicylate gels.

Aliskiren▼ (Rasilez®): risk of angioedema and renal dysfunction

The MHRA warned that angioedema may occur with use of aliskiren▼ (Rasilez®), the first of a new class of medicine that directly inhibits renin. They also warned that extreme caution is required if aliskiren is used in patients with renal artery stenosis or conditions predisposing to kidney dysfunction (such as hypovolaemia, heart disease, liver disease, or kidney disease) because of a risk of acute renal failure. NSAIDs may reduce the antihypertensive effect of aliskiren, and elderly patients or patients with compromised renal function may be at risk of further deterioration of renal function if NSAIDs and aliskiren are used together.

This warning adds to our already cautious view about this product (see previous *On the Horizon Rapid Review blog No. 160*). Data on the long-term safety of aliskiren, including renal and cardiovascular morbidity/mortality, are required before its place in therapy can be more clearly determined.

ACE inhibitors and A2RAs: use during breastfeeding

ACE inhibitors and A2RAs should not be used by breastfeeding mothers in the first few weeks after delivery because of possible profound neonatal hypotension; preterm babies may be at particular risk. In mothers who are breastfeeding older infants, the use of captopril, enalapril, or quinapril may be considered, although careful follow-up of the infant for possible signs of hypotension is recommended.

ACE inhibitors and A2RAs should not be used at **any** stage of pregnancy, as exposure during pregnancy has been associated with adverse kidney effects and other congenital anomalies. An earlier issue of Drug Safety Update (December 2007) warned that use in women who are planning pregnancy should be avoided unless absolutely necessary, in which case the potential risks and benefits should be discussed.

ACE inhibitors and A2RAs are used in a number of indications, and “increasing low cost prescribing of drugs affecting the renin-angiotensin system” is one of four Better Care, Better Value Indicators relating to prescribing recently released by the NHS Institute for

Innovation and Improvement (see previous *MeReC Stop Press blog No. 328* for details). NPCi now includes National Support Materials to help prescribers and prescribing teams address therapeutic and implementation issues arising from this indicator.

NSAIDs: reminder on renal failure and impairment

The MHRA warned that they continue to receive case reports of renal failure in NSAID users, despite prescribing information for NSAIDs including warnings about renal impairment and renal failure. NSAIDs (including COX-2 inhibitors) may rarely precipitate renal failure, and vulnerable (particularly elderly) patients may be at increased risk. It is estimated that NSAID use accounts for about 15% of all cases of drug-induced acute renal failure. A case-control study estimated an increased relative risk (RR 3.2, 95% confidence interval [CI] 1.8 to 5.8) of acute renal failure in otherwise healthy current users of NSAIDs.

Patients at risk of renal impairment or renal failure (particularly elderly people) should avoid NSAIDs if possible. If NSAID treatment is absolutely necessary, then the lowest effective dose for the shortest possible duration should be used to control symptoms. The renal function of such patients should be carefully monitored during NSAID treatment. It is important to consider other concomitant disease states, conditions, or medicines that may precipitate reduced renal function when prescribing NSAIDs. Risk is increased in patients with conditions such as hypovolaemia, congestive heart failure, liver cirrhosis, or multiple myeloma, and with concomitant use of ACE inhibitors, A2RAs and diuretics.

Orlistat: key safety information to support pharmacy availability

Following a European recommendation, orlistat 60mg capsules are now available in pharmacies (under the brand name alli®) as a non-prescription medicine to aid weight loss in conjunction with a reduced-calorie, lower-fat diet. Orlistat remains available as 120mg capsules on prescription (under the brand name Xenical®).

Key safety information that pharmacists should consider when supplying alli® is provided in



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the Drug Safety Update. alli® can be recommended for adults (age 18 years or older) who have a body mass index of at least 28kg/m². It is not suitable for women who are pregnant or breastfeeding. Pharmacists should ensure that patients are not allergic to any of the ingredients in alli®, and that they do not have chronic malabsorption syndrome or cholestasis. Training material for staff is available via www.mypharmacist.co.uk. More information on orlistat can be found on the obesity floor of NPCi.

New advice on topical oral salicylate gels for those younger than 16 years

The MHRA has reviewed the safety of oral topical salicylate-containing products after publication of a case report of

suspected Reye's syndrome associated with use of a dental gel that contained choline salicylate in a 20-month-old child. The CHM acknowledged that, although there is only a theoretical risk of Reye's syndrome, these products should be contraindicated in those younger than age 16 years in line with other oral salicylate-containing preparations. This decision affects four products currently licensed in the UK: Bonjela, Bonjela Cool Mint, Dinnefords Teejel Gel (not marketed), and Pyralvex. A more detailed article on this subject and advice on the use of alternative treatments can be found in the June edition of Drug Safety Update.

References

1. MHRA. Drug Safety Update 2009;2(10):1-9

NICE publishes guidance on rivaroxaban ▼ for prevention of VTE after hip and knee surgery

NICE technology appraisal guidance 170¹ recommends oral rivaroxaban ▼ (Xarelto®) as an option for the prevention of venous thromboembolism (VTE) in adults having elective total hip replacement surgery or elective total knee replacement surgery.

Action

Healthcare professionals involved in the management of adults undergoing orthopaedic surgery should be aware of this and other related NICE guidance.^{2,3} Oral rivaroxaban ▼ is an option for prophylaxis of VTE in patients having hip or knee replacement surgery in the NHS. Other options to consider, in accordance with their licensed indications, are injectable agents such as low-molecular weight heparin or fondaparinux ▼ and the other oral agent dabigatran etexilate ▼.

NICE has developed tools to help organisations implement this guidance: a costing statement explaining the resource

impact of this guidance and audit support for monitoring local practice.

NICE is developing guidance on reducing the risk of VTE in all patients admitted to hospital (both medical and surgical patients) and expects to issue this guidance in November 2009.

References

1. NICE. Rivaroxaban for the prevention of venous thromboembolism after total hip or knee replacement surgery in adults. Technology appraisal guidance 170. April 2009
2. NICE. Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults. Technology appraisal guidance 157. September 2008
3. NICE. Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery. Clinical guideline 46. April 2007

Is clopidogrel ACTIVE for atrial fibrillation?

The ACTIVE A study found that clopidogrel plus aspirin reduced the risk of a composite vascular endpoint compared with aspirin alone in patients with atrial fibrillation (AF) at increased risk of stroke and for whom warfarin-like drugs were unsuitable. However, this benefit should be balanced against a similar increased magnitude of risk of major bleeding with the combination.

Action

Currently clopidogrel is not licensed in atrial fibrillation. Should it receive such a licence, then any potential benefit would need to be weighed against the risk of major bleeding, taking into account the patient's baseline risk of a vascular event as well as their risk of bleeding.

What does this study claim?

The ACTIVE A study included patients with AF, at least one risk factor for stroke (n=7,554), and who were unsuitable for warfarin. The primary outcome of any major vascular event (stroke, non-central nervous system embolism, myocardial infarction, or death from vascular causes) was reduced in patients taking clopidogrel plus aspirin. There were 832 events in the combined group (n=3,772) compared to 924 in the aspirin-only group (n=3,782) (RR 0.89, 95% CI 0.81 to 0.98; P=0.01). The absolute risk reduction was 2.4% giving a number needed to treat of 42 over 3.6 years. The difference in the primary outcome was mainly due to a reduction in the risk of stroke.¹

There were 251 major bleeding events in the clopidogrel plus aspirin group and 162 in the aspirin only group. The increased risk of 2.4% in the clopidogrel plus aspirin group compared to the aspirin-only group gives a number needed to harm of 42 over 3.6 years for those taking clopidogrel in addition to aspirin.¹

Although warfarin therapy is not ideal, its potential benefits and risks in AF are well known. The ACTIVE A study has shown that if 100 people who are unsuitable for warfarin are treated with clopidogrel plus aspirin, rather than aspirin alone, two will be prevented from having a major vascular event but two will have a major bleed.

Details about the study can be found in *On the Horizon Rapid Review blog No. 331*. Information about AF and the use of anticoagulation is available on NPCi and in the NICE clinical guideline on the management of AF.²

References

1. The ACTIVE Investigators. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 2009;360:2066-78
2. NICE. The management of atrial fibrillation. Clinical Guideline 36. June 2006

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