

Drug Safety Update



Latest advice for all medicines users

The monthly newsletter from the **Medicines and Healthcare products Regulatory Agency** and its independent advisor the **Commission on Human Medicines**

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The **Medicines and Healthcare products Regulatory Agency** is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The **Commission on Human Medicines** gives independent advice to ministers about safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

In this month's Drug Safety Update, we highlight an important drug interaction. To follow on from our brief Stop press article last month on an interaction between clopidogrel and proton pump inhibitors, we have further information on the evidence for an interaction between these two commonly coprescribed medicines.

Yellow Card reports can help us identify previously unrecognised adverse drug interactions. Our article on p 6 highlights the key information to include on a Yellow Card when reporting a suspected interaction. The information we receive is vital to helping us monitor the benefit-risk profile of a medicine and identify quickly previously unidentified side effects.

Also this month, we update you on the latest epidemiological studies on the risk of myocardial infarction with abacavir (p 4), and bring you information on an MHRA review of the use of long-acting β -agonists in chronic obstructive pulmonary disease (p 7).

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Drug safety advice

Clonidogrel and proton pump inhibitors: interaction

Keywords: Clonidogrel, proton pump inhibitor, PPI, omeprazole, esomeprazole, pantoprazole, rabeprazole, lansoprazole

Concomitant use of a PPI with clonidogrel should be avoided unless considered essential

Clonidogrel (Plavix) is indicated for the prevention of atherothrombotic events in patients who have had myocardial infarction (MI) or ischaemic stroke, or who have established peripheral arterial disease. Combined with aspirin, it may also 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.

Clonidogrel can cause gastrointestinal symptoms and is therefore frequently coprescribed with a PPI; in the UK omeprazole and lansoprazole are the PPIs most commonly coprescribed with clonidogrel.

In May, the EU Committee for Medicinal Products for Human Use (CHMP) considered the available evidence for an interaction between clonidogrel and PPIs. They concluded that the data supported a clinically significant interaction that makes clonidogrel less effective when given with PPIs. The Committee recommended that product information for clonidogrel should be amended to discourage concomitant use of a PPI and clonidogrel unless considered absolutely necessary.

Concomitant use of other medicines that inhibit CYP2C19 would also be expected to reduce the efficacy of clonidogrel and should be avoided.

Evidence for an interaction

Pharmacokinetics

The active metabolite of clonidogrel is formed by the CYP2C19 isoenzyme. Several studies, including large clinical-outcome studies, have shown that the effectiveness of clonidogrel is diminished in patients with a polymorphism of the CYP2C19 allele that results in reduced activity of this enzyme.¹⁻⁵ As a class, PPIs share many pharmacokinetic features, and in vitro studies have found that all five products licensed in the UK exhibit competitive inhibition for CYP2C19, albeit to different degrees.⁶

Clinical-outcome studies

Cohort studies⁷⁻⁹ and a case-control study¹⁰ have shown an attenuation of the clinical benefit of clonidogrel by concomitant use of PPIs in patients with previous coronary artery restenosis or acute MI, with significant results being observed within as little as 90 days of starting therapy. Although most studies are observational and therefore associated with some limitations, those completed most recently seem to have been appropriately designed to evaluate a potential interaction and account for most of the known biases and confounding factors. Nevertheless, not all studies have been able to reproduce these findings,³ the reasons for which are currently unclear.

Do all PPIs interact with clonidogrel?

The varying affinity of PPIs for the CYP2C19 isoenzyme means that any interaction mediated by this enzyme may not necessarily be a class effect.

See
<http://www.emea.europa.eu/humandocs/PDFs/EPAR/Plavix/32895609en.pdf>

A series of questions and answers for patients is available on the MHRA website at
<http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/index.htm>

Other medicines that inhibit CYP2C19 include fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine, and chloramphenicol

- 1 Kim KA, et al. *Nature* 2008; 84: 236.
- 2 Mega JL, et al. *N Engl J Med* 2009; 360: 354.
- 3 Simon T, et al. *N Engl J Med* 2009; 360: 363.
- 4 Desta Z, et al. *Clin Pharmacokinet* 2002; 41: 913.
- 5 Xie HG, et al. *Pharmacogenetics* 1999; 9: 539.
- 6 Li X-Q, et al. *Drug Metab Dispos* 2004; 32: 821.
- 7 Pezalla E, et al. *J Am Coll Cardiol* 2008; 52: 1038.
- 8 Ho M, et al. *JAMA* 2009; 301: 937.
- 9 SCAI statement on "A national study of the effect of individual proton pump inhibitors on cardiovascular outcomes in patients treated with clonidogrel following coronary stenting: The Clonidogrel Medco Outcomes Study"
http://www.scai.org/drt1.aspx?PAGE_ID=5870 (accessed June 2, 2009).
- 10 Juurlink D, et al. *CMAJ* 2009; 180: 713-18.

Continues...

Clinical-outcome data for an interaction with clopidogrel are relatively sparse for individual PPIs other than omeprazole, for which a reduction in the effectiveness of clopidogrel has been clearly shown.^{8,9}

The Clopidogrel Medco Outcomes Study of 16 690 patients who were taking clopidogrel after stenting presented its findings at the Society for Cardiovascular Angiography and Interventions (SCAI) scientific sessions on May 6, 2009.⁹ This study found that the event rate for a composite risk of admission to hospital for MI, stroke, unstable angina, or repeat revascularisation was 18% for clopidogrel users without concomitant PPIs, 24% for concomitant use of lansoprazole, 25% for concomitant use of esomeprazole, 25% for concomitant use of omeprazole, and 29% for concomitant use of pantoprazole. All event rates were statistically significant compared with the rate in users of clopidogrel alone.

Another study¹⁰ found a significantly increased risk of adverse cardiovascular events in those taking clopidogrel with any PPI (odds ratio 1.4 [95% CI 1.1–1.8]), and no significant increase in those taking clopidogrel with pantoprazole (1.02 [0.7–1.5]); the overlapping 95% CI suggest that any difference between the two groups is not significant.

The outcome studies do not fully reflect the pharmacokinetics of PPIs, so there may be more than one explanation for the effect of this class of medicines on clopidogrel. More evidence from clinical-outcome studies is required before any specific recommendations can be made for the risk associated with the individual PPIs.

Alternative gastrointestinal therapies

On the basis of pharmacokinetic data, other medicines for the treatment of gastrointestinal disorders (such as H₂ blockers or antacids) would not be expected to interact with clopidogrel. However, there are currently no substantial data from clinical-outcome studies to support this.

Advice for healthcare professionals:

- The need for PPI therapy in patients who are also taking clopidogrel should be reviewed at their next appointment: avoid concomitant use of these medicines unless considered essential
- Prescribe PPIs in line with their licensed indications where possible
- Check whether patients who are taking clopidogrel are buying over-the-counter omeprazole and consider whether another gastrointestinal therapy would be more suitable

Has your
colleague seen
this bulletin?

Refer to Summaries of Product
Characteristics at
<http://emc.medicines.org.uk/>

Abacavir: risk of myocardial infarction—update from epidemiological studies

Keywords: HIV infection, abacavir, myocardial infarction, MI, D:A:D study, SMART study, FHDH study

Abacavir should be used in line with current treatment guidelines and with caution in patients with high cardiovascular risk factors

Abacavir is a nucleoside reverse transcriptase inhibitor indicated in the use of combined antiretroviral therapy (CART) for the treatment of HIV infection. There are currently three abacavir-containing products licensed in the UK: Ziagen (abacavir); Kivexa (abacavir and lamivudine); and Trizivir (abacavir, lamivudine, and zidovudine). Abacavir (Ziagen) has been available in the UK since 1999.

Risk of myocardial infarction

Background

In 2008, preliminary results from D:A:D (Data collection on Adverse events of anti-HIV Drugs), a large prospective observational study of more than 33 000 patients with HIV who were receiving CART in the EU, USA, and Australia, suggested a possible increased risk of myocardial infarction (MI) in patients receiving abacavir. The increase in risk seemed to be limited to recent use (ie, <6 months before MI) or current use (relative risk 1.9 [95% CI: 1.48–2.55]) of abacavir.

Healthcare professionals were last informed about this possible adverse effect in Drug Safety Update in May 2008, and were advised to take actions to minimise or control modifiable risk factors for cardiovascular disease, such as smoking, hypertension, hyperlipidaemia, and diabetes. Information was also issued by the European Medicines Agency (EMA).

This article is to update you on the outcome of a European review of the latest data.

New Data

Pooled analysis

A pooled analysis of 54 clinical trials compared the risk of MI in patients who had received an abacavir-containing CART regimen (n=9639) with patients who had received a non-abacavir-containing CART regimen (n=5044).¹ Estimated relative risk of MI in patients taking an abacavir-containing regimen was 0.9 (95% CI 0.40–1.86). However, these studies were not designed to investigate the cardiovascular effects of abacavir.

The SMART study

In June 2008, an analysis of data from the SMART (Strategies for Management of Antiretroviral Therapy) study (n=5742) found a significantly increased risk of MI associated with current use of abacavir (hazard ratio 4.3 [95% CI 1.4–13.0]).²

D:A:D study update

In February 2009, updated results from this study reported that the relative risk estimate for MI in current or recent (<6 months before MI) abacavir users was slightly lower than the previous D:A:D estimate, but still indicated an increased relative risk (1.68 [95% CI: 1.33–2.13]).³

The FHDH study

In February 2009 the FHDH (French Hospital Database on HIV) study, a nested case-control study in a cohort of 115 000 patients with HIV, found that only early exposure

See Drug Safety Update May 2008, p 9;
www.mhra.gov.uk/mhra/drugsafety/update

See
<http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON014498> and
<http://www.emea.europa.eu/humandocs/PDFs/EPAR/Kivexa/14288808en.pdf>

1 Brothers CH, et al. *J Acquir Immune Defic Syndr* 2009; 51: 20–28.

2 Lundgren JD, et al (SMART/INSIGHT and the D:A:D Study Groups). *AIDS* 2008; 22: F17–24.

3 Sabin CA, et al. *Lancet* 2008; 371: 1417–26.

4 Lang S, et al. Proceedings of the 16th Conference on Retroviruses and Opportunistic Infections; Feb 8–11, 2009; Montreal, Canada. Abstr 43LB.

to abacavir (ie, used for <1 year and stopped ≤ 6 months before MI) was associated with an increased risk of MI (odds ratio 1.97 [1.09–2.56]).⁴ Cumulative exposure was not associated with a significant increase in risk.

Conclusions

The preferential use of abacavir in patients with high cardiovascular risk, and lack of an established biological mechanism that could explain a potential increase in risk of MI means that no firm conclusions can be drawn on the association between abacavir and MI that has been recorded in observational studies.

The cardiovascular safety of all abacavir-containing medicines remains under close review.

Further information

16th Conference on Retroviruses and Opportunistic Infections :
<http://www.retroconference.org/2009/>

British HIV Association treatment guidelines:
<http://www.bhiva.org/cms1222226.asp>

European Medicines Agency
<http://www.emea.europa.eu/pdfs/human/press/pr/24966009en.pdf>

Advice for healthcare professionals:

- Abacavir-containing medicines should be used in line with current treatment guidelines and with caution in patients with high cardiovascular risk factors
- When prescribing abacavir-containing medicines, healthcare professionals should take action to minimise all modifiable cardiovascular risk factors (ie, smoking, high blood pressure, high blood-fat levels, and diabetes)

Yellow Card Scheme update

For information on clopidogrel,
see p 2

See Drug Safety Update November
2007; p 7;
[www.mhra.gov.uk/mhra/drugsafety
update](http://www.mhra.gov.uk/mhra/drugsafety/update)

You can report suspected side effects and drug interactions on a Yellow Card

In this issue of Drug Safety Update, we highlight the potential risks from the interaction of clopidogrel with proton pump inhibitors.

Medicines might interact with food, alcohol, herbal remedies, or other drugs a patient is taking, which may result in serious side effects. If you suspect a patient has had an adverse reaction as a result of an interaction please complete a Yellow Card or encourage them to complete one. Healthcare professionals and patients can report online at www.yellowcard.gov.uk.

If you suspect an interaction has taken place, please specify this in the reaction details section of the Yellow Card. Please also tell us:

- The medicines thought to be involved in the interaction (record this in the suspect drug fields)
- The dose of these medicines the patient was receiving
- Any action taken with the medicines as a result of the interaction
- The dates of treatment, if available

Using evidence from Yellow Cards submitted to us, in November 2007 we issued an updated warning about the interaction between St John's wort (*Hypericum perforatum*) and antiepileptic medicines. At that time, continued Yellow Card reporting of possible interactions with St John's wort led to an extension of the warning to include all antiepileptics because some (such as levetiracetam, lamotrigine, and clobazam) were not previously known to interact with this herbal medicine.

All Yellow Cards are treated in the strictest confidence. Receiving further information on the risks and potential side effects from interactions between medicines is key to safeguarding public health.

Hot topic

Use of long-acting β -agonists in chronic obstructive pulmonary disease

The overall benefits of long-acting β -agonists (LABAs), both as monotherapy and in combination with inhaled corticosteroids (ICS), in the treatment of chronic obstructive pulmonary disease (COPD) continue to outweigh any risks. However, healthcare professionals are reminded that ICS should not be used alone in COPD. A key issue remains the increased risk of pneumonia associated with the use of ICS in COPD

Chronic obstructive pulmonary disease

COPD is a slowly progressive, mainly irreversible disease characterised by airflow limitation. It is one of the few diseases associated with an increasing mortality rate, and by 2020 is predicted to be the third most common cause of death.

NICE (National Institute for Health and Clinical Excellence) and GOLD (Global initiative for chronic Obstructive Lung Disease) guidelines recommend the addition of a LABA to short-acting β_2 agonists when moderate COPD is diagnosed (ie, FEV₁ between 80% and 50% of predicted), and the addition of ICS in severe disease (ie, FEV₁ \leq 50% and repeated exacerbations).

However, recent prescribing data suggest that most patients who are prescribed a LABA receive it in conjunction with an ICS, which may suggest that ICS are being introduced earlier than guidelines recommend. The two LABAs currently licensed for treatment of COPD are salmeterol and formoterol (eformoterol). Both are licensed in COPD either as monotherapy or in conjunction with an ICS (fluticasone propionate and budesonide, respectively).

MHRA review of LABA use in COPD

We have recently completed a comprehensive review of the use of LABAs, both as monotherapy and in combination with ICS, in COPD. The review assessed the published literature (for some key examples, see refs 1–10) and unpublished trials investigating the efficacy or safety (or both) of LABA or LABA plus ICS against a range of clinical endpoints. The review concluded that:

- A LABA/ICS combination had greater efficacy than either LABA or ICS monotherapy in every study
- However, the extent of the additional benefit provided by the LABA/ICS combination versus LABA alone was variable and was not always clinically significant. A convincing additional benefit of combination therapy was however seen in the reduction in the rate of exacerbations
- A significant additional benefit of the LABA/ICS combination has not been proven for milder disease and ICS should not be introduced earlier than guidelines suggest
- In terms of efficacy, no clear dose-response relation was shown for either LABAs or ICS. To date, no treatment has been shown to influence the accelerated decline in lung function that is characteristic of COPD, highlighting the limited treatment options for this patient population

Side effects

A range of side effects have been reported after LABA or LABA/ICS therapy. However their incidence should be considered in the context of the patients, many of whom have systemic inflammation and several co-existing conditions (including cardiovascular disease). Despite this, it is now clear that treatment with an ICS in

<http://www.nice.org.uk/guidance/index.jsp?action=download&o=29303>
and
<http://www.goldcopd.com/Guidelineitem.asp?1=2&l2=1&intId=2003>

- 1 Albers R, et al. *Eur Respir J* 2002; **19**: 936–43.
- 2 Appleton S, et al. *Cochrane Database Syst Rev* 2006; **3**: 1–84.
- 3 Calverley PM, et al. *New Engl J Med* 2007; **356**: 775–89.
- 4 Calverley PM, et al. *Lancet* 2003; **361**: 449–56.
- 5 Calverley PM, et al. *Eur Respir J* 2003; **22**: 912–19.
- 6 Campbell M, et al. *Resp Med* 2005; **99**: 1511–20.
- 7 Nannini LJ, et al. *Cochrane Database Syst Rev* 2008; **4**: 1–108.
- 8 Szafranski W, et al. *Eur Respir J* 2003; **21**: 74–81.
- 9 Wadbo M, et al. *Eur Respir J* 2002; **20**: 1138–46.
- 10 Wedzicha JA, et al. *Am J Crit Care Med* 2008; **177**: 19–26.

Hot topic *continued*

COPD—either alone or in combination with a LABA—significantly increases the risk of pneumonia (although in clinical trials there was no associated increase in the rate of mortality due to pneumonia). In the TORCH³ study the probability of pneumonia was 19.6% in the salmeterol/fluticasone group and 18.3% with fluticasone alone versus 12.3% in placebo. No increase in pneumonia risk was observed with salmeterol alone (13.3%). Although β_2 -agonists have the potential to cause cardiac side effects, no strong signal for an increased risk was identified in the review, even when LABAs were prescribed with a potassium-depleting diuretic. However, the patient population is restricted in clinical trials and the risk may therefore be different in clinical practice.

Advice for healthcare professionals

- The overall balance of benefits and risks for LABAs in the treatment of COPD remains positive when used in line with current GOLD and BTS guidelines
- In all trials combination therapy was better than monotherapy. However the benefit is limited and ICS should be introduced only when COPD progresses to severe disease, in line with current guidelines
- ICS should not be used alone in COPD
- A key issue is the increased risk of pneumonia with ICS treatment in COPD. This risk is not apparent with LABAs alone

Stop press

Mycophenolate mofetil: pure red cell aplasia

Mycophenolate mofetil (CellCept) is an immunosuppressant indicated in combination with ciclosporin and corticosteroids for prophylaxis of acute transplant rejection in adults receiving allogeneic renal, cardiac or hepatic transplants, and in children and adolescents (age 2–18 years) receiving renal transplants.

Up to April 2009, 41 cases of pure red cell aplasia had been reported worldwide in association with mycophenolate mofetil. Pure red cell aplasia is a type of anaemia in which there is a selective reduction of red blood cell precursors on bone-marrow examination. Some patients were also receiving other medicines that could have contributed to the development of pure red cell aplasia (eg, alemtuzumab, tacrolimus, azathioprine, and co-trimoxazole). In four cases dose reduction, and in 12 cases discontinuation, of mycophenolate mofetil led to resolution of the condition. The mechanism by which mycophenolate mofetil may cause pure red cell aplasia is unknown.

Further information is available in a letter sent to healthcare professionals in June 2009, available at <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/index.htm>

Advice for healthcare professionals

- Dose reduction or discontinuation of mycophenolate mofetil should be considered in patients who develop pure red cell aplasia. Changes to treatment should be done only under specialist supervision to minimise the risk of graft rejection

Stop press *continued*

Further information is available on our website at <http://www.mhra.gov.uk/Howweregulate/Medicines/Herbalandhomoeopathicmedicines/Herbalmedicines/HerbalSafetyNews/Currentsafetyissues/CON046623> and on the Food Standards Agency website at <http://www.food.gov.uk/news/newsarchive/2009/jun/hydroxycut>

Hydroxycut range of food supplements: risk of liver damage

The Food Standards Agency has issued a warning that people should not take products from the food supplement range called **Hydroxycut**, which are manufactured by Iovate Health Sciences and are marketed as weight-loss and body-building aids. Reports from North America and Finland have linked these supplements to several serious cases of liver damage, including one death. To date there are no reported cases of illness in the UK related to these products.

Hydroxycut products contain various ingredients and herbal extracts. The specific ingredient or doses that might cause adverse effects has not yet been identified.

We concur with the advice of the Food Standards Agency that people should not take Hydroxycut food supplements because of the potential health risks.

Priadel Liquid: potential for dosing errors

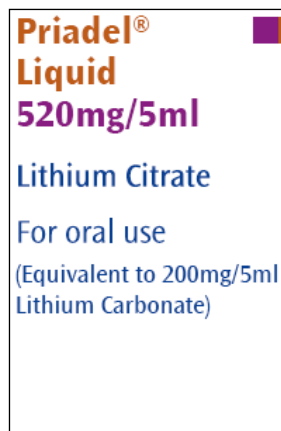
Priadel Liquid is an oral solution of lithium citrate, used for the treatment of various mental disorders.

The current carton and label incorrectly state that the strength of the solution is 200 mg/5mL. This is the equivalent strength of lithium carbonate and not the strength of lithium citrate. The concentration of lithium citrate in the solution is 520 mg/5mL (as stated on the reverse of the carton). There is a high potential for overdose with the product because prescriptions may be written based on the dose of lithium citrate.

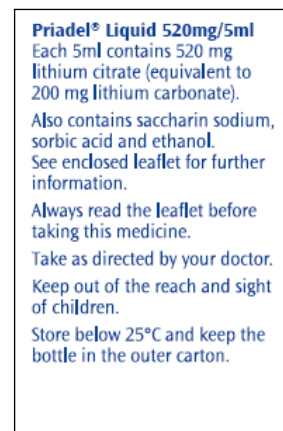
New packaging that displays the correct strength will be available from early September 2009 (see images below). Until then, please take extra care to ensure that when Priadel Liquid has been prescribed, the correct strength is given to the patient.

Further information is available on our website at <http://www.mhra.gov.uk/Publications/Safetywarnings/Drugalerts/CON049188>

Images of the updated packaging (to be available from September 2009) are shown below:



Front



Back

Stop press *continued*

See
www.mhra.gov.uk/mhra/drugsafetyupdate

Clarification: ACE inhibitors and angiotensin II receptor antagonists—use during breastfeeding

We have received some feedback and queries about our drug safety advice article on the use of ACE inhibitors and angiotensin II receptor antagonists during breastfeeding, which was published in the May 2009 issue of the bulletin (p 3).

We would like to clarify that although ACE inhibitors and angiotensin II receptor antagonists are generally not recommended for use by breastfeeding mothers, they are not absolutely contraindicated. Healthcare professionals may prescribe these medicines during breastfeeding if they consider that this treatment is essential for the lactating mother. In particular, the original article advised that in mothers who are breastfeeding older infants, the use of captopril, enalapril, or quinapril may be considered if an ACE inhibitor is necessary for the mother. Careful follow-up of the infant for possible signs of hypotension is recommended.

Other information from the MHRA**Patient Information Leaflet of the month: sulfasalazine**

Patient information leaflets (PILs) are improving in quality as a result of new legal obligations on manufacturers to test the documents with potential patients. Testing makes sure that the presentation of the information enables patients to find and understand key messages for safe use about the medicine within the PIL and thereby enables them to use the medicine safely and effectively. To promote this new initiative, we are publishing a series of examples of best practice on our website. The latest in the series is for **sulfasalazine**, which is indicated for the treatment of rheumatoid arthritis, Crohn's disease, and ulcerative colitis. The leaflet shows how the required information can be designed in a concertina format, which in testing patients found helpful.

Access PIL of the month at
[http://www.mhra.gov.uk/Howweregulate/Medicines/Labelspatientinformationleafletsandpackaging/Patientinformationleaflet\(PIL\)ofthemonth/index.htm](http://www.mhra.gov.uk/Howweregulate/Medicines/Labelspatientinformationleafletsandpackaging/Patientinformationleaflet(PIL)ofthemonth/index.htm)

Consultation: proposals to strengthen and rationalise EU pharmacovigilance

We are inviting comments on the European Commission's legislative proposals to strengthen and rationalise pharmacovigilance in the EU. Further information, including how to comment by Aug 31, 2009, is available on our website.

See
<http://www.mhra.gov.uk/Publications/Consultations/Medicinesconsultations/MLXs/CON049137>

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<http://www.mhra.gov.uk/mhra/CommissiononHumanMedicines>

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