Drug Safety Update

Latest advice for 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 the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

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This month, we give advice regarding the risk of venous thromboembolism (VTE) with the combined oral contraceptive Yasmin. New studies suggest that the risk may be slightly higher than previously estimated, somewhere between the risk associated with combined pills containing levonorgestrel and those containing desogestrel or gestodene. However, the risk of VTE with Yasmin remains very small, and like other oral contraceptives, is less than that associated with pregnancy. The new evidence should be taken into consideration by prescribers when discussing suitable contraception with women (see p 2).

Also this month, we provide updated advice regarding the interaction between clopidogrel and proton pump inhibitors (PPIs). Since our advice last year (see Drug Safety Update July 2009, p 2), new evidence has become available. Sufficient evidence of an interaction exists for omeprazole and esomeprazole to recommend that their use with clopidogrel should be discouraged; however, the previous advice to avoid all other PPIs is no longer considered necessary. Read the latest advice on p 4.

We would like to remind healthcare professionals that intravenous zoledronic acid is associated with reports of renal impairment and renal failure, especially in patients with pre-existing renal dysfunction. Prescribers are reminded to measure renal function before each dose, and ensure patients are adequately hydrated before treatment. Use in patients with severe renal impairment is generally not recommended (see p 6).

Finally this month, we advise prescribers, pharmacists, and nurses when prescribing or administering parenteral amphotericin B to be fully aware of which formulation they are using, and the associated dose regimen, as there is a risk of overdose which may be fatal, due to confusion between lipid-based and non-lipid-based formulations (see p 8).

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Yasmin: Update on risk of venous thromboembolism

Keywords: ethinylestradiol, drospirenone, levonorgestrel, venous thromboembolism, VTE, second generation, third generation, contraceptive

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 pills containing levonorgestrel (otherwise known as 'second generation') and those containing desogestrel or gestodene (known as 'third generation'). 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 combined oral contraceptives (COCs), very small. With all COCs the risk is greatest in the first year of use.

Yasmin contains drospirenone, a relatively new progestogen. Yasmin was first licensed in 2000 and became available for use in the UK in April 2002. In England it is estimated that Yasmin accounts for about 11% of prescriptions dispensed for all combined oral contraceptives in 2008/09.[1] It is estimated that about 19% of prescriptions for Yasmin are for first-time use.[2]

The incidence of VTE in association with the use of levonorgestrel, desogestrel and gestodene-containing pills has been studied extensively. Overall, these studies have shown that women who use desogestrel or gestodene-containing pills have a slightly higher risk of developing VTE than those who use levonorgestrel-containing pills. Because Yasmin was licensed relatively recently, fewer studies on its associated risk have been carried out.

In 2006, the results from two large prospective cohort studies (EURAS and Ingenix),[3,4] 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[5] and a Dutch case-control study[6] have suggested that this risk may be slightly higher than previously estimated and somewhere between the risk associated with levonorgestrel-containing pills and with desogestrel or gestodene-containing pills (relative risks for the comparison of Yasmin with levonorgestrel-containing pills: 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 contraindications.

All hormonal contraceptives are highly effective and safe, and have important health benefits, including those from avoiding unplanned pregnancy. The risk of a venous thrombosis in women who use Yasmin, as for all combined oral contraceptive pills, 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.

Continues...

1 The NHS Information Centre for Health and Social Care. Prescription Cost Analysis 2008. Published April 21, 2009. See www.ic.nhs.uk (accessed March 30, 2010).

2 Data derived from IMS Health Disease Analyzer - Mediplus, October 2008–September 2009, by the MHRA.

3 Dinger JC, et al. *Contraception* 2007; **75:** 344–54.

4 Seeger JD, et al. *Obstet Gynecol* 2007; **110:** 587–93.

5 Lidegaard Ø, et al. *BMJ* 2009; **339:** b2890.

6 van Hylckama Vlieg A, et al. *BMJ* 2009; **339:** b2921.

See the European Pharmacovigilance Working Party (PhVWP) monthly report: http://www.ema.europa.eu/htms/human/phv/reports.htm

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Advice for prescribers

- The risk of a venous thrombosis in women who use Yasmin, as for all combined oral contraceptive pills, is smaller than the risk of VTE associated with pregnancy
- 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 pills and that for desogestrel or gestodene-containing pills. Because of some limitations in the methodology of these recent studies, further analyses are needed before any firm conclusions can be drawn
- 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
- Any prescribing decision should take into account each woman's personal risk factors and any contraindications
- All combined oral contraceptives, including Yasmin, should be prescribed with caution to obese women (BMI >30), or those with a higher baseline risk of VTE for other reasons
- All hormonal contraceptives are highly effective and safe and have important health benefits, including those from avoiding unplanned pregnancy. When used appropriately, the benefits of all combined oral contraceptives far outweigh the risk of VTE, which is rare

Advice for women

- All hormonal contraceptives are highly effective and safe and have important health benefits, including those from avoiding unplanned pregnancy
- Venous thromboembolism (VTE) associated with COC use is not a new issue. The two recently published studies confirm that the risk of VTE in association with Yasmin is comparable with other commonly used combined oral contraceptives, but may be slightly higher than previously estimated
- As with all oral contraceptives, the Patient Information Leaflet for Yasmin already contains extensive warnings about the risk of VTE. These warnings include the information that in healthy women taking any contraceptive pill, 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 pill 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
- If you are already taking Yasmin, there is no need to stop taking it on the basis of these findings. If you stop taking your pill, you will need to use another method of contraception, such as a condom, as you risk becoming pregnant at any time
- A number of combined oral contraceptives and other contraceptive choices are also available. If you have any concerns about your contraception, you should discuss them with your contraceptive provider, but keep taking your contraceptive pill until you have done so. Your contraceptive provider will discuss the most suitable choice of contraceptive for you, taking into consideration your medical history and any contraindications
- When used appropriately, the benefits of all combined oral contraceptives far outweigh the risk of VTE, which is rare

Clopidogrel and proton pump inhibitors: interaction—updated advice

Keywords: Clopidogrel, proton pump inhibitor, PPI, omeprazole, esomeprazole

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

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. Combined with aspirin, the brand leader product (Plavix) 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, and are frequently co-prescribed with clopidogrel.

Previous advice regarding an interaction

See Drug Safety Update July 2009, p 2: www.mhra.gov.uk/drugsafetyupdate

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 has been recently 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);[1] reduces the ability of clopidogrel to inhibit platelet aggregation;[2,3] and reduces the beneficial effect of clopidogrel in patients.[4,5] 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.[6]

New evidence

Since then, 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. However, the evidence in favour of an interaction with omeprazole and esomeprazole is still a concern.

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[7] found that use of PPIs (unspecified) reduced platelet function in patients who were randomly assigned clopidogrel, but did not affect clinical outcome.

Furthermore, the COGENT study,[8] 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[9] 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.

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1 Li X-Q, et al. *Drug Metab Dispos* 2004; **32:** 821.

2 Gilard M, et al. *J Thromb Haemost* 2006; **4:** 2508.

3 Gilard M, et al. *J Amer Coll Cardiol* 2008; **51:** 256.

4 Ho M, et al. *JAMA* 2009; **301:** 937.

5 Juurlink D, et al. *CMAJ* 2009; **180:** 713–718.

6 SCAI statement on "A national study of the effect of individual proton pump inhibitors on cardiovascular outcomes in patients treated with clopidogrel following coronary stenting: The Clopidogrel Medco Outcomes Study" http://www.scai.org/Press/detail.aspx?cid=d5661afe-976d-46fa-aed0-101ab694a9c6 (accessed March 30, 2010).

7 O'Donaghue, et al. *Lancet* 2009; **374:** 989.

8 Clopidogrel and the Optimization of Gastrointestinal Events (COGENT-1). Presented at Transcatheter Cardiovascular Therapeutics conference Sept 21–26, 2009; San Francisco, CA, USA. http://clinicaltrials.gov/ct2/show/NCT00557921 (accessed Feb 2, 2010).

9 Yasuda H, et al. *Intern Medicine* 2009; **48:** 1725–1730.

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Summary of available evidence

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 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. Information for prescribers and patients will be updated with the latest advice.

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 weighed against the potential gastrointestinal benefit of the PPI.

Advice for healthcare professionals:

- Concomitant use of clopidogrel and omeprazole or esomeprazole is to be discouraged unless considered essential
- Doctors should check whether patients who are taking clopidogrel are also buying over-the-counter omeprazole and consider whether other gastrointestinal therapies would be more suitable
- Pharmacists should check whether patients buying omeprazole are also taking clopidogrel
- Consider PPIs other than omeprazole or esomeprazole in patients who are taking clopidogrel. Other gastrointestinal therapy such as H_2 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)

Intravenous zoledronic acid: adverse effects on renal function

Keywords: zoledronic acid, Aclasta▼, Zometa, bisphosphonate, osteoporosis, Paget's disease of the bone, anticancer, renal impairment, renal failure

Zoledronic acid is 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

- 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 is 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 strong warnings and precautions regarding renal impairment and renal failure.

Warnings in the product information for Aclasta▼ are being strengthened following reports of renal failure or renal impairment with its use. There have been 139 worldwide suspected reports (14 fatal) of renal impairment or renal failure up to 14 August 2009, and six UK suspected reports (one fatal) of renal impairment or renal failure up to 5 March 2010, 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 was sent to healthcare professionals in March 2010, regarding the updated product information for Aclasta▼.

See letter sent to healthcare professionals on March 12, 2010: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/index.htm

Advice for healthcare professionals:

The following precautions should be taken into account to minimise the risk of renal adverse reactions with zoledronic acid:

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

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See Aclasta▼ Summary of Product Characteristics: http://emc.medicines.org.uk/medicine/18171/SPC/Aclasta+5+mg+solution+for+infusion/

See Zometa Summary of Product Characteristics: http://emc.medicines.org.uk/medicine/14062/SPC/Zometa+4mg+5ml+Concentrate+for+Solution+for+Infusion/

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 with-held and only resumed when serum creatinine returns to within 10% of baseline

Parenteral amphotericin B: fatal overdose risk due to confusion between lipid-based and non-lipid-based formulations

Keywords: amphotericin B, Fungizone, cardiac arrest, cardiorespiratory arrest

There is a potential risk of fatal overdose due to confusion between lipid-based and non-lipid-based formulations of parenteral amphotericin B. These formulations are not interchangeable: prescribers, pharmacists, and nurses need to be fully aware of the formulation being used and the associated dose regimen

Parenteral amphotericin B is available as lipid-based and non-lipid based formulations for the treatment of fungal infections. These different formulations of amphotericin B have different dose requirements.

Cases of fatal overdose have resulted when Fungizone (a non-lipid-based formulation of amphotericin B) has been mistakenly administered instead of a lipid-based formulation. Amphotericin B overdoses may result in potentially fatal cardiac or cardiorespiratory arrest. The total daily dose of Fungizone should not exceed 1·5 mg/kg.

The appropriate dose and method of administration differ markedly between the marketed parenteral formulations of amphotericin B and they are therefore **not** interchangeable.

Particular care must be taken in prescribing and dispensing the correct parenteral formulation of amphotericin B: prescribers, pharmacists, and nurses need to be fully aware of the formulation being used and the associated dose regimen.

Fungizone packages, cartons, and vial labels are being modified to carry the following cautionary statements: "Fungizone is not interchangeable with other amphotericin products. STOP! Verify product name and dosage. TOTAL DAILY DOSE MUST NOT EXCEED 1·5 MG PER KG." A letter was sent to healthcare professionals in March 2010 to notify them of the updates to product information for Fungizone.

See letter sent to healthcare professionals on 22 March, 2010: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/index.htm

Advice for healthcare professionals:

- For Fungizone, do not exceed a total daily dose of 1·5 mg/kg
- To prevent inadvertent overdose, verify the product name and dose before administration, especially if the dose prescribed exceeds 1·5 mg/kg—the maximum recommended dose for Fungizone
- Suspected adverse reactions associated with amphotericin B should be reported to us via the Yellow Card Scheme (see www.yellowcard.gov.uk)

Rifadin infusion (rifampicin): new solvent formulation and changes to compatible diluents

Keywords: Rifadin, rifampicin, reformulation, compatibility, infections, tuberculosis, leprosy

The solvent used in the preparation of Rifadin infusion has been reformulated. As a result, it can only be diluted with either dextrose 5% solution or sodium chloride 0·9% solution

Access the Summary of Product Characteristics at http://emc.medicines.org.uk/medicine/6435/SPC/Rifadin+For+Infusion+600mg/

Rifadin 600 mg infusion (rifampicin) is used to treat various infections, including tuberculosis and leprosy. It is indicated for acutely ill patients who are unable to tolerate oral therapy. To prevent emergence of resistant strains, Rifadin should be used in combination with another appropriate antibiotic.

New solvent formulation

The solvent used in the preparation of Rifadin infusion has been reformulated. As a consequence the diluents which may be used to administer the medicine have changed.

An animal-derived product, polysorbate 81 (a surfactant), has been removed from the solvent supplied in the pack. This removal is to comply with European Commission requirements to minimise the risk of transmissible spongiform encephalopathy in medicinal products. For this reason, and in view of the limited data available, the diluents that can be used with the reconstituted powder have been restricted to **dextrose 5%** and **normal saline**.

The new formulation is expected to be available in April 2010. The marketing authorisation holder is taking steps to minimise the amount of time that the two formulations are in the supply chain concurrently. Healthcare professionals should use all existing stock before introducing the reformulated product.

The carton has been revised to help identify the reformulated product. It is clearly marked: “Important update on incompatibilities. Please see Technical Leaflet”. A letter announcing the reformulation of Rifadin infusion was sent to healthcare professionals in March 2010.

See letter sent to healthcare professionals on March 25, 2010: http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/index.htm

Advice for healthcare professionals:

- Rifadin infusion has been reformulated
- The new formulation can only be diluted with either dextrose 5% solution or sodium chloride 0·9% solution
- If you are in doubt about which formulation of Rifadin is in use, contact a hospital pharmacist before reconstitution or administration

Stop press

Becaplermin (Regranex) for diabetic ulcers: contraindicated in patients with any known current cancer

Becaplermin (Regranex) is a topical gel indicated to promote the healing of full-thickness, neuropathic, chronic, diabetic ulcers less than or equal to 5 cm^2, in association with other good wound care measures.

A retrospective observational study (unpublished) has raised concerns of a link between becaplermin and malignancies distant from the site of application. The study had several limitations in its design and the evidence is not robust. However, as a precaution, a letter has been sent to healthcare professionals in March 2010 to inform them of the contraindication of becaplermin in patients with any known malignancy.

For further information, see a letter sent to healthcare professionals on March 12, 2010:
http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/index.htm

See also EMA Q&A document and press release:
http://www.ema.europa.eu/humandocs/PDFs/EPAR/Regranex/31245209en.pdf

http://www.ema.europa.eu/humandocs/PDFs/EPAR/Regranex/9232610en.pdf

Advice for healthcare professionals:

- Review treatment at the next routine appointment and do not prescribe becaplermin to patients who have a current cancer at any site
- Ulcers with a suspicious appearance should be biopsied to exclude malignancy

Other information from the MHRA

MHRA conference for doctors in training:

"Unusual Suspects—Patient Safety and the Regulation of Drugs and Medical Devices", May 26 2010, The Royal York Hotel, York

For more information and to register for this event, visit:
www.mhra.gov.uk/ConferencesLearningCentre/Conferences/CON065793

Following on from the successful conference hosted in 2009 in conjunction with the National Institute for Clinical Excellence (NICE), this event will provide trainee doctors with insight into the work of the MHRA and its important role in protecting public health.

This event aims to stimulate interest in the intellectual challenges of regulation, help junior doctors to understand how we learn from adverse events, and how to improve patient safety through reporting. It will also explain how national guidelines are formulated and introduced, while also providing a background to the regulatory framework that underpins the safety of medicines and medical devices in the UK.

Patient Information Leaflet of the month: Methotrexate Tablets

Access PIL of the month at http://www.mhra.gov.uk/Howweregulate/Medicines/Labelspatientinformationleaflets andpackaging/Patientinformationleaflet(PIL) ofthemonth/index.htm

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 enable 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 **Methotrexate Tablets**, which are used to treat severe psoriasis, rheumatoid arthritis and some cancers. The leaflet design uses good navigation tools, and in testing was found to be well received by patients.

Read more about the Commission on Human Medicines, including summaries of minutes from meetings, at www.mhra.gov.uk/Committees/Medicinesadvisory bodies/CommissiononHumanMedicines

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