Drug Safety Update

MHRA

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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Contents

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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Atypical femoral fractures have been reported rarely with bisphosphonate therapy, mainly in patients receiving long-term treatment for osteoporosis. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered while they are evaluated, and should be based on an assessment of the benefits and risks of treatment.

Furthermore, the need to continue bisphosphonate treatment for osteoporosis should be re-evaluated periodically based on the benefits and potential risks of bisphosphonate therapy for individual patients, particularly after 5 or more years of use (see article A1).

Also this month, epidemiological studies have shown that the risk of venous thromboembolism (VTE) for drospirenone-containing combined oral contraceptives (COCs), including Yasmin, is higher than for levonorgestrel-containing COCs (so-called 'second generation' pills) and may be similar to the risk for COCs that contain desogestrel or gestodene (so-called 'third generation' pills). However, 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 updated information when discussing the most suitable type of contraceptive for any woman who wants to start or switch contraception (see article A2).

Also this month, our Yellow Card Scheme update highlights some time-saving tips for sending us your vital reports of suspected adverse reactions (see article Y1).

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Drug safety advice

A1 Bisphosphonates: atypical femoral fractures

Atypical femoral fractures have been reported rarely with bisphosphonate therapy, mainly in patients receiving long-term treatment for osteoporosis. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered while they are evaluated, and should be based on an assessment of the benefits and risks of treatment. The need to continue bisphosphonate treatment for osteoporosis should be re-evaluated periodically based on the benefits and potential risks of bisphosphonate therapy for individual patients, particularly after 5 or more years of use

Individual bisphosphonates have different indications, and are used for: prophylaxis and treatment of osteoporosis; treatment of Paget's disease; and as part of some cancer regimens, particularly for bone metastases and multiple myeloma.

In 2008, a Europe-wide review of bisphosphonates and atypical stress fractures concluded that alendronic acid use was associated with an increased risk of atypical stress fractures of the proximal femoral shaft and a warning was subsequently added to alendronic acid product information. At that time, the available data neither supported nor refuted a possible class effect, and the issue was kept under close review and any emerging data evaluated.

See Drug Safety Update March 2009: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON088118

A further Europe-wide review has now been completed, which included data from the published literature and that provided by the marketing authorisation (licence) holders (including preclinical studies, clinical trials, and case reports) as well as reports produced by professional organisations.[1,2] The key findings and advice for healthcare professionals from this review are given below.

1 Shane E, et al. *J Bone Miner Res* 2010; **25:** 2267–94.
2 Rizzoli R, et al. *Osteoporos Int* 2011; **22:** 373–90.

Key findings:

- Atypical femoral fractures have been reported rarely with bisphosphonate therapy, mainly in patients receiving long-term treatment for osteoporosis. Atypical femoral fractures are considered a class effect of bisphosphonates
- They can occur after minimal or no trauma. Some patients experience thigh or groin pain, often associated with features of stress fractures on radiograph, weeks to months before presenting with a completed femoral fracture. Poor healing of these fractures has been reported.
- The overall balance of risks and benefits of individual bisphosphonates in their authorised indications remains favourable. The absolute number of atypical fractures reported is far lower than the number of osteoporotic fractures prevented[3]

3 Schilcher J and Aspenberg P. *N Engl J Med* 2011; **364:** 1728–37.

Advice for healthcare professionals:

- Atypical femoral fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture
- Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered while they are evaluated, and should be based on an assessment of the benefits and risks of treatment for the individual
- During bisphosphonate treatment, patients should be advised to report any thigh, hip, or groin pain. Any patient who presents with such symptoms should

be evaluated for an incomplete femur fracture

- The optimum duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of bisphosphonate therapy for individual patients, particularly after 5 or more years of use

Further information is available from the European Medicines Agency: see http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Bisphosphonates/human_referral_000266.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580024e99

The risk of atypical femoral fractures with bisphosphonates will be kept under close review in Europe.

To facilitate future case reporting and research, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has adopted a definition of atypical femoral fracture based on the American Society for Bone and Mineral Research (ASBMR) provisional case definition of atypical femoral fracture[1]—major and minor features:[a]

Major features[b]

- Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare
- Associated with no trauma or minimal trauma, as in a fall from a standing height or less
- Transverse or short oblique configuration
- Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex

Minor features

- Noncomminuted
- Localised periosteal reaction of the lateral cortex[c]
- Generalised increase in cortical thickness of the diaphysis
- Prodromal symptoms such as dull or aching pain in the groin or thigh
- Bilateral fractures and symptoms
- Delayed healing
- Comorbid conditions (eg, vitamin D deficiency, rheumatoid arthritis, hypophosphatasia)
- Use of pharmaceutical agents (eg, bisphosphonates, glucocortoids, proton pump inhibitors)

[a]Specifically excluded are fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathologic fractures associated with primary or metastatic bone tumours, and periprosthetic fractures.

[b]All major features are required to satisfy the case definition of atypical femoral fracture. None of the minor features are required, but sometimes have been associated with these fractures.

[c]Often referred to in the literature as 'beaking' or 'flaring'.

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A2 **Yasmin: risk of venous thromboembolism higher than levonorgestrel-containing pills**

Epidemiological studies have shown that the risk of venous thromboembolism (VTE) for drospirenone-containing combined oral contraceptives (COCs), including Yasmin, is higher than for levonorgestrel-containing COCs (so-called 'second generation' pills) and may be similar to the risk for COCs that contain desogestrel or gestodene (so-called 'third generation' pills). 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 updated information when discussing the most suitable type of contraceptive for any woman who wants to start or switch contraception

Venous thromboembolism (VTE) in association with use of combined oral contraceptives (COCs) is not a new issue. For a given dose of oestrogen, the absolute incidence of VTE varies according to the type of progestogen in the pill but is, for all COCs, very small.

The incidence of VTE in association with the use of levonorgestrel-containing,

desogestrel-containing, or gestodene-containing pills has been studied extensively. Overall, these studies have shown that women who use pills that contain desogestrel or gestodene have a slightly higher risk of developing VTE than do those who use levonorgestrel-containing pills. The excess risk of VTE is highest during the first year a woman ever starts or switches their COC.

Yasmin contains drospirenone, a relatively new progestogen, and was first licensed in 2000. Evidence of the level of VTE risk associated with Yasmin has been accruing since then.

The results of two early prospective cohort studies suggested no difference in risk of VTE between Yasmin and levonorgestrel-containing pills[1] or 'other' COCs.[2] However, in 2009, a Danish cohort study[3] and a Dutch case-control study[4] of the risk of VTE in association with a number of COCs found the risk with drospirenone-containing pills to be higher than the risk associated with levonorgestrel-containing pills.

Two further studies were recently published: one using the US PharMetrics database[5] and the other using the UK General Practice Research Database.[6] Both corroborated the findings of the Danish[3] and Dutch[4] studies of an increased risk of VTE in association with use of drospirenone-containing pills relative to levonorgestrel-containing pills.

Recent unpublished re-analyses of data from the Danish study[3] directly compared VTE risk for drospirenone-containing pills, levonorgestrel-containing pills, and desogestrel/gestodene-containing pills. These data strengthen and confirm the original findings, and have enabled firmer conclusions about the relative risk associated with drospirenone-containing pills.

All epidemiological studies have some limitations in their methods; however, the totality of the available evidence now clearly shows that the risk of VTE for drospirenone-containing COCs, including Yasmin, is higher than the risk for levonorgestrel-containing second-generation COCs. Furthermore, it suggests that the level of the risk may be similar to that for third-generation COCs that contain desogestrel or gestodene.

Product information for Yasmin, as for all COCs, already contains extensive warnings about the risk of VTE and these have been updated to reflect the totality of the evidence.

1 Dinger JC, et al. *Contraception* 2007; **75:** 344–54.
2 Seeger JD, et al. *Obstet Gynecol* 2007; **110:** 587–93.
3 Lidegaard Ø, et al. *BMJ* 2009; **339:** b2890.
4 van Hylckama Vlieg A, et al. *BMJ* 2009; **339:** b2921.
5 Jick SS and Hernandez RK, *BMJ;* 2011; 340: d2151.
6 Parkin L et al. *BMJ* 2011; 340: d2139.

Further information:

MHRA safety summary of hormonal contraceptives: http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Product-specificinformationandadvice–G–L/Hormonalcontraceptives/index.htm

See also the European Pharmacovigilance Working Party (PhVWP) monthly report, May 2011: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/05/WC500106708.pdf

Advice for healthcare professionals:

- The risk of VTE in association with drospirenone-containing pills, including Yasmin, is higher than that for levonorgestrel-containing 'second generation' pills and may be similar to the risk for 'third-generation' pills that contain desogestrel or gestodene
- Levonorgestrel-containing pills have the lowest thrombotic risk and are the safest pill for a woman who wants to start or switch contraception. Prescribers should be aware of the updated information 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, including her experience with other contraceptive formulations
- 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
- Estimates are not precise, but for women who do not use a contraceptive pill about one case of VTE per 10 000 is expected each year. By comparison, about six cases of VTE are expected to occur in every 10 000 pregnancies. In healthy women who take Yasmin, between three and four cases of VTE are expected to occur in every 10 000 women each year. The previous estimate was between two and four cases in every 10 000 women each year. All these estimates relate to women who are otherwise in good health

- There is no reason for women to stop taking drospirenone-containing COCs or any other COC on the basis of these findings

Advice for women:

- All hormonal contraceptives are highly effective and safe. They have important health benefits, including those from avoiding unplanned pregnancy. If you take Yasmin, there is no need to stop doing so on the basis of these findings. When used appropriately, the benefits of all combined oral contraceptives, including Yasmin, far outweigh the risk of VTE, which is rare

- 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.** If you stop taking your pill, you will need to use another method of contraception, such as a condom, from then on because you otherwise risk becoming pregnant

- A number of combined oral contraceptives and other contraceptive choices are available. Your contraceptive provider will discuss the most suitable choice of contraceptive for you, taking into consideration your medical history and any contraindications

- Venous thromboembolism (VTE) associated with use of combined oral contraceptives is not a new issue. The risk of a VTE for any combined oral contraceptive, including Yasmin, is very small and smaller than the risk of VTE associated with pregnancy

- The combined pill contains an oestrogen (ethinylestradiol) and a progestogen, and the level of risk of VTE varies slightly according to the type of progestogen. Evidence now shows that the risk is lowest with pills that contain the progestogen levonorgestrel and is slightly higher in pills that contain the progestogens drospirenone (such as Yasmin), desogestrel, or gestodene

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Yellow Card Scheme update

Y1 **Time to report**

Yellow Card reports of suspected adverse drug reactions are vital to the monitoring of side effects to medicines and vaccines. We understand that completing a Yellow Card is another demand on your valuable time, but the success of the Scheme relies on your voluntary reporting.

The following tips could help you save time when reporting Yellow Cards:

Report electronically

Completing a Yellow Card does not necessarily take long if you have access to the SystmOne GP software, which has built-in Yellow Card reporting. This has been also introduced into version 3.1 of MiDatabank pharmacy software.

Also don't forget that registering to report online at www.yellowcard.gov.uk saves time in completing your details and allows you to save a partially completed Yellow Card and return to it later.

Keep to the reporting guidelines

Focus on reporting:

- All reactions for Black Triangle medicines

- Serious reactions for established medicines

We also are particularly interested in receiving Yellow Cards for:

- Adverse reactions in children or the elderly
- Delayed drug effects
- Congenital anomalies
- Reactions to herbal remedies
- Drug interactions

What information to include

Remember for a valid Yellow Card report, we need only four pieces of information:

- Suspect drug(s)
- Suspected reaction(s)
- Patient information (at least one of age, sex, or a local patient identification number)
- Your name and contact details (in case we need to contact you for follow-up information)

It is helpful to have further information such as reaction outcome, concomitant medicines and relevant medical history, but should not prevent you from reporting the suspected adverse reaction if these are unavailable.

Show your support of the Yellow Card Scheme by reporting suspected adverse drug reactions for medicines and vaccines, and you can help make medicines safer.

See www.yellowcard.gov.uk

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