IRISH MEDICINES BOARD

Drug Safety NEWSLETTER

42nd EDITION

Cubicin (daptomycin) – Risk of Eosinophilic Pneumonia

Cubicin (daptomycin) is a lipopeptide antibiotic active against Gram positive bacteria only. It is indicated for the treatment of complicated skin and soft-tissue infections (cSSTI), right-sided infective endocarditis (RIE) due to Staphylococcus aureus and Staphylococcus aureus bacteraemia when associated with RIE or with cSSTI.

Since first licensed via a centralised European assessment procedure in 2006, there have been case reports globally of eosinophilic pneumonia and pulmonary eosinophilia associated with daptomycin use. Although the exact incidence of eosinophilic pneumonia associated with daptomycin is unknown, up to now, the reporting rate has been very low (<1/10 000).

In severe cases, hypoxic respiratory insufficiency requiring mechanical ventilation may occur, making prompt recognition of the clinical syndrome critical. Diagnostic findings include increased eosinophils in the lung tissue or bronchoalveolar lavage fluid, along with diffuse infiltrates on chest radiographs. Although clinical suspicion should be raised if there is an elevated peripheral eosinophil count in the setting of pulmonary infiltrates, there have been cases of eosinophilic pneumonia with normal peripheral eosinophil counts. Therefore the absence of peripheral eosinophils does not exclude a diagnosis of eosinophilic pneumonia.

Information on this issue was previously highlighted via a Direct Healthcare Professional Communication (DHPC) distributed by the manufacturing authorisation holder in agreement with the IMB and is available on **www.imb.ie**.

Advice for Healthcare professionals

- The most common symptoms of eosinophilic pneumonia include cough, fever and dyspnoea. In severe cases, hypoxic respiratory insufficiency requiring mechanical ventilation may occur.
- Most cases have occurred after 2 weeks of treatment. The majority of cases reported to date occurred after 2 weeks of treatment.
- Prompt recognition of the clinical syndrome and its possible association with daptomycin is critical in the care of these patients.
- Clinical management includes drug discontinuation and often includes treatment with corticosteroids.
- Daptomycin should not be readministered to patients who have experienced eosinophilic pneumonia with this drug.
- Prescribers should always consider local guidance on the use of antibacterial agents.

Key Messages

- **If eosinophilic pneumonia is suspected, daptomycin should be discontinued immediately and if appropriate the patient treated with corticosteroids. Daptomycin should not be readministered to patients who have experienced eosinophilic pneumonia with this drug.**
- **Any suspected adverse reactions with daptomycin should be reported to the IMB.**

In this edition

Update on drospirenone-containing combined oral contraceptives (Yasmin, Yasminelle, YAZ and generics*) and Risk of Venous Thromboembolism

Recent epidemiological studies have shown that the risk of venous thromboembolism (VTE) for drospirenone-containing combined oral contraceptives (COCs) is higher than for levonorgestrel-containing COCs (so-called second generation COCs) and may be similar to the risk for COCs containing desogestrel or gestodene (so-called third generation COCs).

Yasmin (ethinylestradiol 0.03mg + drospirenone 3mg) has been authorised in the EU since 2000 and contains the progestogen drospirenone. Since then, other drospirenone-containing COCs have been approved including YAZ and Yasminelle (ethinylestradiol 0.02mg + drospirenone 3mg). The risk of VTE has been continuously monitored since approval and in 2010, the product information was updated to reflect data from two studies which indicated that the risk of VTE with drospirenone-containing COCs was somewhere between the risk associated with levonorgestrel-containing COCs and third generation such as those containing gestodene and desogetrel. (See IMB Drug Safety Newsletter 37th Edition on **www.imb.ie**). Since that time, further data has become available allowing firmer conclusions about the level of risk to be drawn.

The Pharmacovigilance Working Party (PhVWP) of the European Medicines Agency has reviewed all available data regarding the risk of VTE associated with drospirenone-containing COCs including data from epidemiological studies[1-7] analysing/evaluating an association between drospirenone-containing COCs and VTE.

The results from the studies reviewed have shown that drospirenone-containing COCs are associated with a higher risk of VTE than levonorgestrel-containing COCs and that the risk for drospirenone may be similar to the risk for COCs containing desogestrel or gestodene. The PhVWP recommended that the product information for all drospirenone-containing COCs be updated to reflect these conclusions. The assessment has not changed the conclusion that the risk of VTE with any COC (including those containing drospirenone) is very small.

Risk of VTE with COCs

Since the introduction of COCs in 1961, VTE has been a well-known but rare adverse event associated with their use. VTE has been reported with the use of all COCs, including those containing ethinylestradiol + drospirenone, such as Yasmin, Yasminelle and YAZ. Of 100,000 women who are not using a COC and are not pregnant, about 5 to 10 may experience VTE in one year. The corresponding figures for women taking COCs range from about 20 cases per 100,000 women in one year of use for levonorgestrel-containing COCs to 40 cases per 100,000 women in one year of use for desogestrel or gestodene-containing COCs. Of 100,000 women who are pregnant, around 60 may experience VTE.

Advice to Healthcare Professionals

Recent evidence suggests that the risk of VTE for drospirenone-containing COCs is higher than for levonorgestrel-containing COCs (so-called second generation COCs) and may be similar to the risk for COCs containing desogestrel or gestodene (so-called third generation COCs).

- The risk of a venous thrombosis in women who use drospirenone-containing COCs (including Yasmin, Yasminelle and YAZ), as for all combined oral contraceptive pills, is smaller than the risk of VTE associated with pregnancy.
- Prescribers should take this new evidence into consideration when discussing the most suitable type of contraceptive with a woman who wants to start or switch contraception.
- Prescribing decisions should also take into account each woman's relevant medical history and any associated risk factors and contraindications.
- All patients should be advised to report symptoms of unusual pain, redness or swelling in the legs; sudden shortness of breath or difficulty in breathing; sudden coughing for no apparent reason.
- All combined oral contraceptives, including Yasmin, Yasminelle and YAZ, should be prescribed with caution to obese women (BMI>30), or those with a higher baseline risk of VTE for other reasons.
- There is no reason for women to stop taking drospirenone-containing COCs, such as Yasmin, Yasminelle and YAZ, or any other COC on the basis of this review.

Key Messages

- **New epidemiological studies have shown that the risk of venous thromboembolism (VTE) for drospirenone-containing combined oral contraceptives (COCs) is higher than for levonorgestrel-containing COCs (so-called second generation COCs) and may be similar to the risk for COCs containing desogestrel or gestodene (so-called third generation COCs).**
- **The assessment has not changed the conclusion that the risk of VTE with any COC (including Yasmin, YAZ, and Yasminelle) is very small.**
- **When used appropriately, the benefits of all combined oral contraceptives outweigh the risk of VTE, which is rare.**

* Brand names include Liofora, Palandra and Rimendia.

References are available upon request from the Irish Medicines Board

Bisphosphonates – Risk of Atypical Femoral Fracture

Bisphosphonates* are a class of medicines which inhibit osteoclast mediated bone resorption and are indicated in certain malignant and benign diseases, including prophylaxis and treatment of osteoporosis.

In 2008, a European review concluded that the available data supported an association between alendronate and atypical stress fractures of the femur and the product information for alendronate was updated to include a warning about this risk. A class effect could not be ruled out however and the issue was kept under close review.

As part of this ongoing monitoring, a recent evaluation of new data from published literature, case reports and epidemiological studies was conducted by the Pharmacovigilance Working Party (PhVWP) of the European Medicines Agency. The PhVWP concluded that the risk of atypical femoral fractures is likely to be a class effect of bisphosphonates, but that such fractures occur only rarely.

The precise mechanism is unknown however it is possible that the effect of bisphosphonates on the suppression of bone turnover may lead indirectly to the delay or prevention of repair of naturally occurring stress fractures. Atypical femoral fractures can occur after minimal or no trauma. Some patients experience thigh or groin pain, often associated with features of stress fractures on x-ray, weeks to months before presenting with a completed femoral fracture. Poor healing of these fractures has been reported.

The product information for these medicines will be updated to inform healthcare professionals and patients that atypical femoral fractures have been reported rarely with bisphosphonates, primarily in patients receiving long-term treatment for osteoporosis. For bisphosphonates used in osteoporosis, the product information will also advise periodic review of therapy, in particular after five or more years of treatment.

Please see the Summaries of Product Characteristics for the individual products for full details of the specific prescribing information applicable, including details of potential adverse reactions and risk minimisation measures.

Advice for Healthcare Professionals

- During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain. Any patient presenting with such symptoms should be evaluated for an incomplete fracture of the femur.
- 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 fracture of the femur should be considered pending evaluation of the patient, based on an individual benefit risk assessment.
- The optimal 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 on an individual patient basis, particularly after 5 or more years of use.
- Any cases of atypical femoral fractures or atypical fractures at other sites associated with bisphosphonate treatment should be reported to the IMB.

Key Messages

- **Atypical femoral fractures have been reported rarely with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of bisphosphonate therapy on an individual patient basis, particularly after 5 or more years of use.**
- **The overall balance of risks and benefits of individual bisphosphonates in their authorised indications remain favourable.**

* Bisphosphonates currently authorised in Ireland include: alendronate, clodronate, ibandronate, pamidronate, risedronate and zoledronate.

Direct Healthcare Professional Communications published on the IMB website since the last drug Safety Newsletter:

Product	Safety Issue
Revlimid (lenalidomide)	Potential risk of second primary malignancies
Vectibix (panitumumab)	Association with keratitis and ulcerative keratitis
Thalidomide Celgene (thalidomide)	Risk of thromboembolic events

Revlimid – Investigation of potential risk of second primary malignancies

Revlimid (lenalidomide) is an immunomodulating agent first licensed via a European assessment procedure in 2007, subject to a number of risk minimisation measures including a pregnancy prevention plan to ensure its safe use. Structurally related to thalidomide, Revlimid is authorised for use in combination with dexamethasone for the treatment of multiple myeloma in patients who have received at least one prior therapy.

Data from clinical trials have recently come to the attention of regulatory authorities in which lenalidomide was given as maintenance treatment for patients with newly diagnosed multiple myeloma. This treatment population falls outside the currently authorised indication for lenalidomide. These data show an apparent excess of second primary malignancies in patients treated with lenalidomide. In these trials, the malignancies were mainly haematological. Based on this observation, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has commenced a review of the benefit-risk of lenalidomide in the authorised indication. This information was communicated via a Direct Healthcare Professional Communication by the manufacturing authorisation holder in agreement with the IMB in April 2011 and is available on **www.imb.ie**.

The data show a reproducible signal for an excess incidence of second primary haematological and non-haematological malignancies in patients with newly diagnosed multiple myeloma who have been treated with lenalidomide compared with controls. However, at present, it is not possible to conclude that the risk has been categorically established or that the risk is equally relevant to the licensed indication. More comprehensive data are being obtained. Furthermore, the effects of potential confounding risk factors are unknown, including possible imbalances in molecular or biological markers.

The CHMP will now review all available data, including published data, non-clinical and clinical data and post-marketing reports, and will assess their impact on the balance of risks and benefits of this medicine in its authorised indication. Use of lenalidomide for indications other than the authorised indication falls outside the scope of the current benefit-risk review. Further information will be communicated, following the conclusion of the CHMP evaluation, as necessary.

Advice for healthcare professionals

- Use of lenalidomide in patients with newly diagnosed multiple myeloma or other unlicensed indications is not recommended. Healthcare Professionals should carefully consider the balance of risks and benefits of any off-label use.
- While the review is ongoing, the CHMP is not recommending a delay, modification or restriction in the use of lenalidomide for patients treated according to the authorised indication.
- Healthcare Professionals are advised to be vigilant for the occurrence of second primary malignancies whenever lenalidomide has been prescribed, especially in unlicensed indications, and to report such events and any other suspected adverse reactions promptly to the IMB via the usual routes.

Key Messages

- **A higher incidence of second primary malignancies in patients treated with lenalidomide compared to controls has been observed in clinical studies conducted outside of the authorised indication.**
- **The use of lenalidomide in unlicensed indications is not recommended.**

IRISH MEDICINES BOARD

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Drug Safety NEWSLETTER
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IRISH MEDICINES BOARD

Intravenous Paracetamol Solutions for Infusion – Risk of Medication Errors in Infants and Children

Paracetamol 10 mg/ml solutions for infusion are indicated for:

- the short-term treatment of moderate pain, especially following surgery
- the short-term treatment of fever
  - when administration by IV route is clinically justified by an urgent need to treat pain or hyperthermia
  - and/or when other routes of administration are not possible

There have been reports of medication errors leading to overdose received worldwide, many involving children who accidentally received a greater dose than that prescribed. The errors resulted from the prescription of IV paracetamol solution being issued in **mg**, but then administered in **ml**. Erroneously giving the same number of ml as the prescribed dose in mg will result in a dose 10 times that prescribed. Such accidental overdoses may be fatal. It is important to remember the concentration of IV paracetamol solutions for infusion is 10mg per ml.

1ml = 10mg paracetamol

Following identification of this issue, the manufacturing authorisation holders for these products, in agreement with the IMB, issued a communication to healthcare professionals using this product, urging caution when prescribing and administering IV paracetamol infusions in infants. This communication is available on **www.imb.ie**.

The relevant dosing information from the Summary of Product Characteristics for **full-term newborns, infants and children weighing less than 10 kg** (approximately 1 year of age) is summarised below:

	Full-term newborns, infants and children weighing < 10 kg
Dose (per administration)	One intravenous infusion of 7.5 mg/kg **i.e. 0.75 ml solution per kg**
Dosing schedule	A maximum of **four administrations per 24 hours** of 7.5 mg/kg (**0.75 ml per kg**)
	Allow an interval of at least 4 hours between each infusion
Maximum daily dose	Do not exceed 30 mg/kg (**3 ml/kg**) in 24 hours

No efficacy and safety data are available in premature newborn infants.

50ml and 100ml presentations are available* containing 500mg and 1000mg paracetamol respectively. The volumes that are administered in paediatrics will be very small. The 50ml presentation should be used for smaller doses.

In both adults and children care should be taken to avoid duplicating doses, it is advised to check that other medicines being administered do not contain paracetamol. It is recommended that a suitable analgesic oral treatment be used as soon as this route of administration is possible.

The minimum interval between doses should not be less than 4 hours or 6 hours in patients with severe renal impairment. Hepatotoxicity may can occur if therapeutic doses are exceeded. At particular risk for hepatic damage are elderly patients, young children, patients with hepatic disorders, chronic alcoholism, chronic malnutrition and patients receiving enzyme inducers. Symptoms generally appear within 24 hours and include: nausea, vomiting, anorexia, pallor and abdominal pain.

A dosing table example for use in children weighing less than 10 kg, which shows the actual volume of paracetamol solution to be infused according to weight, is outlined below:

Infant weight (kg)	Prescribed dose (mg)	Volume to be infused (ml)	Infant weight (kg)	Prescribed dose (mg)	Volume to be infused (ml)
1 kg	7.5 mg	0.75 ml	6 kg	45.0 mg	4.50 ml
2 kg	15.0 mg	1.50 ml	7 kg	52.5 mg	5.25 ml
3 kg	22.5 mg	2.25 ml	8 kg	60.0 mg	6.00 ml
4 kg	30.0 mg	3.00 ml	9 kg	67.5 mg	6.75 ml
5 kg	37.5 mg	3.75 ml			

An overall summary of dosing information for intravenous paracetamol is also outlined below. The complete product information should be consulted for full dosing information and guidance in the event of overdose, (see **www.imb.ie**).

Patient weight	Dose (per administration)	Minimum interval between doses	Maximum daily dose
≤ 10 kg	7.5 mg/kg i.e. 0.75 ml solution/kg	4 hours	30 mg/kg (i.e.3ml/kg)
> 10 kg and ≤ 33 kg	15 mg/kg i.e. 1.5 ml solution/kg	4 hours	60 mg/kg (i.e.6ml/kg) Without exceeding 2 g (i.e.200 ml)
> 33 kg and ≤ 50 kg	15 mg/kg i.e. 1.5 ml solution/kg	4 hours	60 mg/kg (i.e.6ml/kg) Without exceeding 3 g (i.e. 300ml)
> 50 kg	1g i.e. 1 vial or 1 bag	4 hours	4 g (i.e. 400ml)

Advice for Healthcare Professionals:

- The strength of paracetamol solutions for infusion is **10 mg paracetamol per 1 ml.**
- The product is dosed per patient weight in children and adults ≤ 50kg.
- The volumes that are administered in paediatrics will be very small. The 50ml presentation should be used in these circumstances.
- Extreme care should be taken with prescribing and administration of IV paracetamol, especially in infants.
- IV paracetamol should only be used when other routes of administration are not possible.
- Any suspected adverse reactions associated with IV paracetamol should be reported to the IMB. Medication errors resulting in adverse reactions may also be reported using the same options.

Key Messages

- **IV paracetamol solutions for infusion contain 10mg paracetamol per 1 ml.**
- **Extreme caution is needed when prescribing and administering this product in infants and children.**

* 50ml presentations are only available for some brands of IV paracetamol 10mg/ml solution for infusion.

Correspondence/Comments should be sent to the

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