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

Volume 7, Issue 7, **February 2014**

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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This month, the cetuximab indication has been updated. In the treatment of metastatic colorectal cancer, inferior overall survival, progression-free survival, and objective response rates have been shown in people with *RAS* mutations (at exons 2, 3, and 4 of *KRAS* and *NRAS*) who received cetuximab in combination with FOLFOX4 (oxaliplatin-containing) chemotherapy versus FOLFOX4 alone. Evidence of wild type *RAS* status at these exons is required before initiating treatment with cetuximab alone or in combination with chemotherapy in metastatic colorectal cancer. Cetuximab combined with oxaliplatin-containing chemotherapy is now contraindicated in people with metastatic colorectal cancer who have mutant *RAS* at these exons or unknown *RAS* status—see article A1.

We also inform you of the outcome of a Europe-wide review of the latest evidence on the risk of venous thromboembolism (VTE) in association with combined hormonal contraceptives (CHCs). The review has confirmed previous understanding that the level of VTE risk with all low dose CHCs (ethinylestradiol <50 micrograms) is small. When prescribing a CHC, carefully consider the contraindications for use, a woman's current risk factors, and the differences in risk of VTE between products, with those containing levonorgestrel, norethisterone, or norgestimate having the lowest risk—see article A2.

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Drug safety advice

A1 Cetuximab: importance of establishing wild type *RAS* (*KRAS* and *NRAS*) status before treatment of metastatic colorectal cancer

In the treatment of metastatic colorectal cancer, inferior overall survival, progression-free survival, and objective response rates have been shown in people with *RAS* mutations (at exons 2, 3, and 4 of *KRAS* and *NRAS*) who received cetuximab in combination with FOLFOX4 (oxaliplatin-containing) chemotherapy versus FOLFOX4 alone. Cetuximab is now indicated for the treatment of people with epidermal growth factor receptor (EGFR)-expressing, *RAS* wild-type metastatic colorectal cancer in combination with irinotecan or oxaliplatin based chemotherapy or as a single agent. Evidence of wild type *RAS* status at these exons is required before initiating treatment with cetuximab alone or in combination with chemotherapy in metastatic colorectal cancer. Cetuximab combined with oxaliplatin-containing chemotherapy is now contraindicated in people with metastatic colorectal cancer who have mutant *RAS* at these exons or unknown *RAS* status

Cetuximab (Erbitux) is a treatment for people with metastatic colorectal cancer.

New safety information has become available from a retrospective subset analysis of data from a randomised, multicentre phase II study (OPUS trial EMR 62202-047[1]) of cetuximab plus (oxaliplatin-containing) FOLFOX4 chemotherapy versus FOLFOX4 alone in people with previously untreated metastatic colorectal cancer. The OPUS trial included 337 people, 179 of whom had wild type *KRAS* exon 2 tumour status; incidence of additional *RAS* mutations (at *NRAS* exons 2, 3 and 4, and at *KRAS* exons 3 and 4) in this subset was 30·5%.

1. Bokemeyer C, et al. *J Clin Oncol* 2009; **27:** 663–71

People with *RAS* mutations who were randomly assigned cetuximab plus FOLFOX4 had inferior survival, progression-free survival and objective response rates than did those assigned FOLFOX4 alone. Safety evaluations showed no new findings attributable to cetuximab when comparing wild type and mutated *RAS* populations: the inferior outcome was due to lack of efficacy in combination with the known toxicity profile as outlined in the product information.

Cetuximab product information
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000558/human_med_000769.jsp&mid=WC0b01ac058001d124

Evidence of wild type *RAS* status at exons 2, 3, and 4 of *KRAS* and *NRAS* is required before initiating treatment with cetuximab alone or in combination with chemotherapy in metastatic colorectal cancer. Cetuximab combined with oxaliplatin-containing chemotherapy (eg, FOLFOX4) is now contraindicated in people with metastatic colorectal cancer who have mutant *RAS* (at exons 2, 3, and 4 of *KRAS* and *NRAS*) or unknown *RAS* status.

Advice for healthcare professionals:

- Evidence of wild type *RAS* status (at exons 2, 3, and 4 of *KRAS* and *NRAS*) is required before initiating treatment with cetuximab alone or in combination with chemotherapy in metastatic colorectal cancer
- Cetuximab combined with oxaliplatin-containing chemotherapy (eg, FOLFOX4) is contraindicated in all people with metastatic colorectal cancer who have mutant or unknown *RAS* status
- *RAS* mutation status should be determined by an experienced laboratory using a validated test method
- Prescribing information for cetuximab in the treatment of people with squamous-cell carcinoma of the head and neck is not changed by the new information from this analysis

Further information
Letter sent to healthcare professionals, January 2014
http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON370026

Similar advice issued for panitumumab (Vectibix) in September 2013
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON314896

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A2 Combined hormonal contraceptives and venous thromboembolism: review confirms risk is small—consider risk factors and remain vigilant for signs and symptoms

A review of the latest evidence on the risk of thromboembolism in association with combined hormonal contraceptives (CHCs) has concluded that:

- the risk of blood clots with all low-dose CHCs is small
- there is good evidence that the risk of venous thromboembolism (VTE) may vary between products, depending on the progestogen
- CHCs that contain levonorgestrel, norethisterone, or norgestimate have the lowest risk of VTE
- the benefits of any CHC far outweigh the risk of serious side effects
- prescribers and women should be aware of the major risk factors for thromboembolism, and of the key signs and symptoms

Letter sent through Central Alerting System: https://www.cas.dh.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=102106

European review: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Combined_hormonal_contraceptives/human_referral_prac_000016.jsp&mid=WC0b01ac05805c516f

Risk of VTE

In January we sent a letter through the Central Alerting System to inform prescribers of the outcome of a European review of the latest evidence on the risk of thromboembolism with CHCs. The review confirmed our previous understanding that the level of risk of VTE with all low-dose CHCs (ethinylestradiol <50 micrograms) remains small and products with the lowest risk of VTE are those containing the progestogens levonorgestrel, norethisterone, and norgestimate. Progestogen-specific estimates of VTE incidence are provided in the table.

Table: Risk of VTE with CHCs

Progestogen in CHC (combined with ethinylestradiol, unless stated)	**Relative risk vs levonorgestrel**	**Estimated incidence (per 10 000 women per year of use)**
Non-pregnant non-user	-	2
Levonorgestrel	Ref	5–7
Norgestimate; norethisterone	1.0	5–7
Gestodene; desogestrel; drospirenone	1.5–2.0	9–12
Etonogestrel; norelgestromin	1.0–2.0	6–12
Dienogest (combined with ethinylestradiol or estradiol)/ nomegestrel acetate (estradiol)	To be confirmed*	To be confirmed*

*Further studies ongoing or planned to collect sufficient data to estimate risk for these products.

We have also taken this opportunity to update baseline VTE rates to reflect current evidence. Compared with previous rates, the increased values are likely to be due to improvements in VTE diagnosis and reporting, and due to an increase in obesity over time. The new rates will be included in updated product information (Summary of Product Characteristics and Patient Information Leaflet)

Our recent letter includes the following tools to help prescribers and women jointly make informed choices:

- *Prescribing checklist*

Letter: https://www.cas.dh.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=102106

A prescribing checklist that may be used during a CHC consultation has also been made available (annex 2 of the letter). The checklist:

I. specifies the conditions that contraindicate the use of a CHC
II. lists the factors that increase a woman's risk (such as older age, obesity, prolonged immobilisation, surgery, personal history of thromboembolism, smoking etc)
III. reminds prescribers that the presence of more than one risk factor may constitute a contraindication

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- *Information for women*

A user card and information sheet have also been made available for women. One describes the signs and symptoms of deep vein thrombosis, pulmonary embolism, stroke, and heart attack and states when the risk of a thromboembolism may be particularly high (annex 3 of the letter). The other provides more detailed information on the risk of thromboembolism with CHCs in the form of questions and answers (annex 4 of the letter). You may wish to provide this information to women during their consultation.

Letter: https://www.cas.dh.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=102106

Updated product information

The Summary of Product Characteristics for prescribers and the Patient Information Leaflet for women will be updated to reflect current understanding of the available evidence and to make information on the risk of thromboembolism as clear as possible.

Advice for healthcare professionals:

- There is no need for any woman to change her CHC on the basis of this review and the updated information
- Consider using the prescribing checklist to help CHC consultations
- Carefully consider: any contraindications for use; the difference in risk of VTE between products; and a woman's current risk factors when prescribing a CHC
- Reassess a woman's risk factors at routine appointments
- Discuss the risk of VTE with each woman, and raise awareness of the signs and symptoms of thromboembolism when prescribing a CHC; consider providing her with the further information mentioned above
- Always consider the possibility of a CHC-associated thromboembolism when presented with a woman who has relevant symptoms
- Ask all women with signs and symptoms of thromboembolism if they are "taking any medicines *or if they are using a combined hormonal contraceptive*"

Advice to give to women:

- Remind women to read the Patient Information Leaflet that accompanies each pack of CHCs and if you consider it helpful, recommend that they read the information provided in user card and information sheet
- Remind women to mention that they are using a CHC if asked whether they are taking any medicines

Further information

The additional guidance documents that have been developed to help consultations are available through the Central Alerting System: https://www.cas.dh.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=102106 or the MHRA's website: http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Product-specificinformationandadvice-G-L/Hormonalcontraceptives/Combinedhormonalcontraceptives/index.htm

When discussing the most suitable type of contraceptive for any woman, prescribers should also be aware of current product information: http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/ and clinical guidance (Medical Eligibility Criteria (MEC): http://www.fsrh.org/pdfs/UKMEC2009.pdf and Faculty of Sexual Healthcare: http://www.fsrh.org/pdfs/CEUGuidanceCombinedHormonalContraception.pdf)

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S1 **Abraxane (paclitaxel, formulated as albumin-bound nanoparticles): potential presence of strands in intravenous infusion bag—if visible, filtration advised**

Abraxane (paclitaxel, formulated as albumin-bound nanoparticles) is a treatment for metastatic breast cancer in patients who have not responded to first-line treatment, or for whom standard anthracycline-containing therapy is not indicated.
There have been reports from Europe of thin, translucent or white-to-yellow proteinaceous strands (1–2 mm in length) being observed during visual inspection of bags of reconstituted paclitaxel suspension for intravenous infusion.
The cause of these strands is thought to be an interaction between albumin and silicone oil lubricant within medical devices such as syringes and locks of intravenous bags. There is no evidence of an increased risk of any adverse effect in patients treated with Abraxane containing strands. However, as a precaution we are advising that Abraxane with visible strands should be filtered as outlined below.

Advice for healthcare professionals:

- As a precaution, Abraxane suspension should be inspected visually using standard procedure for presence of particulate matter or discolouration in the infusion bag before administration. The suspension should appear milky and homogenous without visible precipitates
- If strands are visible in the bag, administer Abraxane through an infusion set incorporating a 15 micrometre filter. This filter removes strands and does not change the physical or chemical properties of the reconstituted product. If strands are present and a filter is not available, discard the product
- Suspected adverse reactions or the presence of visible strands in Abraxane can be reported to us on a Yellow Card (www.mhra.gov.uk/yellowcard)

Further information
Letter sent to healthcare professionals, January 2014
http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON370026

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