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## Pharmacovigilance Working Party (PhVWP)

### May 2011 plenary meeting

The CHMP Pharmacovigilance Working Party (PhVWP) held its May 2011 plenary meeting on 16-18 May 2011.

### Safety concerns

Discussions on non-centrally authorised medicinal products are summarised below in accordance with the PhVWP publication policy. The positions agreed by the PhVWP for non-centrally authorised products form recommendations to Member States. For the publication policy, readers are referred to [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2009/10/WC500006181.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2009/10/WC500006181.pdf).

The PhVWP also provides advice to the Committee for Medicinal Products for Human Use (CHMP) on centrally authorised products and products subject to ongoing CHMP procedures at the request of the CHMP. For safety updates concerning these products, readers are referred to the CHMP monthly report (<http://www.ema.europa.eu>, go to: [about us/Committees/CHMP/Committees meeting reports](#)).

### ***Ethinylestradiol + drospirenone-containing oral contraceptives (YASMIN, YASMINELLE and other products) – Risk of venous thromboembolism***

**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 PhVWP completed a review of all available data including recent publications and information on additional analyses regarding the risk of venous thromboembolism (VTE) associated with drospirenone-containing combined oral contraceptives (COCs), such as YASMIN and YASMINELLE. The assessment has not changed the conclusion that the risk of VTE with any COC (including those containing drospirenone) is very small. The PhVWP concluded that the data have shown that drospirenone-containing COCs are associated with a higher VTE risk than levonorgestrel-containing COCs and that

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the risk may be similar to that for COCs containing desogestrel or gestodene. The PhVWP recommended that the product information for all drospirenone-containing COCs should be updated to reflect these conclusions.

There is no reason for women to stop taking drospirenone-containing COCs, such as YASMIN and YASMINELLE, or any other COC on the basis of this review (see Annex 1 for the Summary Assessment Report).

### ***Yttrium citrate (<sup>90</sup>Y) – Risk of osteonecrosis with injection for inflammatory rheumatism of the knee***

#### **Osteonecrosis of the knee may occur as an adverse reaction of radiation synovectomy with YTTRIUM (<sup>90</sup>Y) COLLOID SUSPENSION FOR LOCAL INJECTION CIS BIO INTERNATIONAL used for inflammatory rheumatism.**

The PhVWP reviewed the most recent periodic safety update report for the Yttrium citrate (<sup>90</sup>Y)-containing medicinal product YTTRIUM (<sup>90</sup>Y) COLLOID SUSPENSION FOR LOCAL INJECTION CIS BIO INTERNATIONAL which included 16 cases of osteonecrosis of the knee in association with this product published in the medical literature. The PhVWP concluded that osteonecrosis of the knee should be included as an adverse reaction in the product information and that recommendations regarding safe use of the product should be reinforced where necessary. The PhVWP further recommended that the risk of osteonecrosis in association with radiation synovectomy should continue to be monitored, particularly in Member States where there is significant exposure to this medical procedure (see Annex 2 for the Summary Assessment Report).

## **Guidelines and general matters**

Below is a summary of the main discussions on guidelines and other general matters of an organisational, regulatory or methodological nature.

### ***New term of PhVWP Patient Observers***

The PhVWP thanked Albert van der Zeijden and Greetje Goossens (alternate) for their important contribution as PhVWP Patient Observers during the term from May 2010 to April 2011 and welcomed Albert van der Zeijden and Cristina Cabrita (alternate) for the next term until June 2012.

Patient/consumer observers have been attending the meetings of the PhVWP since May 2010 and contribute their views to the PhVWP discussions. They are appointed following a call for expression of interest issued to eligible patient and consumer organisations. For more information on the involvement of patients and consumers in the work of the agency, interested readers are referred to [http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners\\_and\\_networks/general/general\\_content\\_000317.jsp&murl=menus/partners\\_and\\_networks/partners\\_and\\_networks.jsp&mid=WC0b01ac058003500c](http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000317.jsp&murl=menus/partners_and_networks/partners_and_networks.jsp&mid=WC0b01ac058003500c). More specifically, a report on the experience gained from a pilot phase of patient and consumer involvement in the PhVWP is available under: [www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2010/02/WC500074871.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/02/WC500074871.pdf).

## **Regulatory abbreviations**

CHMP – Committee for Medicinal Products for Human Use

CMD(h) – Co-ordination Group for Mutual Recognition and Decentralised Procedures for Human Medicines

EU – European Union

HMA – Heads of Medicines Agencies

PASS – post-authorisation safety study

PhVWP – CHMP Pharmacovigilance Working Party

PL – package leaflet

PSUR – periodic safety update report

RMP – risk-management plan

SmPC – summary of product characteristics

## **Annex 1**

### ***Summary Assessment Report of the PhVWP May 2011***

## **Ethinylestradiol + drospirenone-containing oral contraceptives (YASMIN, YASMINELLE and other products) – Risk of venous thromboembolism**

### **Key message**

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).

### **Safety concern and reason for current safety review**

Since the introduction of combined oral contraceptives in 1961, venous thromboembolism (VTE) has been a well-known but rare adverse event. VTE has been reported with the use of all combined oral contraceptives (COCs; combination of the two hormone types oestrogen and progestogen), including those containing ethinylestradiol + drospirenone, such as YASMIN and YASMINELLE. Of 100,000 women who are not using a COC and are not pregnant, about 5 to 10 may have a 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 have a VTE.

Drospirenone-containing COCs have been authorised in the EU since 2000 under various product names, including YASMIN (ethinylestradiol 0.03mg + drospirenone 3mg) and YASMINELLE (ethinylestradiol 0.02mg + drospirenone 3mg). The risk of VTE has been continuously monitored since approval. The product information was last updated in April 2010 to reflect data from two epidemiological studies on the risk of VTE [1, 2].

The PhVWP agreed to review all available data including recent publications and information on the additional analyses [3, 4] regarding the risk of VTE associated with drospirenone-containing COCs [1-7].

### **Information on the data assessed**

Seven epidemiological studies [1-7] analysing/evaluating an association between drospirenone-containing COCs and VTE, including some further re-analyses, have been reviewed.

### **Outcome of the assessment**

The PhVWP has now completed their review. The assessment has not changed the conclusion that the risk of VTE with any COC (including YASMIN and YASMINELLE) is very small. The results from the reviewed studies have shown that drospirenone-containing COCs are associated with a higher risk of VTE than levonorgestrel-containing COCs. Data indicate 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 should be updated to reflect these conclusions. The patient leaflet already contains clear information on the symptoms of VTE.

There is no reason for women to stop taking drospirenone-containing COCs, such as YASMIN and YASMINELLE, or any other COC on the basis of this review.

## References

- [1] Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. *Br Med J.* 2009; 339: b2890.
- [2] van Hylckama Vlieg A, Helmerhorst FM, Vandembroucke JP, Doggen CJ, Rosendaal FR. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestagen type: results of the MEGA case-control study. *Br Med J.* 2009; 339: b2921.
- [3] Jick SS, Hernandez RK. Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. *Br Med J.* 2011; 342: d2151.
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- [6] Dinger JC, Heinemann LA, Kühl-Habich D. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation. *Contraception.* 2007; 75: 344-354.
- [7] Dinger J, Assmann A, Möhner S, Minh TD. Risk of venous thromboembolism and the use of dienogest- and drospirenone-containing oral contraceptives: results from a German case-control study. *J Fam Plann Reprod Health Care.* 2010; 36: 123-129.

## **Annex 2**

### **Summary Assessment Report of the PhVWP May 2011**

## **Yttrium citrate (<sup>90</sup>Y) – Risk of osteonecrosis with injection for inflammatory rheumatism of the knee**

### **Key message**

Osteonecrosis of the knee may occur as an adverse reaction of radiation synovectomy with YTTRIUM (<sup>90</sup>Y) COLLOID SUSPENSION FOR LOCAL INJECTION CIS BIO INTERNATIONAL used for inflammatory rheumatism.

### **Safety concern and reason for current safety review**

The most recent periodic safety update report for the medicinal product YTTRIUM (<sup>90</sup>Y) COLLOID SUSPENSION FOR LOCAL INJECTION CIS BIO INTERNATIONAL contained information on 16 cases of osteonecrosis of the knee in association with use of this product for radiation synovectomy. These cases were published in the medical literature in a single article [1]. Osteonecrosis is a disease resulting from the temporary or permanent loss of blood supply to the bones and if serious may result in the death of bone tissue and collapse of the bone.

### **Clinical setting**

The medicinal product YTTRIUM (<sup>90</sup>Y) COLLOID SUSPENSION FOR LOCAL INJECTION CIS BIO INTERNATIONAL contains Yttrium citrate (<sup>90</sup>Y) and is used for radiation synovectomy in patients with chronic inflammatory rheumatism, particularly rheumatoid arthritis, of the knee. A synovectomy is a procedure to remove inflamed and hence enlarged lining, the synovial membrane, of a joint. The Yttrium citrate (<sup>90</sup>Y)-containing product is injected into the knee joint to treat enlarged synovial membrane of the knee by therapeutic irradiation.

### **Information on the data assessed**

The PhVWP reviewed the periodic safety update report, including the published retrospective study of 16 cases of osteonecrosis of the knee following radiation synovectomy reported to an orthopaedic service in Germany over a 12 year period [1]. 15 of the 16 patients underwent treatment with Yttrium citrate (<sup>90</sup>Y) for osteoarthritis and 8 of the cases had been treated more than once.

### **Outcome of the assessment**

The PhVWP reviewed the data and the biological plausibility and concluded that osteonecrosis of the knee should be included as an adverse reaction in the product information of YTTRIUM (<sup>90</sup>Y) COLLOID SUSPENSION FOR LOCAL INJECTION CIS BIO INTERNATIONAL and that recommendations regarding safe use of the product should be reinforced where necessary. The PhVWP further recommended that the risk of osteonecrosis in association with radiation synovectomy should continue to be monitored, particularly in Member States where there is significant exposure to this medical procedure.

### **References**

[1] Kisielinski K, Bremer D, Knutsen A, Röttger P, Fitzek JG. Complications following radiosynoviorthesis in osteoarthritis and arthroplasty: osteonecrosis and intra-articular infection. *Joint Bone Spine*. 2010; 77: 252-257.