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Patient Health Protection

PhVWP Monthly report on safety concerns, guidelines and general matters

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The CHMP Pharmacovigilance Working Party (PhVWP) held its April 2012 plenary meeting on 16-18 April 2012.

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.

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 meeting highlights from the CHMP published under http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/landing/news_and_events.jsp&mid=.

Blue dyes (e.g. Patent Blue V, Sulphan Blue) – Risk of serious allergic reactions

Blue dyes used for lymphatic mapping during breast tumour surgery may cause serious allergic reactions, including anaphylaxis, and it is recommended that emergency facilities are available for at least 1 hour after their administration.

The PhVWP concluded their review on safety concerns about allergic reactions following the use of blue dyes, such as Patent Blue V and Sulphan Blue (syn.: Isosulfan Blue), in sentinel lymph node biopsy (SLNB). In light of the data and the use of blue dyes in SLNB in the EU, it was concluded that awareness among surgeons on the risk of severe allergic reactions, including anaphylaxis, is important and it is recommended that emergency facilities are available for at least 1 hour after administration of the blue dye. The PhVWP recommended that the competent authorities in Member States should

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consider communicating this information to healthcare professionals within their territory as necessary, based on this review (see Annex 1 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.

ICH-E2C (R2) guideline on periodic benefit-risk evaluation report (PBRER)

The PhVWP noted that the CHMP has adopted the draft ICH-E2C (R2) guideline for release for public consultation. This guideline has been developed in the framework of the ICH process (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use), and as a revision of the current ICH-E2C (R1) guideline on periodic safety update reports (PSURs) it provides recommendations on a new format for periodic benefit-risk evaluation reports (PBRERs). The draft has already served as a basis for the good pharmacovigilance practice (GVP) module on PSURs (see PhVWP Monthly Report February 2012, issue nr 1202), as in future PSURs submitted by marketing authorisation holders to competent authorities in the EU should follow the format of the PBRER. Experts from the EU regulatory network, including the PhVWP, have contributed to the development of ICH-E2C (R2), and the PhVWP was consulted during the preparatory as well as development phase of this guideline revision. The public consultation closes on 21 May 2012. Interested readers and those wanting to participate in the public consultation are referred to the EMA website (http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/04/news_detail_001491.jsp&mid=WC0b01ac058004d5c1&jsenabled=true).

Regulatory abbreviations

CHMP – Committee for Medicinal Products for Human Use

CMDh – Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human

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 April 2012

Blue dyes (e.g. Patent Blue V, Sulphan Blue) – Risk of serious allergic reactions

Key message

Blue dyes used for lymphatic mapping during breast tumour surgery may cause serious allergic reactions, including anaphylaxis, and it is recommended that emergency facilities are available for at least 1 hour after their administration.

Safety concern and reason for current safety review

The UK competent authorities were contacted by the UK Association of Breast Surgery (ABS) to raise concern about allergic reactions following the use of blue dyes in sentinel lymph node biopsy (SLNB). A number of grade II and grade III allergic reactions were reported in the UK in association with the use of blue dyes in SLNB.

Therefore, the PhVWP agreed to review this safety concern.

Clinical setting

In sentinel lymph node biopsy (SLNB), blue dye stains the breast's lymphatic tract following subcutaneous injection (lymphatic mapping) and thus allows identification of lymph nodes draining from a tumour.

Blue dyes such as Patent Blue V and Sulphan Blue (syn.: Isosulfan Blue) are widely used in sentinel lymph node biopsy (SLNB) during tumour surgery but these substances are only authorised for use in this indication in a few Member States. In some Member States, blue dyes are used on a named patient basis.

Information on the data assessed

In the UK, a total of 70 case reports of allergic reactions in association with blue dyes in SLNB have been reported since 1975. 58 of these reports have been received since 2007, of which 26 were serious reactions.

Information from other Member States showed that the use of blue dyes in SLNB appears to vary significantly within the EU, but case reports of serious allergic reactions have been received by most Member States where blue dyes are used in SLNB.

The marketing authorisation holder for Patent Blue V informed the UK competent authorities that between 1997 and 2011 a total of 2,015,601 units were sold in Europe and that they had received 186 case reports on serious adverse reactions, including reports arising from the UK, between 1970 and 2011. These included 177 serious cases of allergic reactions where a causal relationship with Patent Blue V could not be excluded.

Data from the ALMANAC trial and NEW START, a training programme for surgeons launched in the UK in 2004, were also reviewed [1, 2].

Outcome of the assessment

The PhVWP considered the available data, and in particular the combined incidence rate of allergic reactions in association with Patent Blue V from the ALMANAC trial, a major study, and the NEW START training programme in the UK. This was 0.9% for all allergic reactions and 0.06% for serious (grade III) reactions. However, the PhVWP considered that the combined incidence rate for grade III allergic reactions from these two UK studies is likely to be an underestimate and that, in light of information on Sulphan Blue used in the US, the incidence rate for serious allergic reactions is more likely to be around 0.1%. The PhVWP also considered that while spontaneous reporting data have not reached reporting rates that could be expected on the basis of the incidence rate observed in the ALMANAC trial and the NEW START training programme, a significant rate of underreporting must be taken into account. It was noted that no deaths have been reported from these studies to date.

The PhVWP noted that regulatory action has already been taken in Portugal and France: In 2008, an article was published in Portugal's national pharmacovigilance bulletin. Also in 2008, the French competent authorities updated the summary of product characteristics for Patent Blue V with regard to allergic reactions and additionally healthcare professionals were informed by means of a direct healthcare professional communication.

The PhVWP, in light of the data and the use of blue dyes in SLNB in the EU, concluded that awareness among surgeons on the risk of severe allergic reactions, including anaphylaxis, is important and recommended that emergency facilities be available for at least 1 hour after administration of the blue dye. Depending on knowledge of use patterns, the PhVWP recommended that the competent authorities in Member States should consider communicating this information to healthcare professionals within their territory as necessary, based on this review.

References

[1] Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, Dixon JM, Yiangou C, Horgan K, Bundred N, Monypenny I, England D, Sibbering M, Abdullah TI, Barr L, Chetty U, Sinnett DH, Fleissig A, Clarke D, Ell PJ. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. J Natl Cancer Inst. 2006; 98: 599-609.

[2] Barthelmes L, Goyal A, Newcombe RG, McNeill F, Mansel RE; NEW START and ALMANAC study groups. Adverse reactions to patent blue V dye - The NEW START and ALMANAC experience. Eur J Surg Oncol. 2010; 36: 399-403.