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Patient Health Protection

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Pharmacovigilance Working Party (PhVWP)

September 2011 plenary meeting

The CHMP Pharmacovigilance Working Party (PhVWP) held its September 2011 plenary meeting on 19-21 September 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.

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 19-22 September 2011 (http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/09/news_detail_001338.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1).

Active substances with a known risk of Stevens-Johnson syndrome and toxic epidermal necrolysis

The PhVWP recommended key elements of warnings for the product information of allopurinol, carbamazepine, lamotrigine, phenobarbital, phenytoin, meloxicam, piroxicam, tenoxicam, nevirapine, sulfadiazine, sulfadoxine, sulfafurazole, sulfamethoxazol and sulfasalazine regarding their rare risk of life-threatening Stevens-Johnson syndrome and toxic epidermal necrolysis for early detection of these adverse reactions and subsequent permanent discontinuation of the medicine to improve their outcomes.

European Medicines Agency
7 Westferry Circus ● Canary Wharf
London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

HMA Management Group
Kevin O'Malley House ● Earlsfort Centre
Earlsfort Terrace ● Dublin 2 ● Ireland
Telephone +353 1 634 3453 **Facsimile** +353 1 661 4764
E-mail hma-ps@imb.ie **Website** www.hma.eu

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The PhVWP concluded their review of the product information of 14 active substances considered to have a known risk for Stevens-Johnson syndrome and toxic epidermal necrolysis, two potentially life-threatening adverse reactions of the skin. The PhVWP agreed key elements for the summaries of product characteristics (SmPCs) and package leaflets (PLs) of products containing any of these active substances and authorised in the EU[1] (see Annex 1 for the Summary Assessment Report). The PhVWP recommended that the SmPCs and PLs are checked to see if they need to be updated. In addition to the key elements agreed, the PhVWP also recommended that additional text might be included in the product information of specific active substances depending on the evidence available and national requirements.

The PhVWP informed the CMD(h) accordingly. For practical information on implementation, interested readers are advised to consult the HMA website (http://www.hma.eu/cmdh.html) for upcoming information.

For the centrally authorised active substance nevirapine, the PhVWP informed the CHMP.

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

[1] The recommendations refer to the active substances allopurinol, carbamazepine, lamotrigine, phenobarbital, phenytoin, meloxicam, piroxicam, tenoxicam, nevirapine, sulfadiazine, sulfadoxine, sulfafurazole, sulfamethoxazol and sulfasalazine.

Annex 1

Summary Assessment Report of the PhVWP September 2011

Active substances with a known risk of Stevens-Johnson syndrome and toxic epidermal necrolysis

Key message

The PhVWP recommended key elements of warnings for the product information of allopurinol, carbamazepine, lamotrigine, phenobarbital, phenytoin, meloxicam, piroxicam, tenoxicam, nevirapine, sulfadiazine, sulfadoxine, sulfafurazole, sulfamethoxazol and sulfasalazine regarding their rare risk of life-threatening Stevens-Johnson syndrome and toxic epidermal necrolysis for early detection of these adverse reactions and subsequent permanent discontinuation of the medicine to improve their outcomes.

Safety concern and reason for current safety review

In April 2010, the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) [1] contacted the European Medicines Agency with information about their analysis of how severe adverse skin reactions are reflected in the product information of medicinal products and the underlying evidence. The PhVWP acknowledged the need to increase awareness amongst healthcare professionals and patients on medicines known to cause Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), in order to allow earlier detection and treatment of these potentially life-threatening adverse reactions.

Therefore, the PhVWP agreed to develop key elements for the product information of 14 active substances identified by RegiSCAR as having a known risk of SJS or TEN to ensure that the product information contains consistent and clear information.

The active substances were

- the antigout medicine allopurinol;
- the antiepileptics carbamazepine, lamotrigine, phenobarbital and phenytoin;
- the analgesics meloxicam, piroxicam and tenoxicam;
- the antiviral nevirapine;
- the sulfonamide antibacterials sulfadiazine, sulfadoxine, sulfafurazole and sulfamethoxazol; and
- the sulfonamide anti-inflammatory sulfasalazine.

Clinical setting

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe, potentially life-threatening adverse reactions of the skin. Clinical characteristics of SJS and TEN are erythema (redness or rash), evolving sometimes into extensive blistering which resembles a second-degree burn. The erythema is accompanied by mucosal erosions of the mouth, eyes and genitals and in addition often by fever and influenza-like symptoms.

Since early detection is critical for the outcome, appropriate product information plays a key role in risk minimisation, helping patients and healthcare professionals to recognise the conditions early for immediate initiation of adequate measures.

Information on the data assessed

The PhVWP reviewed the data submitted by RegiSCAR to the Agency and other studies [2-5].

Outcome of the assessment

The PhVWP agreed key elements for inclusion in the summaries of product characteristics (SmPCs) and package leaflets (PLs) of the EU medicinal products containing any of the 14 active substances considered to have a known risk for SJS or TEN (allopurinol, carbamazepine, lamotrigine, phenobarbital, phenytoin, meloxicam, piroxicam, tenoxicam, nevirapine, sulfadiazine, sulfadoxine, sulfafurazole, sulfamethoxazol, sulfasalazine).

Prior to agreement, the proposed key elements were sent to Prof. JC Roujeau, RegiSCAR for his expert opinion in April 2011. The key elements for the PL were consulted with the European Medicines Agency Human Scientific Committees' Working Party with Patients' and Consumers' Organisations (PCWP) in June 2011. The comments were addressed and incorporated in the final key elements.

The following key elements should be included in the product information:

SmPC section 4.4:

- Life-threatening cutaneous reactions (Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)) have been reported with the use of <name of active substance>.
- Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.
- If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, <name of active substance> treatment should be discontinued.
- The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.
- If the patient has developed SJS or TEN with the use of <name of active substance>, <name of active substance> must not be re-started in this patient at any time.

SmPC section 4.8:

- Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.4).
- Frequency: very rare

PL section 2:

- Potentially life-threatening skin rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis) have been reported with the use of <name of active substance>, appearing initially as reddish target-like spots or circular patches often with central blisters on the trunk.
- Additional signs to look for include ulcers in the mouth, throat, nose, genitals and conjunctivitis (red and swollen eyes).
- These potentially life-threatening skin rashes are often accompanied by flu-like symptoms. The rash may progress to widespread blistering or peeling of the skin.
- The highest risk for occurrence of serious skin reactions is within the first weeks of treatment.

- If you have developed Stevens-Johnson syndrome or toxic epidermal necrolysis with the use of <name of active substance>, you must not be re-started on <name of active substance> at any time.
- If you develop a rash or these skin symptoms, seek immediate advice from a doctor and tell that you are taking this medicine.

PL section 4:

- Potentially life-threatening skin rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis) have been reported (see section 2).
- Frequency: very rare

In addition to the key elements agreed, the PhVWP also recommended that additional text might be included in the SmPCs and PLs of specific active substances depending on the evidence available and national requirements. In particular, the advice to patients may additionally include stopping the medicine if symptoms occur, depending on the available data and on national requirements. The extent and nature of the information in the SmPCs and PLs in addition to the key elements should be specific to the active substance and be weighed against the extent of information provided on other serious adverse reactions.

The PhVWP also recommended that the warnings should be placed prominently in SmPC section 4.4 and PL section 2 rather than at the end of these sections.

References

[1] The RegiSCAR project. Information accessible under http://regiscar.uni-freiburg.de/.

[2] Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, Auquier A, Bastuji-Garin S, Correia O, Locati F, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med. 1995; 333: 1600-1607.

[3] Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN, Sidoroff A, Schneck J, Roujeau JC, Flahault A. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs: the EuroSCAR-study. J Invest Dermatol. 2008; 128: 35-44.

[4] Mockenhaupt M. Severe drug-induced skin reactions: clinical pattern, diagnostics and therapy. J Dtsch Dermatol Ges. 2009; 7: 142-162.

[5] Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Roujeau JC. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death?. Arch Dermatol. 2000; 136: 323-327.