

24 March 2011  
EMA/CHMP/PhVWP/217595/2011  
Patient Health Protection

Monthly report

Issue number: 1103

## Pharmacovigilance Working Party (PhVWP)

### March 2011 plenary meeting

The CHMP Pharmacovigilance Working Party (PhVWP) held its March 2011 plenary meeting on 14-16 March 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](#)).

### ***High-ceiling diuretics – Evidence does not confirm risk of basal cell carcinoma***

**Evidence does not confirm a causal association between high-ceiling diuretics and basal cell carcinoma.**

Following the recent publication of a study showing an increased risk of basal cell carcinoma (BCC) with the use of high-ceiling diuretics, the PhVWP reviewed this possible safety concern<sup>1</sup>. The PhVWP concluded that the evidence does not confirm a causal association between the use of the high-ceiling diuretics and the development of BCC and that no regulatory action is currently necessary (see Annex 1 for the Summary Assessment Report).

<sup>1</sup> The active substances included in this review were bumetanide, etacrynic acid, furosemide, piretanide and torasemide.

---

#### 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](mailto:info@ema.europa.eu) Website [www.ema.europa.eu](http://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](mailto:hma-ps@imb.ie) Website [www.hma.eu](http://www.hma.eu)

## **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 March 2011***

## **High-ceiling diuretics – Evidence does not confirm risk of basal cell carcinoma**

### **Key message**

Evidence does not confirm a causal association between high-ceiling diuretics and basal cell carcinoma.

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

An observational study investigating a possible risk of basal cell carcinoma (BCC) in relation to the use of diuretics was published recently in 2010 [1]. The study was conducted because little is known about BCC in relation to diuretics, despite the photosensitising abilities of some of them (i.e. thiazides, potassium-sparing agents and furosemide). The study found that cumulative exposure to high-ceiling diuretics was associated with an increased risk of BCC but a significant dose-dependency was not demonstrated.

The PhVWP agreed to review the possible risk of BCC for the high-ceiling diuretics bumetanide, etacrynic acid, furosemide, piretanide and torasemide.

### **Clinical setting**

Diuretics have been available since the late 1950s and are widely used for the treatment of heart failure, hypertension and oedema (specific indications may differ for each diuretic). Their main effect is promoting the excretion of water and electrolytes by the kidneys.

Basal cell carcinoma (BCC), a type of skin cancer, is among the most frequently diagnosed cancers in Caucasians and its incidence is increasing. Known risk factors for the development of BCC are age and phenotypic characteristics such as hair colour, eye colour and skin phototype. The major environmental risk factor for the development of BCC is excessive exposure to ultraviolet radiation (UV), both chronic and intermittent. UV-induced risk of BCC may be enhanced in patients with increased photosensitivity because they are more likely to get (severe) sunburn due to a lower Minimal Erythema Dose (the minimum UV dose producing sunburn in a person).

A wide range of medicines have photosensitising abilities, including sulfonylurea derivatives used in diabetes mellitus, non-steroidal anti-inflammatory drugs, antipsychotics, amiodarone, cardiovascular medicines and some diuretics.

Although a possible causal relation between the total dispensed amount of photosensitising diuretics in mg (i.e. thiazides, potassium-sparing agents and furosemide) and the risks of squamous cell carcinoma (SCC) and malignant melanoma has been described in the scientific literature [5], no clear causal association has been established between diuretics and BCC.

## Information on the data assessed

The PhVWP reviewed the study [1], which was designed as a cohort study with 3 cohorts: a) patients using thiazide diuretics (ATC-code C03A and C03EA<sup>2</sup>); b) patients using potassium-sparing diuretics (ATC-code C03D); and c) patients using high-ceiling diuretics (ATC-code C03C).

In addition, a literature search was performed to identify other publications that investigated the possible causal association between the use of high-ceiling diuretics and the development of BCC [2-8].

Also, a search for relevant cases in Vigibase, the worldwide adverse reaction report database maintained by the Uppsala Monitoring Centre (World Health Organization Collaborating Centre for International Drug Monitoring), was performed for the possible causal association between diuretics (ATC-code C03) and the MedDRA<sup>3</sup> Preferred Term "Basal cell carcinoma".

## Outcome of the assessment

The PhVWP considered that the study [1] showed an increased risk of BCC in relation to the use of high-ceiling diuretics, but not with other diuretics. In general, the study was well performed and no major methodological limitations were identified, although some minor methodological issues were identified (e.g. collection of data on possible confounders).

No other studies confirming this finding were found in the literature. The two other studies specifically published on this subject showed no increased risk of BCC with diuretics [4, 5].

Further, the literature search did not identify studies describing a possible mechanism that could be involved in the development of BCC in relation to the use of high-ceiling diuretics.

Vigibase contained only two cases of BCC reported in association with diuretics. It was noted that the well-known limitations of spontaneous reporting systems are also valid for this search (e.g. underreporting of suspected adverse reactions and low sensitivity to detect adverse reactions with delayed time to onset).

The PhVWP concluded that the evidence does not confirm a causal association between the use of the high-ceiling diuretics and the development of BCC and that no regulatory action is currently necessary.

## References

[1] Ruiter R, Visser LE, Eijgelsheim M, Rodenburg EM, Hofman A, Coebergh JWW, Nijsten T, Stricker BHCh. High-ceiling diuretics are associated with an increased risk of basal cell carcinoma in a population-based follow-up study. *Eur J Cancer*. 2010; 46: 2467-2472.

[2] Addo HA, Ferguson J, Frain-Bell W. Thiazide-induced photosensitivity: a study of 33 subjects. *Br J Dermatol*. 1987; 116: 749-760.

[3] Harber LC, Lashinsky AM, Baer RL. Photosensitivity due to chlorothiazide and hydrochlorothiazide. *N Engl J Med*. 1959; 261: 1378-1381.

[4] Jensen AØ, Thomsen HF, Engebjerg MC, Olesen AB, Søre HT. Use of photosensitising diuretics and risk of skin cancer: a population-based case-control study. *Br J Cancer*. 2008; 99: 1522-1528.

[5] Kaae J, Boyd HA, Hansen AV, Wulf HC, Wohlfahrt J, Melbye M. Photosensitizing medication use and risk of skin cancer. *Cancer Epidemiol Biomarkers Prev*. 2010; 19: 2942-2949.

[6] Karagas MR, Stukel TA, Umland V, Tsoukas MM, Mott LA, Sorensen HT, Jensen AO, Nelson HH, Spencer SK, Perry AE, Stern RS. Reported use of photosensitizing medications and basal cell and squamous cell carcinoma of the skin: results of a population-based case-control study. *J Invest Dermatol*. 2007; 127: 2901-2903.

[7] Norins AL. Chlorothiazide drug eruption involving photosensitisation. *Arch Dermatol*. 1959; 79: 592.

<sup>2</sup> ATC stands for the international Anatomical Therapeutic Chemical Classification System for medicines.

<sup>3</sup> MedDRA stands for the international Medical Dictionary for Regulatory Activities.

[8] Robinson HN, Morison WL, Hood AF. Thiazide diuretic therapy and chronic photosensitivity. Arch Dermatol. 1985; 121: 522-524.