# The use of thiazide diuretics and risk of skin cancer – a systematic literature review and meta-analysis

| | |
|---|---|
| **Title** | The use of thiazide diuretics and risk of skin cancer – a systematic literature review and meta-analysis |
| **Protocol version identifier** | 3.0 |
| **Date of last version of protocol** | 11th February 2019 |
| **EU PAS register number** | |
| **Active substance** | C03AA Thiazides, plain |
| **Research question and objectives** | The aim of this study is to summarize the evidence regarding the association between thiazide class and NMSC and MM by means of systematic review and meta-analysis of previously published studies. |
| **Author** | Alexandra Pacurariu, PhD (alexandra.pacurariu@ema.europa.eu)<br>Daniel Morales, PhD, MD (Daniel.Morales@ema.europa.eu)<br>Patricia McGettigan, MD (Patricia.McGettigan@ema.europa.eu)<br>DanielZondag, MSc (danielantonio.nogueraszondag@ema.europa.eu)<br>Xavier Kurz, PhD, MD (Xavier.Kurz@ema.europa.eu)<br>Helle Wallach Kildemoes (helle.wallach@sund.ku.dk) |

# 1. Rationale and background

In December 2017, a signal about a potential association between hydrochlorothiazide (HCTZ) and non-melanoma skin cancer (NMSC) was discussed at PRAC. The signal was based on two recently published Danish pharmacoepidemiological studies which have shown that HCTZ use is associated with a marked increased risk of lip cancer and other NMSC (1,2). These two studies form the basis for the initiation of a signal management procedure regarding HCTZ and NMSC. While photosensitisation is listed as a rare adverse drug reaction (ADR) in the summary of product characteristics, skin-cancer is not listed as an ADR.

Since the evidence was not conclusive enough at this moment (certain methodological limitations cannot be avoided) it was considered that a literature review of existing studies exploring the association between NMSC and different thiazides, including the knowledge about photosensitizing and possible carcinogenic effect, would help PRAC in evaluation of the signal. Of note, failing to adjust for sun-exposure and skin phenotype as confounders in the two Danish studies were the key methodological limitations raised by the PRAC.

Due to the nature of the outcome (lag long-term between first exposure and NMSC diagnosis, complex aetiology) and the fact that HCTZ is used mostly in combination-products, in combination with other drugs and in patients with comorbidities, this association is difficult to study in an epidemiological setting and virtually impossible in clinical trials.

Therefore, we rely on evidence from observational studies for establishing or discarding a causal association between HCTZ exposure and skin cancer.

A range of studies has explored the possible carcinogenic effect of antihypertensive and/or diuretics. While HTCZ is included in many combination products, covering antihypertensive medications (beta blocking agents, calcium blocking agents, and agents acting on the renin-angiotensin system), and potassium sparing diuretics (mainly amiloride), few studies has focused on the carcinogenic properties of a specific substance.

For comprehensiveness, the current review has been extended to include malignant melanoma (MM), which will be presented separately.

This report aims to provide a review of existing available evidence regarding the association between thiazide diuretics and NMSC/MM.

# 2. Research question and objectives

The primary objective is to summarize the evidence regarding the association between thiazide class and NMSC and MM by means of

1.1 Systematic review of studies that investigated this association

1.2 Quantitative meta-analysis studies providing effect estimates evaluating the association between HCTZ or thiazide class and a) NMSC or b) MM

# 3. Research methods

## 3.1. *Literature search*

A search in Medline and Embase was conducted in order to identify interventional and non-interventional studies that investigated the association between HCTZ and other thiazides and NMSC or MM in any population (see details of the searches in the **Annex 1**). The search was supplemented with articles included in the signal assessment procedure and individual studies identified from existing reviews or meta-analysis.

The exposure of interest in this literature review was the treatment with any thiazide diuretic, single or in combination, at class level or substance level.

The outcomes of interest were NMSC and MM. These two outcomes are presented separately in this report.

## 3.2. *Inclusion criteria*

General inclusion criteria

- interventional and non-interventional studies.
- effect estimates should be reported in the study (i.e. incidence rate ratio, hazard ratio, risk ratio, odds ratio, etc.)
- exposure of interest: any antihypertensive/diuretic, at substance or class level
- outcome of interest: NMSC with its two main subtypes, basal cell carcinoma (BCC),squamous cell carcinoma (SCC), and MM.
- population: any
- the search was restricted to English language and humans.

General exclusion criteria:

-case reports or case series

-reviews, commentaries or opinion papers

-clinical guidelines

-mechanistic or preclinical studies

-meta-analysis and reviews.

Specific exclusion criteria:

In order to keep studies with acceptable quality, criteria will need to be applied for the inclusion/exclusion of studies in the set of accepted studies based on the specificity of the research question. These aspects to be considered include:

- An etiological study design able to produce effect estimates of the association

-Objective assessment of exposure through prescription, dispensing or claims data.

- measure of important confounders

- use of a relevant comparator group

- statistical analysis adjusted for important confounders.

- the ability to measure a dose/duration-effect relationship

The full list can be found in **Annex 2**.

## 3.3. *Selection process*

Initially, the studies were reviewed at title and abstract level and in a second round, the full text was assessed. The following information was extracted by two assessors experienced in pharmacovigilance and pharmacoepidemiology: type of study design, setting, population, exposure, comparators, outcomes of interest, confounders considered in the analysis, type of statistical analysis.

The full literature review if presented in the Annex 1.

# 4. Annexes

**Annex 1.** Literature search strings

**Pubmed:**

("Antihypertensive Agents"[Mesh] OR"Diuretics"[Mesh] OR "Antihypertensive Agents" [Pharmacological Action] OR Hypotensive medication[tiab] OR hydrochlorothiazide[tiab] OR clorothiazide[tiab] OR Antihypertensive[tiab] OR Diuretics [tiab] OR thiazides [tiab] OR Calcium channel blockers [tiab] OR ACE inhibitors [tiab] OR Angiotensin II receptor [tiab] OR "Adrenergic alpha-1 Receptor Antagonists" [Pharmacological Action] OR Adrenergic receptor antagonists [tiab] OR Vasodilator* [tiab] OR Renin Inhibitor* [tiab] OR Aldosterone receptor antagonist* [tiab] OR beta-blocker* [tiab] OR statin*[tiab] OR bendroflumethiazide[tiab] OR indapamide*[tiab] OR bumetanide[tiab] OR furosemide[tiab] OR Chlorthalidone[tiab])

AND ("Skin Neoplasms/epidemiology"[Mesh] OR "Carcinoma, Basal Cell/epidemiology"[Mesh] OR "Carcinoma, Squamous Cell/epidemiology"[Mesh] OR Basal Cell carcinoma [tiab] OR Skin Neoplasm*[tiab] OR Squamous Cell carcinoma[tiab] OR cutaneous T cell lymphoma [tiab] OR skin cancer[tiab] OR lip cancer[tiab] OR melanoma[tiab])

AND english[Language]

**Embase:**

'skin tumor'/exp AND 'epidemiology'/lnk OR ('basal cell carcinoma'/exp AND 'epidemiology'/lnk) OR ('squamous cell carcinoma'/exp AND 'epidemiology'/lnk) OR 'basal cell carcinoma':ab,ti OR 'skin neoplasm*':ab,ti OR 'squamous cell carcinoma':ab,ti OR 'cutaneous t cell lymphoma':ab,ti OR 'skin cancer':ab,ti OR 'lip cancer':ab,ti OR 'melanoma':ab,ti

AND

'antihypertensive agent'/mj OR 'diuretic agent'/mj OR 'antihypertensive agents pharmacology'/mj OR 'hypotensive medication':ab,ti OR 'hydrochlorothiazide':ab,ti OR 'clorothiazide':ab,ti OR 'antihypertensive':ab,ti OR 'diuretics':ab,ti OR 'thiazides':ab,ti OR 'calcium channel blockers':ab,ti OR 'ace inhibitors':ab,ti OR 'angiotensin ii receptor':ab,ti OR ('alpha 1 adrenergic receptor blocking agent'/mj AND 'pharmacology'/lnk) OR 'adrenergic receptor antagonists':ab,ti OR 'vasodilator*':ab,ti OR 'renin inhibitor*':ab,ti OR 'aldosterone receptor antagonist*':ab,ti OR 'beta-blocker*':ab,ti OR 'statin*':ab,ti OR 'bendroflumethiazide':ab,ti OR 'indapamide*':ab,ti OR 'bumetanide':ab,ti OR 'furosemide':ab,ti OR 'chlorthalidone':ab,ti

**Annex 2.** Exclusion criteria for studies to be included in the systematic review

**Background**

EMA will carry-out systematic review about hydrochlorothiazides (HCTZ) and the risk of cancer. In order to keep studies with acceptable quality, criteria will need to be applied for the inclusion/exclusion of studies in the set of accepted studies based on the specificity of the research question. These aspects to be considered include:

- an etiological study design able to produce effect estimates of the association

- objective assessment of exposure through prescription, dispensing or claims data

- measure of important confounders, such as sun exposure

- use of a relevant comparator group

- statistical analysis adjusted for important confounders

- the ability to measure a dose/duration-effect relationship

**Objective**

- To propose criteria to be applied in a first round of selection of studies assessing the risk of cancer in association with exposure to HCTZ.
- Based on a preliminary literature search, to propose examples of studies that may have to be excluded based on the proposed criteria.

**Exclusion criteria**

1. No measure of association between HCTZ and occurrence of cancer

Examples: Cognetta 2016: case series, no comparator group

Jahen-Tigh, 2013: case series, no estimate of association

2. Inadequate measurement of exposure (including dose and duration), outcome and important confounders

Example: Robinson, 2013: face-to face interview to measure sun exposure and medication use

Moscarelli, 2010: Pooling of exposure classes in the analysis

De Vries, 2012, Traianou, 2012: exposure measured by self-administered questionnaire/dermatologist

3. Inadequate statistical analysis

Example: Kaae, 2010: no control for confounding in the analysis

**Additional considerations**

- "Incomplete" control of confounding is not considered an exclusion criterion because not all potential confounders are actual confounders and is debatable what exacly should be adjusted for.
- Duration of lag time before diagnosis is not considered an exclusion criterion because this would suppose good pathophysiological knowledge, time-dependent analysis can be performed and outcome of systematic review can be stratified by dose/duration
- Dose and length of duration of treatment are not considered exclusion criteria because this would suppose good pathophysiological knowledge, and dose and duration can be considered in the analysis.

- Based on the above criteria, examples of acceptable studies could include: Lindholm 2001, Westerdahl, Friedman 2012, Schmidt 2010, Armspang/Pottegard 2012, Pedersen 2017, Ruiter 2010