Medicines Adverse Reactions Committee

Meeting date	**6 December 2018**	Agenda item	3.2.1
Title	**Hydrochlorothiazide (HCTZ) and Non-Melanoma Skin Cancer**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active constituent	**Medicines**	**Sponsors**
Amiloride/HCTZ	*Moduretic* (5mg/50mg)	Pharmacy Retailing Pty Ltd
Cilazapril/HCTZ	*Apo-Cilazapril/Hydrochlorothiazide* (5mg/12.5mg)	Apotex NZ Ltd
Losartan/HCTZ	*Hyzaar* (50mg/12.5mg)	Merck Sharp & Dohme NZ Ltd
	Arrow- Losartan & Hydrochlorothiazide (50mg/12.5mg)	Teva Pharma NZ Ltd
Quinapril/HCTZ	*Accuretic* (10mg/12.5mg)	Pfizer NZ Ltd
	Accuretic (20mg/12.5mg)	

Funding	According to the November 2018 New Zealand Pharmaceutical Schedule: **Amiloride/HCTZ** *Moduretic* (5mg/50mg) – Fully Subsidised **Cilazapril/HCTZ** *Apo-Cilazapril/Hydrochlorothiazide* (5mg/12.5mg) – Fully Subsidised **Losartan/HCTZ** *Hyzaar* (50mg/12.5mg) – Not Subsidised *Arrow-Losartan & Hydrochlorothiazide* (50mg/12.5mg) – Fully Subsidised **Quinapril/HCTZ** *Accuretic (10mg/12.5mg)* – Fully Subsidised *Accuretic (20mg/12.5mg)* – Fully Subsidised
Previous MARC meetings	Hydrochlorothiazide containing products have been discussed previously at the following meetings: – 131st Meeting — 13 September 2007 Amiloride/hydrochlorothiazide - hyponatraemia and hyperkalaemia
International action	Pharmacovigilance Risk Assessment Committee (PRAC) – 3-6 September 2018: the PRAC recommended updating the EU product information and package leaflets of all hydrochlorothiazide containing products to include safety information about non-melanoma skin cancer. The Committee also recommended that a direct healthcare professional communication (DHPC) about this issue is distributed in EU countries. Medicines and Healthcare products Regulatory Agency (MHRA) – 14 November 2018: the MHRA have published an alert on their website which highlights the findings from the two Danish case-control studies assessed by the PRAC. The alert also describes risk

<table>
<tr><td></td><td>minimisation strategies for patients who may be prescribed hydrochlorothiazide.</td></tr>
<tr><td>Prescriber Update</td><td>Summer Reminder – Photosensitivity Reactions - Prescriber Update 31(1), Feb 2010
Drug- Induced Photosensitivity - Prescriber Update 37(4), Dec 2016</td></tr>
<tr><td>Schedule</td><td>Prescription medicine</td></tr>
<tr><td>Usage data</td><td>DataPharm (beta) shows the following usage data for 2017 (the most recent year for which data is available). The data shows the number of people who received a dispensing in 2017. The data presented are limited to medicines which are funded by PHARMAC and dispensed from a community pharmacy.
Medicine — Number of people
Amiloride/HCTZ (5mg/50mg) — 3035
Cilazapril/HCTZ (5mg/12.5mg) — 68054
Losartan/HCTZ (50mg/12.5mg) — 11710
Quinapril/HCTZ (10mg/12.5mg) — 8255
Quinapril/HCTZ (20mg/12.5mg) — 21181</td></tr>
<tr><td>Advice sought</td><td>The Committee is asked to advise whether:
– The risk of non-melanoma skin cancer should be described in the data sheets for all hydrochlorothiazide containing products, based on the available evidence, industry responses and international regulatory action?
– If so, how should these risks be presented in the data sheets?
– Any further communication on this issue is required besides MARC's Remarks?
– If so, how should this issue be communicated?</td></tr>
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Contents

1.0 PURPOSE

Medsafe reviewed a Danish case control study by *Pedersen et al*, published in the Journal of the American Academy of Dermatology (Annex 1). The study examined cumulative hydrochlorothiazide use and Basal Cell Carcinoma (BCC) and Squamous Cell Carcinoma (SCC) of the skin. Medsafe was of the opinion that the results from this study warranted further investigation of this signal.

Internationally, the Pharmacovigilance Risk Assessment Committee (PRAC) have completed a signal assessment of this topic. Their assessment was based on the results of two Danish studies, including *Pedersen et al*, as well a prior study by *Pottegard et al* that examined hydrochlorothiazide use and SCC of the lip (Annex 2).

[redacted]

The PRAC's recommendations regarding distribution of a direct healthcare professional communication (DHPC) in EU countries and updates to the European product information/package leaflets of all hydrochlorothiazide containing products are also described.

Currently, the risk of developing non-melanoma skin cancer is not described in the New Zealand data sheets for hydrochlorothiazide-containing products.

The advice sought from the Committee is whether the New Zealand data sheets for hydrochlorothiazide-containing products should contain safety information related to non-melanoma skin cancer, given the literature, international regulatory action and company responses.

Medsafe would also like to ask whether further communication on this topic outside of *MARC's Remarks* is required.

2.0 BACKGROUND

2.1 Hydrochlorothiazide

Hydrochlorothiazide is a low-ceiling thiazide diuretic that acts on the kidneys by inhibiting sodium reabsorption in the distal convoluted tubule, connecting segment and possibly the cortical collecting tubule of the nephron. This effect leads to increased natriuresis and diuresis, although to a lesser extent than a loop diuretic (1).

In New Zealand, hydrochlorothiazide is only available in combination with Angiotensin Converting Enzyme Inhibitors (ACEIs), Angiotensin Receptor Blockers (ARBs) or potassium sparing diuretics (2). When used in combination it is indicated for the following conditions:

- hypertension where a patient is not adequately controlled on monotherapy (3-6),
- hypertension where potassium depletion might be anticipated (7)
- reduction in the risk of cardiovascular morbidity and mortality in hypertensive patients with left ventricular hypertrophy (5, 6)
- oedema of cardiac origin (7)
- hepatic cirrhosis with ascites (7)

All combination products in New Zealand contain 12.5mg of hydrochlorothiazide per tablet, with the exception of *Moduretic*, which contains a higher dose of 50mg of hydrochlorothiazide per tablet.

Table 1 shows the standard recommended daily dosage range for hydrochlorothiazide-containing products in New Zealand and how much hydrochlorothiazide this equates to per day.

Table 1: Recommended daily dosing range for hydrochlorothiazide (HCTZ) containing products in New Zealand (3-7)

Combination	Standard recommended daily dosage range	Amount of Hydrochlorothiazide per day
Cilazapril/HCTZ (5mg/12.5mg)	Hypertension one tablet daily	12.5mg
Losartan/HCTZ (50mg/12.5mg)	Hypertension One tablet daily, but may be increased up to a maximum of two tablets Hypertensive patients with left ventricular hypertrophy One tablet daily increased up to two tablets daily, if necessary.	12.5mg-25mg 12.5mg-25mg
Quinapril/HCTZ (10mg/12.5mg + 20mg/12.5mg)	Hypertension One 10mg/12.5mg tablet increased to one 20mg/12.5mg tablet or even two 10mg/12.5mg tablets if necessary.	12.5mg-25mg
Amiloride/HCTZ (5mg/50mg)	Oedema of cardiac origin Usually, one to two tablets daily, but may be increased up to a maximum of four tablets daily, if necessary. Hypertension Usually, one to two tablets daily. Can be increased up to a maximum of four tablets daily, if necessary. Hepatic cirrhosis with ascites Initiate low dose (one tablet daily) but dosage may be increased gradually if necessary up to a maximum of four tablets daily.	50mg -200mg 50mg- 200mg 50mg-200mg

DataPharm (beta) usage data suggests that over 110,000 New Zealand patients received a dispensing of a subsidised hydrochlorothiazide-containing product from a community pharmacy in 2017. This means that locally there is real public interest in this signal.

Hydrochlorothiazide is a medication that is commonly associated with photosensitivity reactions (8).

The Pharmaceutical Society of New Zealand (PSNZ) has developed Cautionary and Advisory Labels (CALs), which are designed to be stuck on to the dispensing pack and/or included on the pharmacy

generated medicine label. They provide additional instructions or advice to patients taking a medicine (9).

CAL number eight warns a patient to protect themselves from too much natural or artificial sunlight while being treated with a medicine that has been shown to cause photosensitizing reactions. CAL number eight is considered appropriate when the daily dose of hydrochlorothiazide is greater or equal to 25mg (9).

Medsafe has previously published two *Prescriber Update* articles communicating the need for patients to take extra precautions in the sun when a medicine(s) associated with photosensitivity reactions, including hydrochlorothiazide, is/are taken (10, 11).

In 2016, the International Agency for Research on Cancer (IARC) within the World Health Organisation (WHO) considered hydrochlorothiazide to be a group 2B carcinogen, being possibly carcinogenic to humans (12).

The IARC monograph for hydrochlorothiazide states that in the presence of ultraviolet A (UVA) irradiation, hydrochlorothiazide significantly enhanced the production of DNA cyclobutane pyrimidine dimers (thymine-thymine dimers) in isolated DNA and in the skin of mice defective in DNA repair. The possible association between exposure to hydrochlorothiazide and cancer of the skin may result from drug-related photosensitization, which would cause DNA damage (production of dimers by hydrochlorothiazide in the presence of sunlight) and may also lead to a chronic inflammatory reaction in the skin (12).

The human skin cancer data presented in the hydrochlorothiazide monograph appear to be limited to observational study findings, suggesting that a mechanism(s) for potential hydrochlorothiazide induced non-melanoma skin cancer in humans is/are not fully understood.

2.2 Non-Melanoma Skin Cancer

The term non-melanoma skin cancers (keratinocyte carcinomas) encompasses cutaneous lymphomas, adnexal tumours, Merkel-cell carcinomas as well as other rare cutaneous neoplasms. However, the term is mainly used to define basal-cell carcinomas (BCC) and squamous-cell carcinomas (SCC) (13).

Non-melanoma skin cancers are rarely fatal and the majority are curable, however, if left untreated they can result in substantial destruction of local tissue and disfigurement.

Locally, the New Zealand Cancer Registry (NZCR) does not collect reports related to basal cell carcinoma or squamous cell carcinoma, unless they arise in the skin of the genitalia (14). This means that the total number of people affected by these cancers in New Zealand is difficult to quantify.

2.2.1 Basal Cell Carcinoma (BCC)

Basal cell carcinoma (BCC) is a common skin cancer arising from the basal layer of epidermis and its appendages and is the most common form of non-melanoma skin cancer (15).

Approximately 70 percent of BCCs occur on the face, consistent with the etiologic role of solar radiation. Fifteen percent present on the trunk, and only rarely is BCC diagnosed on areas like the penis, vulva, or perianal skin (15).

Sun exposure is the most important environmental cause of BCC, and most risk factors relate directly to a person's sun exposure habits or susceptibility to solar radiation. The type, quantity, and timing of sun exposure associated with an increased risk of BCC are not clearly defined. Childhood sun exposure appears to be more important than exposure during adult life (15).

Risk factors for BCC include (16) :

- Age and gender: BCCs are particularly prevalent in elderly males. However, they also affect females and younger adults
- Previous BCC or other form of skin cancer (squamous cell carcinoma, melanoma)
- Sun damage (photoageing, actinic keratoses)
- Repeated prior episodes of sunburn
- Fair skin, blue eyes and blond or red hair—note; BCC can also affect darker skin types
- Previous cutaneous injury, thermal burn, disease (e.g. cutaneous lupus, sebaceous naevus)
- Inherited syndromes: BCC is a particular problem for families with basal cell naevus syndrome (Gorlin syndrome), Bazex-Dupree-Christol syndrome, Rombo syndrome, Oley syndrome and xeroderma pigmentosum
- Ionising radiation, exposure to arsenic and immune suppression due to disease or medicines.

The prognosis for most patients with BCC is excellent as the lesions are typically slow growing, and metastatic disease is a very rare event (17).

It is important to note that although the BCC-specific mortality rate is extremely low, these cancers may result in significant morbidity and can cause considerable disfigurement by locally destroying skin, cartilage, and even bone (17).

2.2.2 Squamous Cell Carcinoma (SCC)

Cutaneous squamous cell carcinoma (SCC) is the second most common type of non-melanoma skin cancer behind basal cell carcinoma.

SCC arises from malignant proliferation of the keratinocytes of the epidermis that have invaded into the dermis or beyond. SCC can present with a wide variety of clinical manifestations, including papules, plaques, or nodules, and smooth, hyperkeratotic, or ulcerative lesion (18).

In fair-skinned individuals, SCCs most commonly arise in sites frequently exposed to the sun. The development of SCC on non-sun-exposed skin is less common overall, but represents the most common distribution in individuals with dark skin (18).

In contrast to basal cell carcinoma (BCC), which rarely metastasizes, around 2 to 5 percent of cutaneous SCCs metastasize to regional lymph nodes or more distant sites (19).

Risk factors for cutaneous SCC include (20) :

- Age and gender: SCCs are particularly prevalent in elderly males. However, they also affect females and younger adults.
- Previous SCC or other form of skin cancer (basal cell carcinoma, melanoma) are a strong predictor for further skin cancers
- Actinic keratoses
- Outdoor occupation or recreation
- Smoking
- Fair skin, blue eyes and blond or red hair
- Previous cutaneous injury, thermal burn, disease (e.g. cutaneous lupus, epidermolysis bullosa, leg ulcer)
- Inherited syndromes: SCC is a particular problem for families with xeroderma pigmentosum and albinism

- Other risk factors include ionising radiation, exposure to arsenic, and immune suppression due to disease (e.g. chronic lymphocytic leukaemia) or medicines. Organ transplant recipients have a massively increased risk of developing SCC.

Epidemiologic studies indicate that cumulative sun exposure (principally UVB radiation) is the most important environmental cause of cutaneous SCC (18).

2.3 Data sheets

2.3.1 New Zealand

The following safety information, relating to photosensitivity and/ or risk of non-melanoma skin cancer is listed in the data sheets for hydrochlorothiazide containing products available in New Zealand.

2.3.1.1 Moduretic

Non-melanoma skin cancer is not mentioned in the data sheet. Photosensitivity is listed as an adverse reaction to the hydrochlorothiazide component of *Moduretic*.

2.3.1.2 Apo-Cilazapril/Hydrochlorothiazide

Non-melanoma skin cancer is not mentioned in the data sheet. Photosensitivity is listed as an adverse reaction for both cilazapril and hydrochlorothiazide components.

2.3.1.3 Hyzaar

Non-melanoma skin cancer is not mentioned in the data sheet. Photosensitivity is listed as an adverse reaction.

2.3.1.4 Arrow- Losartan and Hydrochlorothiazide

Non-melanoma skin cancer is not mentioned in the data sheet. Photosensitivity is listed as an adverse reaction.

2.3.1.5 Accuretic

Non-melanoma skin cancer is not mentioned in the data sheet. Photosensitivity is listed as an adverse reaction for the combination and is mentioned as a rare adverse effect of ACE inhibitors in the precautions.

Comment: Currently, the risk of non-melanoma skin cancer is not described in any New Zealand data sheet.

[redacted]

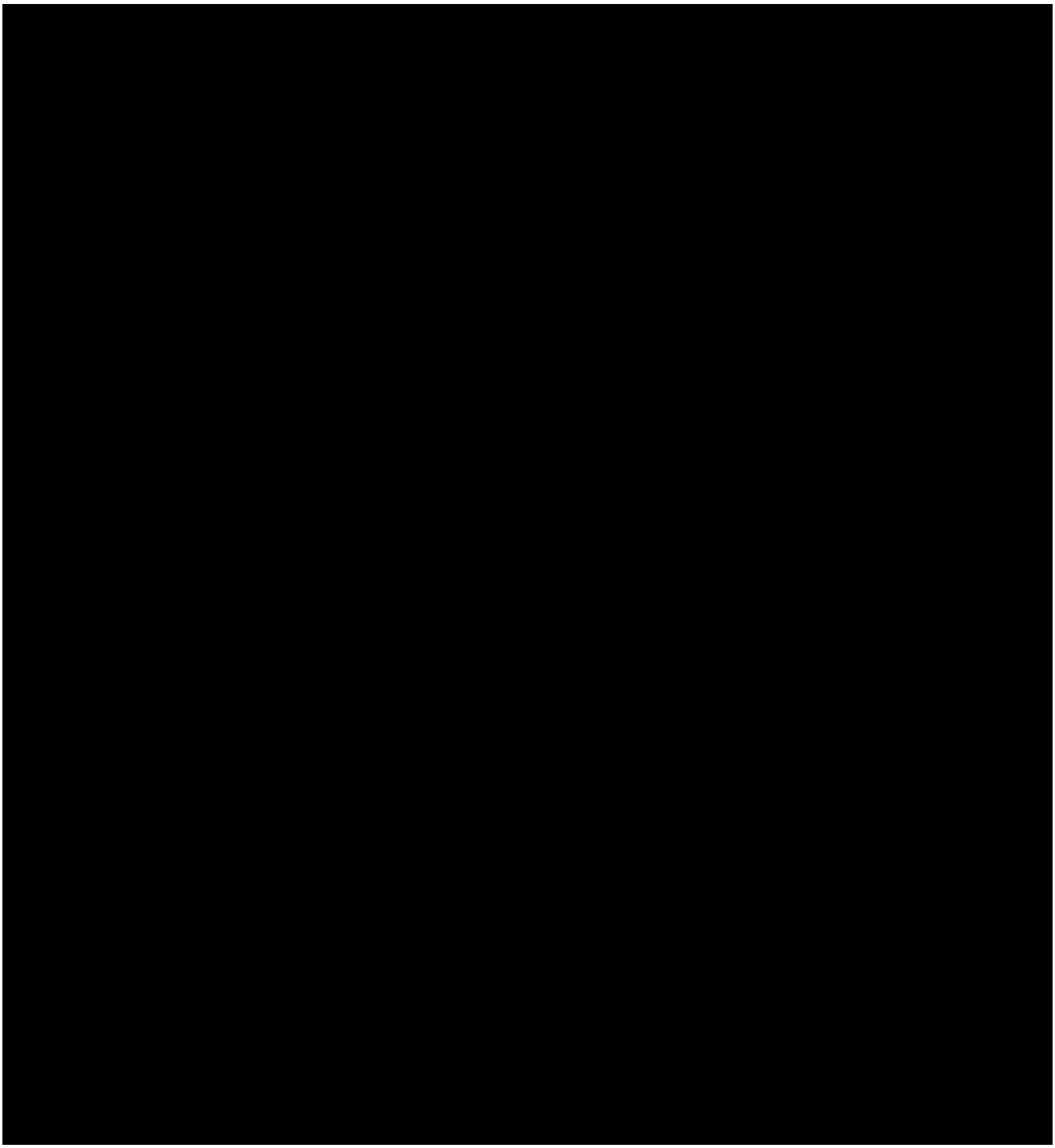
3.0 SCIENTIFIC INFORMATION

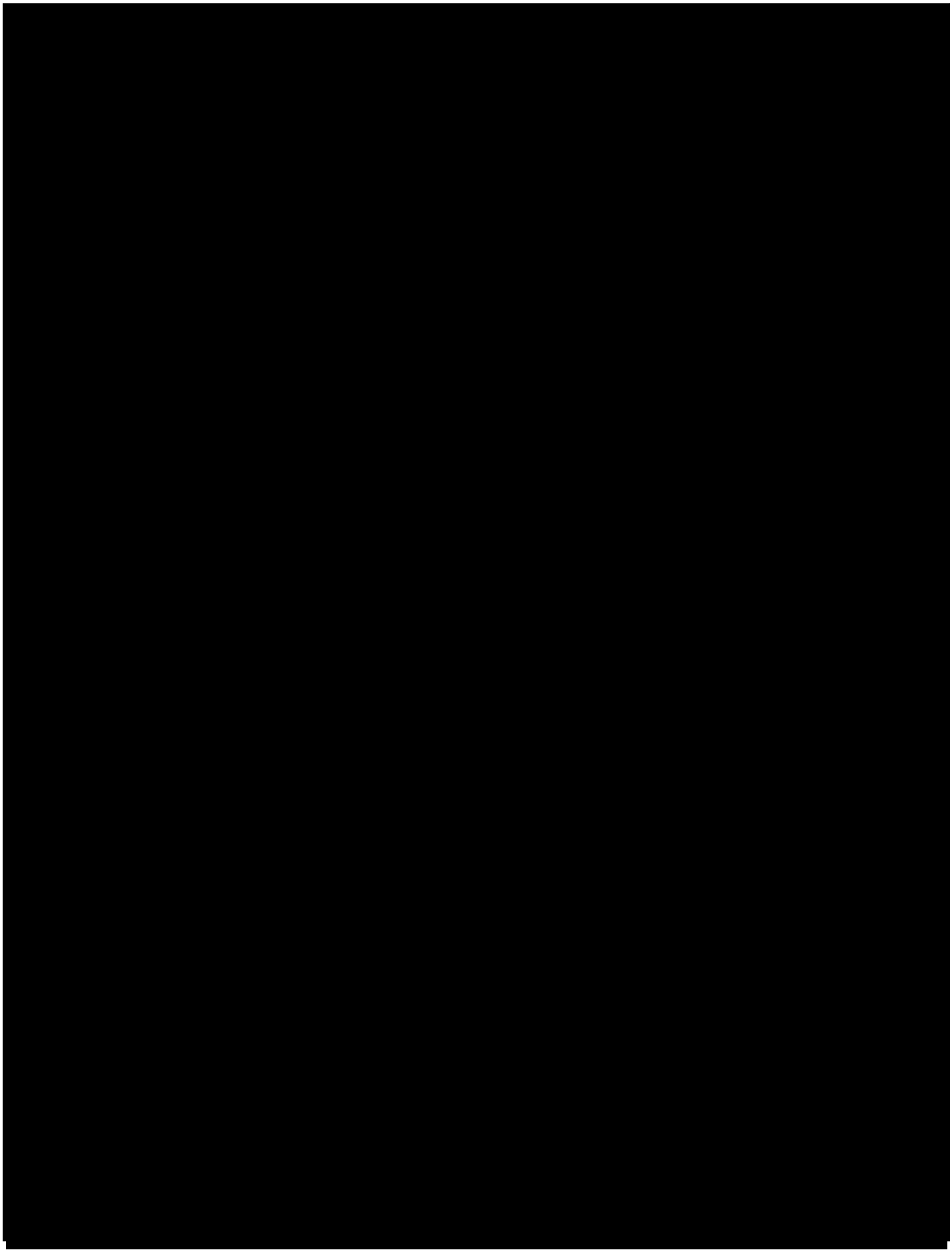
3.1 Literature Review

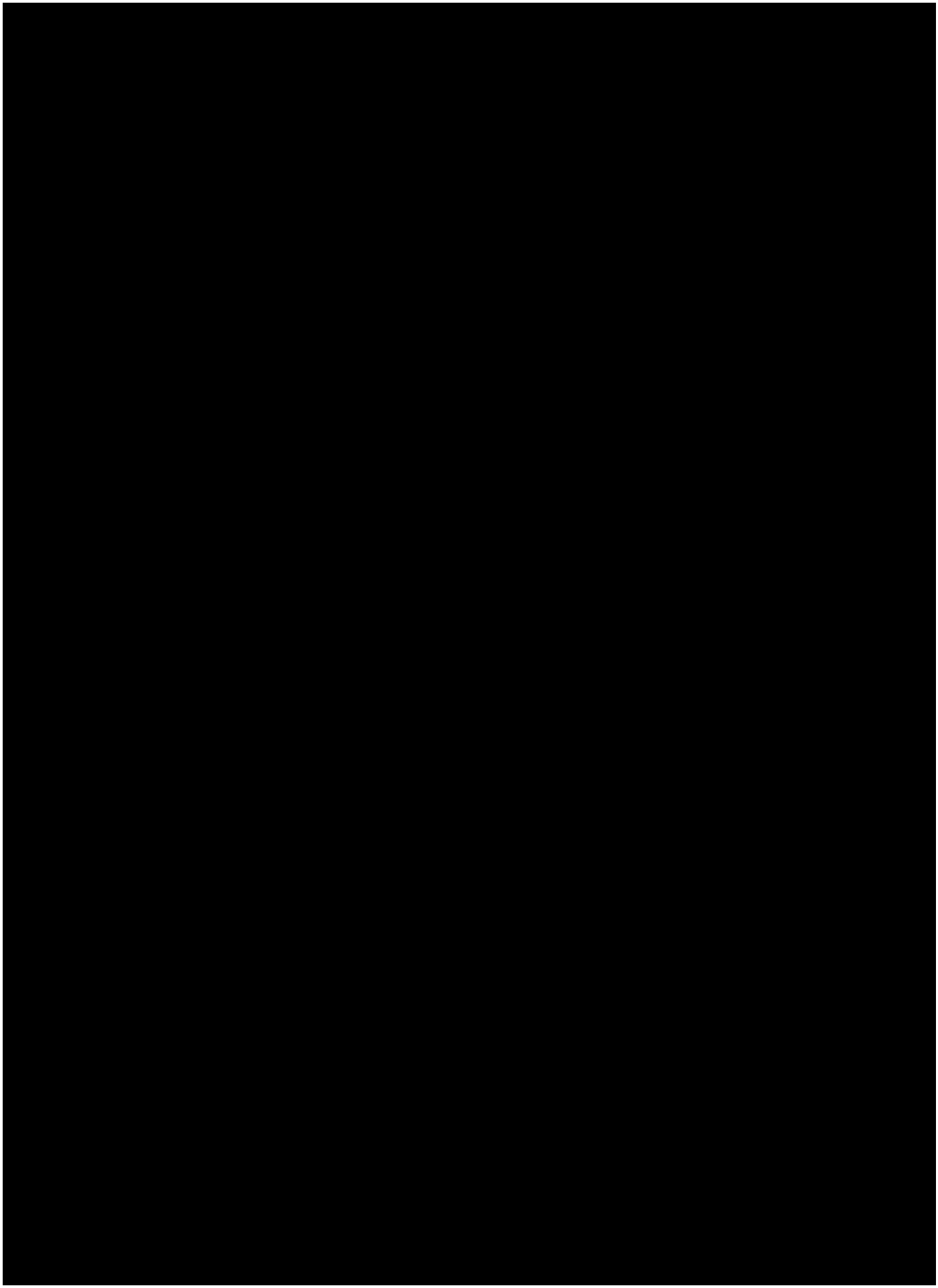
3.1.1 FDA literature review of thiazide diuretics/ hydrochlorothiazide and non-melanoma skin cancers (Annex 6)

[redacted]

[redacted]







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4.0 INTERNATIONAL REGULATORY ACTION

4.1 Europe

4.1.1 Pharmacovigilance Risk Assessment Committee (PRAC)

4.1.1.1 8-11 January 2018 meeting

The PRAC reviewed the papers by *Pedersen et al* (Annex 1) and *Pottegard et al* (Annex 2). After considering the available evidence from the two publications the PRAC agreed that the signal of hydrochlorothiazide and non-melanoma skin cancer warranted further assessment.

The PRAC agreed to request the publication authors to provide additional clarification on their study findings in order to better perform an in-depth analysis of the results and assess the need for further actions on this issue.

[redacted]

4.1.1.2 11-14 June 2018 meeting

The study authors (*Pottegard* et al and *Pedersen* et al) replied to the request for information on the signal of skin cancer.

Based on the assessment of the available data sources (i.e. literature and Eudravigilance), the PRAC considered there was a biologically plausible mechanistic model supporting the increased risk of non-melanoma skin cancer following higher cumulative dosing of hydrochlorothiazide, and therefore that an update of the product information for hydrochlorothiazide containing products was warranted.

The PRAC recommended that the Marketing Authorisation Holders (MAH) for hydrochlorothiazide containing products should submit a proposal for amending the product information accordingly.

4.1.1.3 9-12 July 2018 meeting

The MAHs of originator products containing hydrochlorothiazide replied to the request to submit a proposal on the updates to the product information on the signal of non-melanoma skin cancer.

The PRAC agreed that the product information (PI) should be updated to include special warnings and precautions on the observed increased risk of non-melanoma skin cancer and to add non-melanoma skin cancer as an undesirable effect with a frequency 'not known'.

The Committee recommended that the MAHs of the originator hydrochlorothiazide-containing products should comment on the proposed PI update.

Additionally, the PRAC recommended that a direct communication for healthcare professionals (DHPC), at European national level, should be considered.

"The MAHs of originator hydrochlorothiazide-containing products should make a proposal for a communication plan as well as for a DHPC with a particular focus on defined key elements. Of note, a single consistent message should be delivered."

4.1.1.4 3-6 September 2018 meeting

The PRAC agreed on the content of the DHPC, [redacted]

The Committee also made their final recommendation to update the product information of hydrochlorothiazide containing products with information on non-melanoma skin cancer as follows:

Summary of product characteristics

4.4. Special warnings and precautions

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

4.8. Undesirable effects

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Frequency 'not known': Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)

Description of selected adverse reactions

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

5.1. Pharmacodynamic properties

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

Comment: Additions to precautions, undesirable effects and pharmacodynamics properties sections of the product information were recommended.

The PRAC recommendations were endorsed by CHMP on 21 September 2018.

[redacted]

[redacted]

5.0 SPONTANEOUS ADVERSE DRUG REACTION (ADR) REPORTING

[redacted]

6.0 COMPANY RESPONSES

[redacted]

[redacted]

7.0 DISCUSSION AND CONCLUSIONS

Hydrochlorothiazide is a widely used thiazide diuretic according to local usage data from 2017 and is exclusively available in New Zealand in combination with Angiotensin Converting Enzyme Inhibitors (ACEIs), Angiotensin Receptor Blockers (ARBs) and potassium sparing diuretics. Given that there were over 110,000 patients who received a dispensing of a hydrochlorothiazide containing product in 2017, locally there is real public interest in this signal.

Hydrochlorothiazide is a medication commonly associated with photosensitivity reactions and recently in 2016 it has been considered by the IARC to be possibly carcinogenic to humans (group 2B carcinogen).

The results of two Danish case-control studies (*Pedesen et al and Pottegard et al*) published in 2018/2017 were the basis of a signal assessment by the EMA PRAC, which resulted in regulatory action to include safety information about the risk of non-melanoma skin cancer in the European hydrochlorothiazide-containing product information. The Committee also recommended that a direct healthcare professional communication (DHPC) be distributed in the EU about this issue.

Currently, photosensitivity is a listed adverse reaction in the data sheets for each New Zealand hydrochlorothiazide-containing product. It is also strongly recommended that additional information on sun avoidance (Cautionary and Advisory Label number 8) is added to the pharmacy labelling when the daily dose of hydrochlorothiazide is equal or greater than 25mg. However, there is currently no safety information in our data sheets relating to the possibility of developing non-melanoma skin cancer when taking hydrochlorothiazide.

[redacted]

The questions asked of the Committee are whether all data sheets for approved hydrochlorothiazide-containing products in New Zealand should be updated and whether further communication on this topic is required.

8.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- The risk of non-melanoma skin cancer should be described in the data sheets for all hydrochlorothiazide containing products, based on the available evidence, industry responses and international regulatory action?
- If so, how should these risks be presented in the data sheets?
- Any further communication on this issue is required besides MARC's Remarks?
- If so, how should we communicate this issue?

9.0 ANNEXES

1. Pedersen SA, Gaist D, Schmidt SAJ, Holmich LR, Friis S, Pottegard A. 2018. Hydrochlorothiazide use and risk of nonmelanoma skin cancer: A nationwide case-control study from Denmark. *J Am Acad Dermatol* 78: 673-81 e9
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6. FDA - epidemiological review of thaizide diuretics/hydrochlorothiazide and non-melanoma skin cancers [confidential]
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