NEW ZEALAND DATA SHEET

1. PRODUCT NAME
MODURETIC 50mg/5mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains hydrochlorothiazide 50 mg and amiloride hydrochloride dihydrate 5 mg. For full lists of excipients, see section6.1.

3. PHARMACEUTICAL FORM
MODURETIC tablets are plain, peach, diamond shaped, compressed tablets

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
MODURETIC is indicated in the treatment of patients with:

- oedema of cardiac origin;
- hepatic cirrhosis with ascites;
- hypertension in whom potassium depletion might be anticipated.

MODURETIC, with its combination of amiloride HCl and hydrochlorothiazide, minimises the possibility of the development of excessive potassium loss in patients during vigorous diuresis for prolonged periods. MODURETIC, with its built-in potassium sparing agent, is especially indicated in those conditions where the positive effect on potassium balance is particularly important.

MODURETIC may be used alone, or as an adjunct to other antihypertensive drugs. Since it enhances the action of these agents, the dosage of these antihypertensive drugs may need to be reduced to avoid the risk of an excessive drop in blood pressure.

4.2 Dose and method of administration
MODURETIC tablets are available for oral use containing amiloride HCl 5 mg and hydrochlorothiazide 50 mg.

<u>Oedema of Cardiac Origin</u>

MODURETIC may be started at a dosage of 1 or 2 tablets a day. Dosage may be increased if necessary, but must not exceed four tablets a day. The optimal

dosage is determined by the diuretic response and the serum potassium level. Once an initial diuresis has been achieved, reduction in dosage should be attempted for maintenance therapy. Maintenance therapy may be on an intermittent basis.

Hypertension

The usual dosage is one or two tablets given once a day or in divided doses. The dosage may be increased if necessary, but must not exceed four tablets a day.

Hepatic Cirrhosis with Ascites (see PRECAUTIONS)

Treatment should be initiated with a small dose of MODURETIC (1 tablet once a day). If necessary, dosage may be increased gradually until there is effective diuresis. The dosage should not exceed four tablets per day.

Maintenance doses may be lower than those required to initiate diuresis: therefore, reduction in the daily dose should be attempted when the patient's weight is stabilised. Gradual weight reduction in cirrhotic patients is especially desirable to reduce the likelihood of untoward reactions associated with diuretic therapy.

4.3 CONTRAINDICATIONS

Hyperkalaemia
MODURETIC should not be used in the presence of elevated plasma potassium levels (interpreted as over 5.5 mmol/litre).

Antikaliuretic therapy or potassium supplementation
Other antikaliuretic agents and potassium supplements or a potassium-rich diet are contraindicated in patients receiving MODURETIC (such combination therapy is commonly associated with rapid increases in plasma potassium levels).

Impaired renal function
Anuria, acute renal failure, severe progressive renal disease and diabetic nephropathy are contraindications to the use of MODURETIC. When creatine clearance falls below
30 mL/min thiazide diuretics are ineffective. Patients with increases in blood urea nitrogen (BUN) over 10.7 mmol/L, in serum creatinine levels over 0.13 mmol/L, or in whole blood urea values over 10.0 mmol/L, should not receive the drug without careful, frequent monitoring of serum electrolytes and BUN levels. Potassium retention in the presence of renal impairment is accentuated by the addition of an antikaliuretic agent and may result in the rapid development of hyperkalaemia.

Known Sensitivity to the Drug
MODURETIC is contraindicated in patients who are hypersensitive to this product, or to other sulphonamide-derived drugs.
In Children
The safety for use of amiloride HCl in children has not be established; therefore, MODURETIC is not recommended in the paediatric age group.

(See also Use in Pregnancy and the Nursing Mother under section 4.4).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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)

Hyperkalaemia
Hyperkalaemia, defined as serum potassium levels over 5.5 mmol per litre, has been observed in patients who received amiloride HCl either alone or in combination with other diuretic drugs. This has been noted particularly in aged patients, diabetic patients and in hospitalised patients with hepatic cirrhosis or cardiac oedema who have known renal involvement, are seriously ill, or are undergoing vigorous diuretic therapy. These patients should be monitored carefully for clinical, laboratory and electrocardiographic (ECG) evidence of hyperkalaemia. Some deaths have been reported in this group of patients.

Warning signs of hyperkalaemia include paraesthesiae, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia, shock, and serum potassium and ECG abnormalities. Careful monitoring of the plasma potassium level is important because hyperkalaemia is not always associated with an abnormal electrocardiogram.

When abnormal, the electrocardiogram in hyperkalaemia is characterised primarily by tall, peaked T waves or elevations from previous tracings. There may also be lowering of the R wave and
increased depth of the S wave, widening and even disappearance of the P wave, progressive widening of the QRS complex and prolongation of the PR interval and ST depression.

Treatment of Hyperkalaemia
Should hyperkalaemia occur in patients taking MODURETIC, the drug should be discontinued immediately, and if necessary, active measures taken to reduce the plasma potassium level. Discontinuation of antikaliuretic therapy should be followed by intravenous administration of sodium bicarbonate solution, or oral or parenteral glucose with a rapid-acting insulin. If needed, a cation exchange resin such as sodium polystyrene sulphonate may be given orally or by enema. Patients with persistent hyperkalaemia may require dialysis.

Diabetes Mellitus
In diabetic patients, hyperkalaemia has commonly occurred during therapy with amiloride HCl, particularly if chronic renal disease or prerenal azotaemia is present. Therefore, before initiating therapy in diabetic or suspected diabetic patients, the status of renal function should be known. MODURETIC should be discontinued for at least three days before glucose tolerance testing.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged due to the hydrochlorothiazide component. Diabetes mellitus which has been latent may become manifest during thiazide administration.

Metabolic or Respiratory Acidosis
Antikaliuretic therapy should be instituted only with caution in severely ill patients in whom respiratory or metabolic acidosis may occur, such patients with cardiopulmonary disease and patients with decompensated diabetes. Shifts in acid-base balance alter the balance of extracellular/intracellular potassium and the development of acidosis may be associated with rapid increases in serum potassium levels.

Electrolyte Imbalance and Reversible BUN Increases
Determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Patients should be observed for clinical signs of fluid or electrolyte imbalance: ie, hyponatraemia, hypochloraemic alkalosis, hypokalaemia and hypomagnesaemia. It is particularly important to make serum and urine electrolyte determinations when the patient is vomiting excessively or receiving

parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance include: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, seizures, confusion, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hyponatraemia and hypochloraemia may occur during the use of thiazide and other oral diuretics even when amiloride HCl is used. Any chloride deficit during thiazide therapy is generally mild and may be lessened by the amiloride HCl component of MODURETIC. Hypochloraemia usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatraemia may occur in oedematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatraemia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hypokalaemia may develop during thiazide therapy especially with brisk diuresis, when severe cirrhosis is present, during concomitant use of corticosteroids or ACTH, or after prolonged therapy. However this is usually prevented by the amiloride HCl component of MODURETIC.

Interference with adequate oral electrolyte intake will also contribute to hypokalaemia. Hypokalaemia may cause cardiac arrythmia and may sensitise or exaggerate the response of the heart to the toxic effects of digitalis (eg increased ventricular irritability).

Reversible increases in BUN levels have been reported; these have accompanied vigorous fluid elimination, especially when diuretic combinations were used in seriously ill patients, such as those who have hepatic cirrhosis with ascites and metabolic alkalosis or those with resistant oedema. Therefore, careful monitoring of serum electrolytes and BUN levels is important when MODURETIC is given to such patients.

Azotaemia

As azotaemia may be precipitated or increased by hydrochlorothiazide, special caution is necessary in patients with impaired renal function to avoid cumulative or toxic effects of the components. If increasing azotaemia and oliguria occur during treatment MODURETIC should be discontinued.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma:

Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug

initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy

Hepatic Disease
In patients with pre-existing severe liver disease hepatic encephalopathy, manifested by tremors, confusion, and coma, and increased jaundice have been reported in association with diuretic therapy including amiloride HCl and hydrochlorothiazide.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Metabolic
Hyperuricaemia may occur or gout may be precipitated in certain patients receiving thiazide therapy.

Because calcium excretion is decreased by thiazides, MODURETIC should be discontinued before carrying out tests for parathyroid function. Pathological changes in the parathyroid glands, with hypercalcaemia and hypophosphataemia have been observed in a few patients on prolonged thiazide therapy; however, the common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration have not been seen.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Sensitivity Reactions
Sensitivity reactions to thiazides may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported with the use thiazides.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Angiotensin-Converting Enzyme Inhibitors/Amiloride HCl
When amiloride HCl is administered concomitantly with an angiotensin-converting enzyme inhibitor, an angiotensin II receptor antagonist, cyclosporine

or tacrolimus, the risk of hyperkalaemia may be increased. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

Thiazide Diuretic - when given concurrently the following drugs may interact with thiazide diuretics.

Alcohol, barbiturates, or narcotics - potentiation of orthostatic hypotension may occur.

Antidiabetic drugs - (oral agents and insulin) - dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs - additive effect. Diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with an ACE inhibitor to reduce the likelihood of first dose hypotension.

Corticosteroids, ACTH - intensified electrolyte depletion, particularly hypokalaemia.

Pressor amines (eg noradrenaline) - possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarising (e.g. tubocurarine) - possible increased responsiveness to the muscle relaxant.

Lithium - generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package inserts for lithium preparations before use of such preparations.

Non-steroidal Anti-inflammatory Drugs - Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive drugs. Therefore, the antihypertensive effect of angiotensin II receptor antagonists or ACE inhibitors may be attenuated by NSAIDs including selective COX-2 inhibitors.

In some patients, the administration of a non-steroidal anti-inflammatory agent including a selective cyclooxygenase-2 inhibitor can reduce the diuretic, natriuretic and antihypertensive effects of diuretics. Concomitant administration of non-steroidal anti-inflammatory drugs (NSAIDs) and potassium-sparing agents, including amiloride HCl may cause hyperkalemia and renal failure, particularly in elderly patients. Therefore, when amiloride HCl is used

concomitantly with NSAIDs, renal function and serum potassium levels should be carefully monitored.

In some patients with compromised renal function (e.g. elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible.

These interactions should be considered in patients taking NSAIDs including selective COX-2 inhibitors concomitantly with diuretics and angiotensin II antagonists or ACE inhibitors. Therefore, the combination should be administered with caution, especially in the elderly.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics
The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Cholestyramine and colestipol resins - Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single dose of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce it's absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Drug/Laboratory Test Interactions - Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see PRECAUTIONS).

4.6 FERTILITY, PREGNANCY AND LACTATION

Use in Pregnancy (Category C)
Thiazides, related diuretics and loop diuretic enter the fetal circulation and may cause electrolyte disturbances. Neonatal thrombocytopenia has been reported with thiazides and related diuretics. Loop diuretics like frusemide and bumetanide are probably also associated with this risk. During the latter part of

pregnancy products of this type should therefore only be given on sound indications, and then in the lowest effective dose.

Because clinical experience is limited, MODURETIC is not recommended for use during pregnancy. Thiazides cross the placental barrier and appear in the cord blood. Therefore, the use of MODURETIC when pregnancy is present or suspected requires that the potential benefits of the drug must be weighed against possible hazards to the foetus. These hazards include foetal or neonatal jaundice, thrombocytopenia and possibly other side effects that have occurred in the adult.

The routine use of diuretics in otherwise healthy pregnant women with or without mild oedema is not indicated.

Use in Lactation
Thiazides appear in breast milk. If use of the drug is deemed essential, the patient should stop nursing.

4.8 UNDESIRABLE EFFECTS

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to https://nzphvc.otago.ac.nz/reporting/.
MODURETIC is usually well tolerated. Although minor adverse reactions have been reported relatively frequently, significant adverse effects have been reported infrequently.

Adverse effects that have been reported with MODURETIC are generally those known to be associated with diuresis, thiazide therapy, or with the underlying disease being treated. Clinical trials have not demonstrated that combining amiloride and hydrochlorothiazide increases the risk of adverse reactions over those seen with the individual components.

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).

MODURETIC

Body as a whole - headache, weakness, fatigue, malaise, chest pain, back pain, syncope.

Cardiovascular - arrhythmia, tachycardia, digitalis toxicity, orthostatic hypotension, angina pectoris.

Digestive - nausea/anorexia, vomiting, diarrhoea, constipation, abdominal pain, GI bleeding, appetite changes, abdominal fullness, flatulence, thirst, hiccups.

Metabolic - elevated serum potassium levels (>5.5 mmol/L), electrolyte imbalance, hyponatraemia, gout, dehydration, symptomatic hyponatraemia.

Integumentary - rash, pruritus, flushing, diaphoresis.

Musculoskeletal - leg ache, muscle cramps, joint pain.

Nervous - dizziness, vertigo, paraesthesia, stupor.

Psychiatric - insomnia, nervousness, mental confusion, depression, sleepiness.

Respiratory - dyspnoea.

Special Senses - bad taste, visual disturbance, nasal congestion.

Urogenital - impotence, dysuria, nocturia, incontinence, renal dysfunction including renal failure.

Other adverse effects that have been reported with the individual components are listed below:

AMILORIDE

Body as a Whole - neck/shoulder ache, pain in extremities.

Digestive - abnormal liver function, activation of probable pre-existing peptic ulcer, dyspepsia, jaundice.

Integumentary - dry mouth, alopecia, diaphoresis

Nervous - tremors, encephalopathy

Haematologic - aplastic anaemia, neutropenia.

Cardiovascular - one patient with a partial heart block developed complete heart block, palpitation.

Psychiatric - decreased libido, somnolence.

Respiratory - cough.

Special Senses - tinnitus, increased intraocular pressure.

Urogenital - polyuria, urinary frequency, bladder spasm.

HYDROCHLOROTHIAZIDE

Body as a Whole - anaphylactic reaction, fever.

Cardiovascular - necrotizing angiitis (vasculitis, cutaneous vasculitis).

Digestive - jaundice (intrahepatic cholestatic jaundice), pancreatitis, cramping, gastric irritation.

Endocrine/Metabolic - glycosuria, hyperglycaemia, hyperuricaemia, hypokalemia.

Haematologic - agranulocytosis, aplastic anaemia, haemolytic anaemia, leucopenia, purpura, thrombocytopenia.

Integumentary - photosensitivity, sialoadenitis, urticaria, toxic epidermal necrolysis.

Psychiatric - restlessness.

Renal - interstitial nephritis.

Respiratory - respiratory distress including pneumonitis and pulmonary oedema.

Chlortalidone- and indapamide-containing products:
Eye disorders: choroidal effusion (frequency not known)

Special Senses - transient blurred vision, xanthopsia.

4.9 OVERDOSE

No data are available with regard to overdosage in humans. The oral LD_{50} of the combination drug is 189 and 422 mg/kg for female mice and female rats, respectively.

It is not known whether the drug is dialysable.

No specific information is available on the treatment of overdosage with MODURETIC, and no specific antidote is available. Treatment is symptomatic and supportive. Therapy with MODURETIC should be discontinued and the patient observed closely.

In the case of overdose, immediately telephone the New Zealand Poisons Information Centre for advice on 0800 764 766 or 0800 POISON.

AMILORIDE HCl
No data are available in regard to overdosage in humans.

The oral LD_{50} of amiloride hydrochloride (calculated as the base) is 56 mg/kg in mice and 36 to 85 mg/kg in rats, depending on the strain.
The most common signs and symptoms to be expected with overdosage are dehydration and electrolyte imbalance. If hyperkalaemia occurs, active measures should be taken to reduce the serum potassium levels.

HYDROCHLOROTHIAZIDE
The oral LD_{50} of hydrochlorothiazide is greater than 10.0 g/kg in both mice and rats.

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has been administered, hypokalaemia may accentuate cardiac arrhythmias.

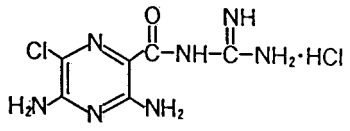
5.PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

MODURETIC® (amiloride HCl and hydrochlorothiazide) combines the potassium-conserving action of amiloride HCl with the natriuretic action of hydrochlorothiazide.

Amiloride HCl is a pyrazinecarbonylguanidine that is unrelated chemically to other known diuretic or antikaliuretic agents. It is not acidic like the thiazides or ethacrynic acid, but is the salt of a moderately strong base, amiloride, pKa 8.7. Its chemical name is 3,5-diamino-N-(aminoimineomethyl)-6-chloropyrazinecarboxamide monohydrochloride and its structure is as follows:

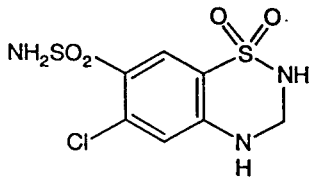
$C_6H_8ClN_7O \cdot HCl$



The CAS Number is: 17440-83-4.

Hydrochlorothiazide is the 3,4-dihydro derivative of chlorothiazide (CHLOTRIDE*). It is a white, or practically white, crystalline compound, slightly soluble in water, but freely soluble in sodium hydroxide solution. Its chemical name is:6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide, and its structure is as follows:

$C_7H_8ClN_3O_4S_2$



The CAS Number is: 58-93-5.

Mechanism of Action

MODURETIC provides diuretic and antihypertensive activity (principally due to the hydrochlorothiazide component), while acting through the amiloride component to prevent the excessive potassium loss that may occur in patients receiving a thiazide diuretic. Due to its amiloride component, the urinary excretion of magnesium is less with MODURETIC than with a thiazide or loop diuretic used alone (see PRECAUTIONS). The onset of the diuretic action of MODURETIC is within 1 to 2 hours and this action appears to be sustained for approximately 24 hours.

Amiloride HCl:

Amiloride HCl is a potassium-conserving (antikaliuretic) drug that possesses weak (compared to the thiazide diuretics) natriuretic, diuretic and antihypertensive activity. These effects have been partially additive to the effects of thiazide diuretics in some clinical studies. Amiloride HCl has potassium-conserving activity in patients receiving kaliuretic-diuretic agents.

Amiloride HCl is not an aldosterone antagonist and the effects are seen even in the absence of aldosterone.

Amiloride HCl exerts its potassium sparing effect through the inhibition of sodium reabsorption at the distal convoluted tubule, cortical collecting tubule and collecting duct; this decreases the net negative potential of the tubular lumen and reduces both potassium and hydrogen secretion and their subsequent excretion. This mechanism accounts in large part for the potassium sparing action of amiloride.

Hydrochlorothiazide:

The mechanism of the antihypertensive effect of thiazides is unknown. Hydrochlorothiazide does not usually affect normal blood pressure. Hydrochlorothiazide is a diuretic and antihypertensive agent. It affects the renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. After oral use diuresis begins within two hours, peaks in about four hours and lasts about 6 to 12 hours.

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 (≥50,000mg 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 (~25,000mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (100,000 mg) (see also section 4.4).

5.2 Pharmacokinetic properties

Amiloride HCl usually begins to act within two hours after an oral dose. Its effect on electrolyte excretion reaches a peak between 6 and 10 hours and lasts about 24 hours. Peak plasma levels are obtained in 3 to 4 hours and the plasma half-life varies from 6 to 9 hours. Effects on electrolytes increase with single doses of amiloride HCl up to approximately 15 mg.
Amiloride HCl is not metabolised by the liver but is excreted unchanged by the kidneys. About 50 percent of a 20 mg dose of amiloride HCl is excreted in the urine and 40 percent in the stool within 72 hours. Amiloride HCl has little effect

on glomerular filtration rate or renal blood flow. Because amiloride HCl is not metabolised by the liver, drug accumulation is not anticipated in patients with hepatic dysfunction, but accumulation can occur if the hepatorenal syndrome develops.
Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney. When plasma levels have been followed for a least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placenta but not the blood-brain barrier and is excreted in breast milk.

6. PHARMACEUTICAL PRECAUTIONS

6.1 List of excipients

lactose, dibasic calcium phosphate dihydrate (calcium hydrogen phosphate), starch - maize, guar gum, starch – pregelatinised maize, magnesium stearate and sunset yellow FCF lake CI15985.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Blister pack, PVC/PVdC/Al – 50 tablets

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Pharmacy Retailing Pty Ltd
t/a Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland
New Zealand
Telephone (09) 9185 100
Email: aspen@aspenpharma.co.nz

9. DATE OF FIRST APPROVAL

4 August 2010

10. DATE OF REVISION OF TEXT

3 May 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All sections revised	Update to the SPC-style format
4.4, 4.8 & 5.1	information about non-melanoma skin cancer
4.4 & 4.8	Choroidal effusion