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PO Box 5013
Wellington 6140
New Zealand
T +64 4 496 2000

1 February 2019

[redacted]

Response to your request for official information

I refer to your request of 4 January 2019 to the Ministry of Health (the Ministry), under the Official Information Act 1982 (the Act), for:

> *"I wish to request the following information regarding (the now lapsed) Aldactone, film coated tablets, spironolactone 25 mg and 100mg (TT50-1764, 1764a):*
>
> - *Please provide a copy of the most recent datasheet (approved in a CMN or notified in a SACN).*
> - *Please provide a copy of the most recent primary and secondary labelling (approved in a CMN or notified in a SACN).*
> - *Please advise if the approved NZ labelling included an ARTG number."*

Information held by the Ministry relating to your request is itemised below, with copies of documents attached.

Attachment number	Details and decision
1	Data sheet for Aldactone 25 mg and Aldactone 100 mg. Information released in full.
2	Copy of the primary and secondary labelling for Aldactone 25 mg and Aldactone 100 mg. Information released in full.

In response to part three of your request, the Ministry confirms that the approved secondary labelling for Aldactone 25 mg and Aldactone 100 mg in New Zealand contained Australian Register of Therapeutic Goods (ARTG) numbers: AUST R 68953 (Aldactone 25 mg) and AUST R 68954 (Aldactone 100 mg).

I trust this information fulfils your request.

Please note this response (with your personal details removed) may be published on the Ministry of Health website.

Yours sincerely

Chris James
Group Manager
Medsafe

DATA SHEET

NAME OF THE MEDICINE

ALDACTONE

Spironolactone 25 mg & 100 mg tablets

PRESENTATION

ALDACTONE 25 mg

Tablet (11/32 inch diameter), round, biconvex, buff coloured, peppermint flavoured, film coated, stamped 'SEARLE' over 39 on one side and unmarked on the other, each containing spironolactone B.P. 25 mg.

ALDACTONE 100 mg

Tablet (7/16 inch diameter), round, biconvex, buff coloured, peppermint flavoured, film coated, stamped 'SEARLE' over 134 on one side and unmarked on the other, each containing spironolactone B.P. 100 mg.

PHARMACOLOGY

Actions

ALDACTONE (spironolactone) is a specific pharmacologic antagonist of aldosterone, acting primarily through competitive binding of receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule. ALDACTONE acts as a potassium-sparing diuretic by causing increased amounts of sodium and water to be excreted, while potassium and magnesium are conserved.

ALDACTONE acts both as a diuretic and as an antihypertensive agent. It may be given alone or with other diuretic agents that act more proximally in the renal tubule.

Increased levels of the mineralocorticoid, aldosterone, are present in primary and secondary hyperaldosteronism. Oedematous states in which secondary aldosteronism is usually involved include congestive cardiac failure, hepatic cirrhosis, and nephrotic syndrome. By competing with aldosterone for receptor sites, ALDACTONE provides effective therapy for oedema and ascites in those conditions.

ALDACTONE is effective in lowering the systolic and diastolic blood pressure in patients with primary hyperaldosteronism. It is also effective in most cases of essential hypertension despite the fact that aldosterone secretion may be within normal limits in benign essential hypertension.

Through its action in antagonising the effect of aldosterone, ALDACTONE inhibits the exchange of sodium for potassium in the distal renal tubule and helps to prevent potassium loss.

ALDACTONE has not been demonstrated to elevate serum uric acid, to precipitate gout or to alter carbohydrate metabolism.

ALDACTONE has moderate anti-androgenic activity in humans by inhibition of the interaction between dihydrotestosterone and the intracellular androgen receptor. It also inhibits several steps in ovarian steroidogenesis resulting in lowered plasma levels of testosterone and some other weak androgenic steroids. Through this activity ALDACTONE is effective in the treatment of female hirsutism.

Pharmacokinetics

In the human, the bioavailability of spironolactone from orally administered ALDACTONE tablets exceeds 90% when compared with an optimally-absorbed solution (spironolactone in polyethylene glycol 400).

Spironolactone is rapidly and extensively metabolised. Approximately 25% to 30% of the dose administered is converted to canrenone. Canrenone and 7-alpha-(thiomethyl) spironolactone are its active metabolites. The activity of canrenone is reported to be 10% to 33% that of spironolactone. Both spironolactone and canrenone are more than 90% bound to plasma proteins. Food increases the bioavailability of spironolactone by increasing the absorption and possibly decreasing the first-pass metabolism of spironolactone.

ALDACTONE has a gradual onset of diuretic action with a maximum effect being reached on the third day of therapy. Diuresis continues for two or three days after discontinuation.

Following the administration of 100 mg of spironolactone daily for 15 days in non-fasted healthy volunteers, time to peak plasma concentration (t_{max}), peak plasma concentration (C_{max}), and elimination half-life ($t_{1/2}$) for spironolactone is 2.6 hr., 80 ng/ml, and approximately 1.4 hr., respectively. For the 7-alpha-(thiomethyl) spironolactone and canrenone metabolites t_{max} was 3.2 hr. and 4.3 hr., C_{max} was 391 ng/ml and 181 ng/ml, and $t_{1/2}$ was 13.8 hr. and 16.5 hr respectively.

Elimination of metabolites occurs primarily in the urine and secondarily through biliary excretion in the faeces.

INDICATIONS

Essential hypertension; oedematous conditions including congestive cardiac failure, cirrhosis of the liver, (with or without ascites) and the nephrotic syndrome; diagnosis and treatment of primary aldosteronism, as adjunctive therapy in malignant hypertension; in diuretic induced hypokalaemia/hypomagnesaemia when other measures are considered inappropriate or inadequate; prophylaxis of hypokalaemia in patients taking digitalis when other measures are considered inadequate or inappropriate, hirsutism.

<u>Hirsutism in Females</u>

ALDACTONE is effective in the treatment of females with hirsutism, an androgen-related increase in facial and body hair. A reduction in hair growth, hair shaft diameter and hair pigmentation is seen.

<u>Essential Hypertension</u>

ALDACTONE, when used alone, is effective in lowering both systolic and diastolic blood pressure. ALDACTONE improves the hypotensive action of thiazide diuretics while at the same

time reducing or preventing potassium loss due to the thiazide. ALDACTONE enhances the effectiveness of other antihypertensive agents such as beta blockers, vasodilators, etc.

Congestive Cardiac Failure

ALDACTONE, when used alone, is effective in the management of oedema and sodium retention associated with congestive cardiac failure. ALDACTONE may be used in combination with a thiazide or other conventional diuretics for achieving diuresis in patients whose oedema is resistant to a thiazide or other conventional diuretics. Unlike conventional diuretics ALDACTONE does not produce hypokalaemia. When administered with a thiazide or other conventional diuretics, ALDACTONE offsets hypokalaemia induced by these diuretics. The prevention of potassium loss is particularly important in the treatment of digitalised patients since digitalis intoxication may be precipitated if hypokalaemia is induced by conventional diuretic therapy.

Hepatic Cirrhosis with Ascites and Oedema

ALDACTONE when used alone is frequently adequate for the relief of ascites and oedema associated with hepatic cirrhosis. ALDACTONE provides a mild and even diuresis and prevents excessive potassium excretion caused by thiazide diuretics thus avoiding possible precipitation of hepatic coma.

Nephrotic Syndrome

Although glucocorticoids, whose anti-inflammatory activity appears to benefit the primary pathologic process in the renal glomerulus, should probably be employed first, ALDACTONE either alone or in combination with a conventional diuretic is useful for inducing diuresis.

Primary Hyperaldosteronism

ALDACTONE may be used to establish the diagnosis of primary hyperaldosteronism by therapeutic trial. ALDACTONE may also be used for the short-term pre-operative treatment of patients with primary hyperaldosteronism, long-term maintenance therapy for patients with discrete aldosterone-producing adrenal adenomas who are judged to be poor operative risks (or who decline surgery), and the long-term maintenance therapy for patients with bilateral micro or macronodular adrenal hyperplasia (idiopathic hyperaldosteronism).

DOSAGE AND ADMINISTRATION

Adults

Essential Hypertension: 50 mg/day to 100 mg/day which for difficult or severe cases may be gradually increased at 2-weekly intervals up to 200 mg/day. The daily dose may be given either in divided doses or as a single daily dose.

Treatment should be continued for at least 2 weeks to ensure an adequate response to therapy. Dosage should subsequently be adjusted according to the response of the patient.

Oedematous Disorders: The daily dose may be given either in divided doses or as a single daily dose.

Congestive Cardiac Failure: Initial dose – 100 mg/day. In difficult or severe cases the dosage may be gradually increased up to 200 mg/day. When oedema is controlled, the usual maintenance level is 25 mg/day to 200 mg/day. Maintenance dose should be individually determined.

Cirrhosis: If urinary Na+/K+ ratio is greater than 1 (one) the recommended dose is 100 mg/day. If the ratio is less than 1 (one) the recommended dose is 200 mg/day to 400 mg/day. Maintenance dosage should be individually determined.

Nephrotic Syndrome: Usually 100 mg/day to 200 mg/day. Spironolactone is not anti-inflammatory, has not been shown to affect the basic pathological process, and its use is only advised when treatment of the underlying disease, restriction of fluid intake and sodium intake, and the use of other diuretics do not provide an adequate response.

Children

Oedema in Children: The initial daily dosage is 3.3 mg/kg body weight daily in divided doses. Dosage should be adjusted on the basis of response and tolerance. For small children, ALDACTONE tablets may be pulverised and administered as a suspension with a few drops of glycerine and adding cherry syrup. When refrigerated, such a suspension is stable for 1 month.

Diagnosis and Treatment of Primary Aldosteronism

ALDACTONE may be employed as an initial diagnostic measure to provide presumptive evidence of primary hyperaldosteronism while patients are on normal diets.

Long Test: ALDACTONE is administered at a daily dosage of 400 mg for 3 to 4 weeks. Correction of hypokalaemia and hypertension provides presumptive evidence for the diagnosis of primary hyperaldosteronism.

Short Test: ALDACTONE is administered at a daily dosage of 400 mg for 4 days. If serum potassium increases during ALDACTONE administration but drops when ALDACTONE is discontinued, a presumptive diagnosis of primary hyperaldosteronism should be considered.

After the diagnosis of hyperaldosteronism has been established by more definitive testing procedures, ALDACTONE may be administered in doses of 100 mg to 400 mg daily in preparation for surgery. For patients who are considered unsuitable for surgery, ALDACTONE may be employed for long-term maintenance therapy at the lowest effective dosage determined for the individual patient.

Malignant Hypertension: ALDACTONE should be used as adjunctive therapy only, where there is an excessive secretion of aldosterone, hypokalaemia and metabolic alkalosis. Initial dosage: 100 mg/day increased as necessary in two weekly intervals to 400 mg/day. Initial therapy should include a combination of other antihypertensive drugs and spironolactone. Do not automatically reduce the dose of other treatments as is recommended for essential hypertension.

Hypokalaemia/Hypomagnesaemia: ALDACTONE administered at a dosage of 25 mg to 100 mg daily may be useful in treating diuretic-induced hypokalaemia and/or hypomagnesaemia when oral potassium and/or magnesium supplements are considered inappropriate.

Female Hirsutism: 100 mg/day to 200 mg/day in divided doses is usual however 50 mg/day has also been shown to be effective.

Clinical improvement is usually shown within 3 to 6 months and an initial course of treatment should continue for 12 months.

ALDACTONE may be administered continuously or as a cyclical dosage for approximately 3 weeks out of every 4 weeks. Dosing from Day 5 to Day 21 of the menstrual cycle, with a drug free interval during menstruation has been effective.

Cyclical dosing may reduce menstrual irregularities in women with previously regular cycles.

Combined use with oestrogen-progestogen oral contraceptives may also be considered to provide both regular menstrual cycles and adequate contraception.

CONTRAINDICATIONS

Acute renal insufficiency, significant impairment of renal function, anuria.

Addison's disease or other conditions associated with hyperkalaemia (see **WARNINGS AND PRECAUTIONS**).

Hyperkalaemia.

Pregnancy.

Hypersensitivity to spironolactone.

Concomitant use of eplerenone.

WARNINGS AND PRECAUTIONS

Concomitant use of spironolactone with angiotensin converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs, angiotensin II antagonists, aldosterone blockers, heparin, low molecular weight heparin, other drugs or conditions known to cause hyperkalaemia. potassium supplements, a diet rich in potassium, including salt substitutes containing potassium, or other potassium sparing agents is not recommended as it may lead to severe hyperkalaemia.

Hyperkalaemia may be fatal in patients with Severe Heart Failure (New York Heart Association [NYHA] class III-IV). Potassium and creatinine levels should be closely monitored 1 week after initiation or monthly for the first 3 months, then quarterly for a year, and then every 6 months when increasing the dose of spironolactone. Concomitant use of spironolactone and other potassium-sparing diuretics in patients with severe heart failure should be avoided. If serum potassium is >3.5 mEq/L, oral potassium supplements should be avoided. Treatment with spironolactone should be discontinued or interrupted in patients with serum potassium >5 mEq/L or with serum creatinine >4 mg/dL.

Periodic estimation of serum electrolytes is desirable due to the possibility of hyperkalaemia, hyponatraemia and possible transient blood urea nitrogen (BUN) elevation especially in the elderly and/or patients with pre-existing impaired renal or hepatic function, in whom the risk/benefit ratio should always be weighed.

Reversible hyperchloraemic metabolic acidosis, usually in association with hyperkalaemia, has been reported to occur in some patients with decompensated hepatic cirrhosis, even in the presence of normal renal function.

Spironolactone should be considered for hirsutism only after other possible measures have been explored and should not be prescribed for hirsutism in women of reproductive age unless appropriate steps are taken to prevent conception while taking ALDACTONE.

Pregnancy and Lactation

Spironolactone is contraindicated for use during pregnancy. Women of reproductive age should take appropriate steps to prevent conception.

Canrenone, an active metabolite of spironolactone, appears in breast milk. If use of the drug is deemed essential an alternative method of infant feeding should be instituted.

Effects on Ability to Drive and Use Machines

Somnolence and dizziness have been reported to occur in some patients. Caution is advised when driving or operating machinery until the response to initial treatment has been determined.

Effects on Laboratory Tests

Several reports of possible interference with digoxin radioimmunoassays by spironolactone, or its metabolites have appeared in the literature. Neither the extent nor the potential clinical significance of its interference (which may be assay-specific) has been fully established.

Other

Animal Studies: - Spironolactone has been shown to be a tumorigen in chronic toxicity studies performed in rats with its proliferative effects manifested on endocrine organs, and the liver. In one study using 25, 75 and 250 times the usual daily human dose (2 mg/kg) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes.

In female rats, there was a statistically significant increase in malignant mammary tumours at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg/kg), the range of effects included hepatocytomegaly, hyperplastic nodules, and hepato- cellular carcinoma; the last was not statistically significant at a value of p=0.05. Tumours were not observed in monkeys administered 20 mg/kg to 250 mg/kg daily for up to 52 weeks.

In a 2 year oral carcinogenicity study in which rats were administered 10 mg/kg/day, 30 mg/kg/day, 100 mg/kg/day, and 150 mg/kg/day of spironolactone, the range of proliferative effects observed was consistent with earlier studies. There were statistically significant increases at the higher doses in hepatocellular adenomas and testicular interstitial cell tumours in males, and in thyroid follicular cell adenomas and carcinomas in both sexes. There was also a statistically significant, but not dose-related, increase in benign uterine endometrial polyps in females. There was an increase in hepatocellular carcinomas in males at 150 mg/kg but this was not statistically significant. There was no significant increase in the incidence of mammary tumours.

The significance of these findings with respect to clinical use is not certain. However, it is likely that the effects in rats are secondary to the induction of hepatic P-450 metabolising enzymes in this species.

Spironolactone is metabolised to a minor extent to canrenone. Canrenone and canrenoic acid are the major metabolites of potassium canrenoate. A dose-related (above 20 mg/kg/day) incidence of myelocytic leukaemia was observed in rats fed daily doses of potassium canrenoate for a period of 1 year. In a long-term (2 year) oral carcinogenicity study of potassium canrenoate in rats, myelocytic leukaemia and hepatic, thyroid, testicular, and mammary tumours were observed. Potassium canrenoate did not produce a mutagenic effect in tests using bacteria or yeast. It did produce a positive mutagenic effect in several *in vitro* tests in mammalian cells following metabolic activation. In an in *vivo* mammalian system, potassium canrenoate was not mutagenic. An increased incidence of leukaemia was not observed in chronic rat toxicity or carcinogenicity studies conducted with spironolactone at doses up to 500 mg/kg/day.

Spironolactone was devoid of teratogenic effects in mice (0 mg/kg/day to 20 mg/kg/day). Rabbits receiving 20 mg/kg/day showed a reduced conception rate, increased resorption rate and a lower number of live births. No embryotoxic effects were seen in rats at doses up to 50 mg/kg/day but limited, dose-related teratogenic effects (hypoprolactinaemia and decreased ventral prostate and seminal vesicle weights in males; increased luteinizing hormone secretion and ovarian and uterine weights in females) were reported in one study at doses of approximately 50 mg/kg/day and 100 mg/kg/day. Feminisation of the external genitalia of male fetuses was reported in another study in rats at doses of approximately 200 mg/kg/day.

ADVERSE EFFECTS

Gynaecomastia may develop in association with the use of spironolactone, and physicians should be alert to its possible onset. The development of gynaecomastia appears to be related to both dosage level and duration of therapy and is normally reversible when ALDACTONE is discontinued. In rare instances some breast enlargement may persist.

Other adverse reactions that have been reported in association with ALDACTONE are: gastrointestinal symptoms including cramping, diarrhoea, nausea, vomiting, gastric bleeding, ulceration and gastritis; drowsiness, malaise, dizziness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, leucopenia (including agranulocytosis), thrombocytopenia, abnormal hepatic function, electrolyte disturbances, hyperkalaemia, leg cramps, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), alopecia, hypertrichosis, pruritus, rash, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, changes in libido, benign breast neoplasm, breast pain, menstrual disorders, including irregular menses or amenorrhoea, and post-menopausal bleeding, and acute renal failure.

Adverse reactions are usually reversible upon discontinuation of the drug.

INTERACTIONS

Concomitant use of spironolactone with other potassium-sparing diuretics, ACE-inhibitors, angiotensin II antagonists, aldosterone blockers or other drugs known to cause hyperkalaemia,

potassium supplements, a diet rich in potassium or salt substitutes containing potassium may lead to severe hyperkalaemia (see **WARNINGS AND PRECAUTIONS**).

ALDACTONE potentiates the effects of other diuretics and antihypertensives given concomitantly. The dose of such drugs may need to be reduced when ALDACTONE is added to the treatment regimen.

Spironolactone reduces the vascular responsiveness to noradrenaline. Therefore caution should be exercised in the management of patients subjected to regional or general anaesthesia while they are being treated with ALDACTONE.

Nonsteroidal anti-inflammatory drugs such as aspirin, indomethacin and mefenamic acid may attenuate the natriuretic efficacy of diuretics due to inhibition of intrarenal synthesis of prostaglandins and have been shown to attenuate the diuretic effect of spironolactone.

As carbenoxolone may cause sodium retention and thus decrease the effectiveness of spironolactone, concurrent use of the two agents should be avoided.

Spironolactone enhances the metabolism of antipyrine.

Spironolactone has been shown to increase the half-life of digoxin. This may result in increased serum digoxin levels and subsequent digitalis toxicity. It may be necessary to reduce the digoxin dose when spironolactone is administered and the patient should be carefully monitored to avoid over- or under-digitalisation.

Hyperkalaemic metabolic acidosis has been reported in patients given spironolactone concurrently with ammonium chloride or cholestyramine.

OVERDOSAGE

Overdosage may be manifested by nausea and vomiting and (more rarely) by drowsiness, mental confusion, maculopapular or erythematous rash or diarrhoea. Electrolyte imbalances and dehydration may occur. Hyperkalaemia may be produced; symptoms include paraesthesia, weakness, flaccid paralysis and tetany.

The earliest signs are characteristic electrocardiographic abnormalities including tall "tent shaped" T waves, decreased amplitude of the P waves and widening of the QRS complex.

Symptomatic and supportive measures should be employed. There is no specific antidote. Treat fluid depletion, electrolyte imbalances, and hypotension by established procedures.

Hyperkalaemia can be treated promptly by the rapid intravenous administration of glucose (20% to 50%) and regular insulin, using 0.25 to 0.5 units of insulin per gram of glucose. Potassium excreting diuretics and ion exchange resins may also be administered, repeating as required.

ALDACTONE should be discontinued and potassium intake (including dietary potassium) restricted.

Contact the National Poisons Centre on 0800 764 766 for advice on the management of an overdose.

PHARMACEUTICAL PRECAUTIONS

Store below 30°C.

MEDICINE CLASSIFICATION

Prescription Medicine.

PACKAGE QUANTITIES

ALDACTONE 25 mg - blister packs of 100 tablets.

ALDACTONE 100 mg - blister packs of 100 tablets.

NAME AND ADDRESS OF THE SPONSOR

Pfizer New Zealand Ltd
PO Box 3998
Auckland, New Zealand

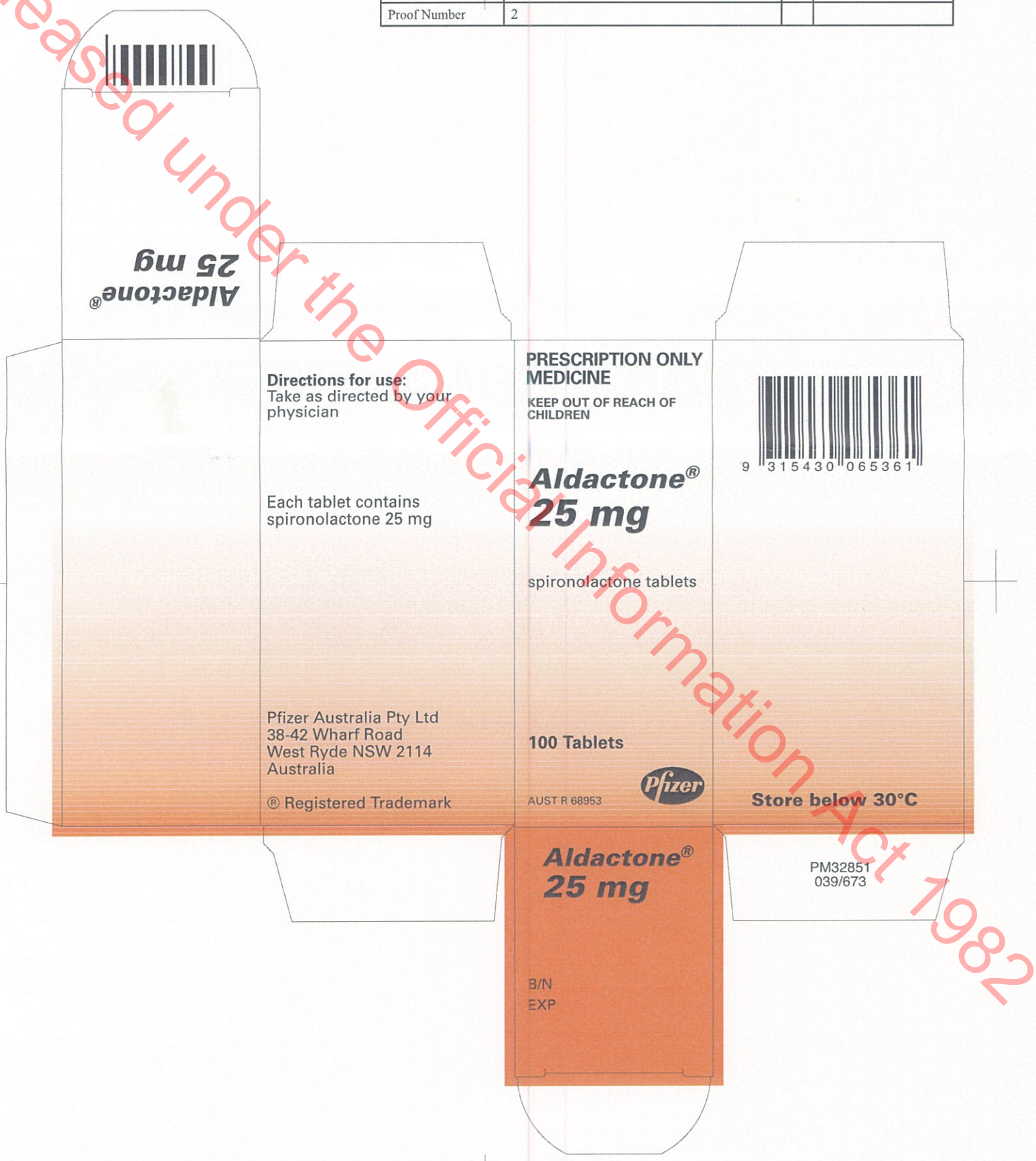
Toll Free number: 0800 736 363

DATE OF PREPARATION

4 September 2014

039-673paths 3/2/05 8:43 am Page 1

Pfizer Packaging Technology		
Title	Aldactone 25mg 100's Carton - Australia	Fonts
Code Number	039/673	Univers 55
Profile Ref.	UPS 6	
Dimensions	39 x 50 x 96mm	
Laetus Code	2533	
Bar Code	9315430065361	Colours
Designer	CD	Black
Software	Freehand MX	Pantone 172C
Date	03 FEB 2005	
Proof Number	2	

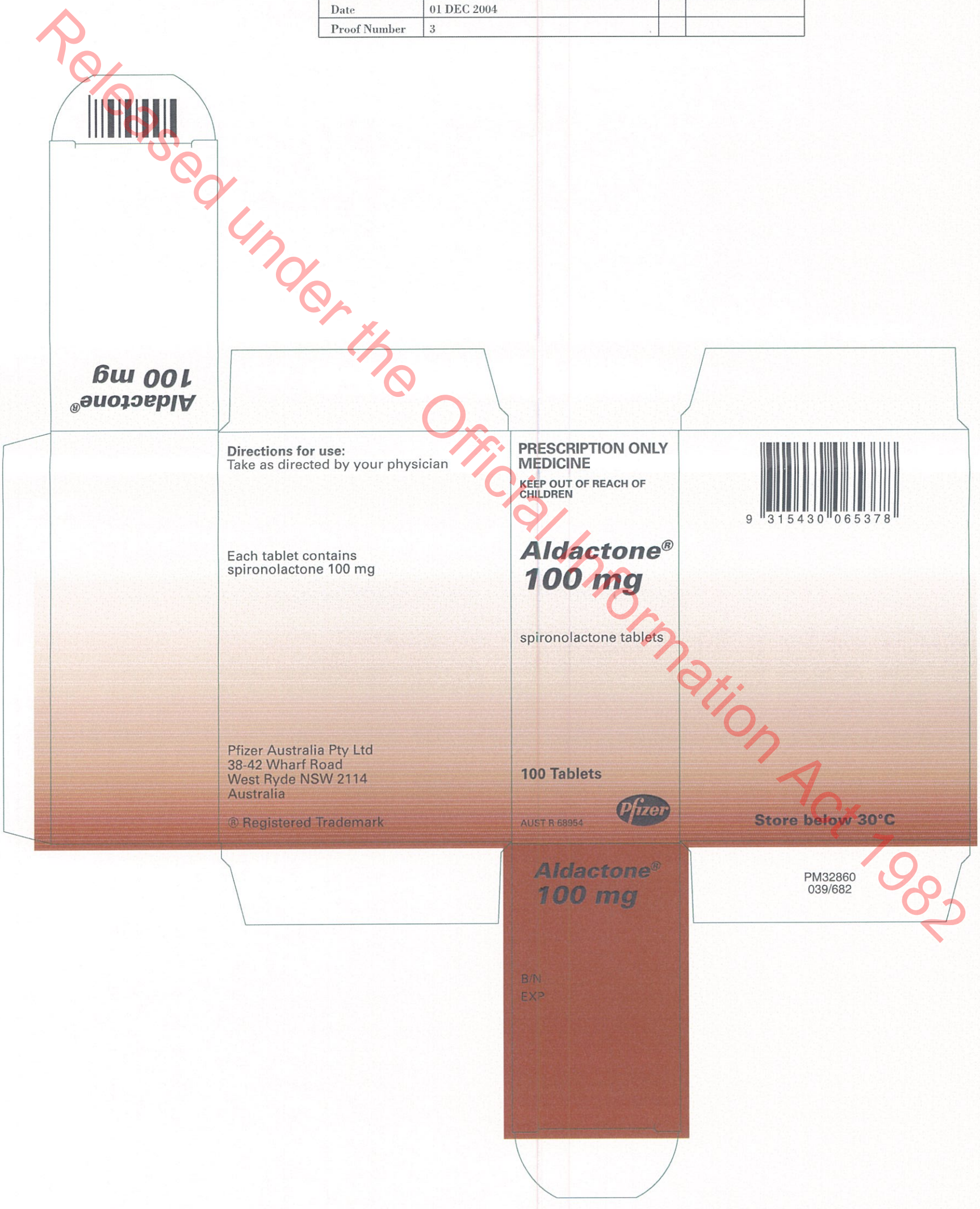


Composite

Attachment 2: Primary and secondary labelling for Aldactone 25 mg and Aldactone 100 mg

Packaging Technology

Title	Aldactone 100 mg 100s Carton - AUSTRALIA	Fonts Used	
Code Number	039/682	Univers	
Profile ref.	UPS08		
Dimensions	39 x 68 x 96mm		
Laetus Code	2220		
Bar Code	9315430065378	Colours	
Designer	Leon Wilkes		Black No. 14
Software	Freehand MX		Pantone 181C
Date	01 DEC 2004		
Proof Number	3		



Attachment 2: Primary and secondary labelling for Aldactone 25 mg and Aldactone 100 mg

Pfizer	Packaging Technology	
Title	Aldactone 25 mg Australia	Fonts Used
Code Number	012/852	Helvetica
Reel Width	183 mm	
Design Repeat	Random	
Laetus Code	N/A	
Bar Code	N/A	
Designer	Leon Wilkes	
Software	Freehand MX	Colours
Date	01 DEC 2004	Pantone 306U
Proof Number	5	

BLISTER OUTLINES DO NOT PRINT

BN and EXP is printed on the line.

SEARLE ALDACTONE 100MG AUSTRALIA GS/1664

START

CYLINDER AROUND = 8 REPEATS @ 68.465mm = 547.72mm

Aldactone® 25 mg
spironolactone

PM85530 012/852

CYLINDER ACROSS = 3 REELS @ 183mm = 549mm

DULL

Attachment 2: Primary and secondary labelling for Aldactone 25 mg and Aldactone 100 mg

Pfizer	Packaging Technology	
Title	Aldactone 25 mg Australia	Fonts Used
Code Number	012/842	Helvetica
Reel Width	183 mm	
Design Repeat	Random	
Laetus Code	N/A	
Bar Code	N/A	
Designer	Leon Wilkes	
Software	Freehand MX	Colours
Date	01 DEC 2004	Pantone 306U
Proof Number	5	

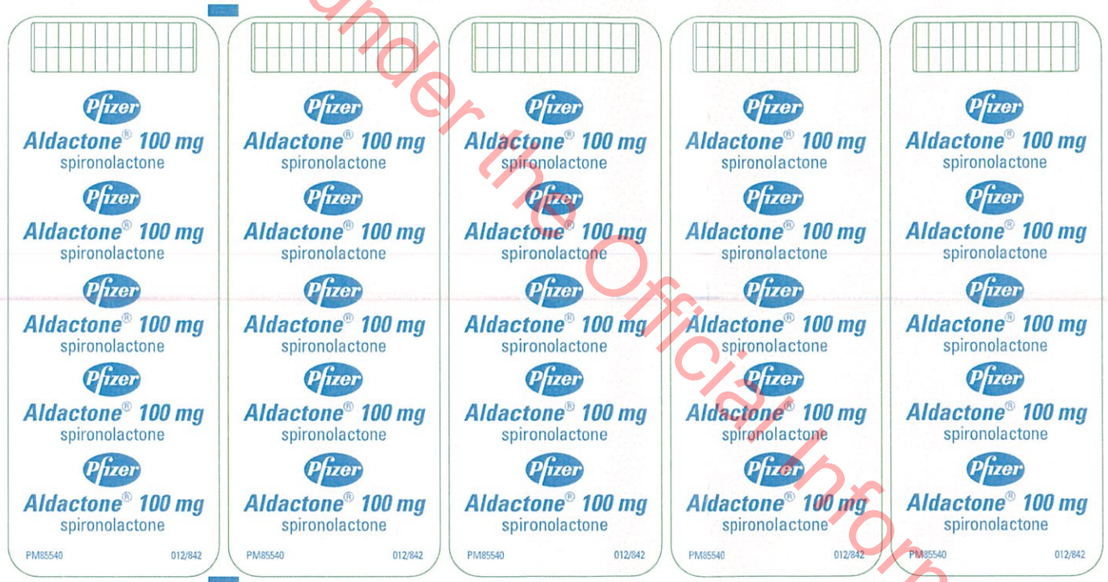
BLISTER OUTLINES DO NOT PRINT

BN and EXP is printed on the line.

SEARLE ALDACTONE 100MG AUSTRALIA 65/1664

START

CYLINDER AROUND = 8 REPEATS @ 68.465mm = 547.72mm



CYLINDER ACROSS = 3 REELS @ 183mm = 549mm

DULL