SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

FORTZAAR® Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each FORTZAAR Tablet contains 100 mg losartan potassium and 25 mg hydrochlorothiazide.

FORTZAAR contains 8,48 mg (0,216 mEq) of potassium.

FORTZAAR contains 126,26 mg lactose hydrous per tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

FORTZAAR tablets are light yellow, oval shaped, film-coated tablets, with “747” on one side and plain on the other side, approximately 15,49 mm long and 8,76 mm wide.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

FORTZAAR is indicated for the treatment of hypertension in patients established on identical doses of the individual agents.

4.2 Posology and method of administration

The maximum dose is one tablet of FORTZAAR (100 mg losartan potassium and 25 mg hydrochlorothiazide) once daily (see section 4.1). The maximum antihypertensive effect is

usually attained within three weeks after initiation of therapy.

Special populations

FORTZAAR should not be initiated in patients who are intravascularly volume-depleted (e.g. those treated with high-dose diuretics).

FORTZAAR is not recommended for patients with severe renal impairment or for patients with hepatic impairment (see section 4.3 and section 4.4).

FORTZAAR should not be used as initial therapy in elderly patients.

Paediatric population: N/A

Method of administration

FORTZAAR may be administered with other antihypertensive agents, such as calcium channel blockers and beta-blockers.

FORTZAAR may be administered with or without food.

4.3 Contraindications

- Hypersensitivity to losartan, hydrochlorothiazide or any of the other ingredients of FORTZAAR.
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs). These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Severe renal function impairment (creatinine clearance less than 30 mL/min).

- Anuria.
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene or amiloride (see section 4.5).
- Porphyria.
- FORTZAAR should not be given to patients with Addison's disease.
- Hypersensitivity to sulphonamides or to other sulphonamide-derived medicines.
- Lithium therapy: Concomitant administration with FORTZAAR may lead to toxic blood concentrations of lithium (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- Hepatic impairment.
- The concomitant use of FORTZAAR with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1,73 m^2) (see sections 4.4 and 4.5).
- Concomitant use of fluoroquinolones with ACE inhibitors/Renin-Angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment.

Paediatric Use

Safety and efficacy in children have not been established.

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving FORTZAAR, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see sections 4.3 and 4.6).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure).

Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended.

Dual blockade of RAAS through the combined use of FORTZAAR and aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1,73 m^2) (see section 4.3). If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

Hypotension and electrolyte/fluid imbalance

In patients who are intravascularly volume-depleted (e.g. those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of FORTZAAR or a lower starting dose should be used (see section 4.2). Periodic determination of serum electrolytes must be performed at appropriate intervals.

Metabolic and endocrine effects

Hydrochlorothiazide, a component of FORTZAAR, therapy may impair glucose tolerance. Dosage adjustment of antidiabetic medicines including insulin, may be required (see section 4.5).

Hydrochlorothiazide, a component of FORTZAAR, may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. FORTZAAR should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with hydrochlorothiazide, a component of FORTZAAR, therapy. Hydrochlorothiazide, a component of FORTZAAR, therapy may precipitate hyperuricaemia and/or gout.

Concomitant use with Lithium

Concomitant administration of lithium with FORTZAAR may lead to toxic blood concentrations of lithium (see section 4.5).

Hepatic and renal impairment

FORTZAAR is not recommended for patients with hepatic impairment or severe renal impairment (see section 4.3 and section 4.2). As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported.

Concomitant use of fluoroquinolones and ACE inhibitors/Renin-Angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment, with fluoroquinolones or ACE inhibitors/Renin-Angiotensin receptor blockers.

FORTZAAR may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. Similar effects have been reported with losartan (see section 4.3).

Increases in serum potassium

Concomitant use of other medicines that may increase serum potassium may lead to hyperkalaemia (see section 4.5).

Other

In patients receiving hydrochlorothiazide, a component of FORTZAAR, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of hydrochlorothiazide, as contained in FORTZAAR.

Non-Melanoma Skin Cancer

An increased risk of non-melanoma skin cancer (basal cell carcinoma [BCC] and squamous cell carcinoma [SCC] with increasing cumulative dose of hydrochlorothiazide has been observed in epidemiological studies. Photosensitising actions of hydrochlorothiazide could act as a possible mechanism for non-melanoma skin cancer.

Patients taking hydrochlorothiazide should be informed of the risk of non-melanoma skin cancer and advised to take preventive measures to reduce sun and artificial UVA exposure. Patients should regularly check their skin for new lesions and promptly report suspicious skin lesions to their physicians for evaluation. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous non-melanoma skin cancer (see also section 4.8).

Lactose

FORTZAAR contains lactose. Patients with rare hereditary problems of galactose intolerance, e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take FORTZAAR.

4.5 Interaction with other medicines and other forms of interaction

Losartan potassium

In clinical pharmacokinetic trials no interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital (see hydrochlorothiazide, alcohol, barbiturates or narcotics below) ketoconazole and erythromycin. Rifampicin and fluconazole have been reported to reduce levels of the active metabolite of FORTZAAR. The clinical consequences of these interactions have not been evaluated.

Concomitant use of medicines that block angiotensin II or its effects and potassium-sparing diuretics (e.g. spironolactone, triamterene and amiloride), potassium supplements, salt substitutes containing potassium or other medicines that may increase serum potassium (e.g. trimethoprim-containing products) may lead to increases in serum potassium.

Lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully, if lithium salts are co-administered with FORTZAAR.

Non-steroidal anti-inflammatory medicines (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of FORTZAAR.

In patients with compromised renal function (e.g. elderly patients or patients who are volume-depleted including those on diuretic therapy) being treated with non-steroidal anti-inflammatory drugs (NSAIDs), the co-administration of FORTZAAR may result in a further

deterioration of renal function, including possible acute renal failure. Therefore, the combination should be administered with caution in patients with compromised renal function.

Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see section 4.3 and section 4.4).

Concomitant use of fluoroquinolones and ACE inhibitors/Renin-Angiotensin receptor blockers may precipitate acute kidney injury (see section 4.3).

Hydrochlorothiazide (HCTZ)

When administered concurrently, the following medicines may interact with HCTZ diuretics:

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

Antidiabetic medication (oral agents and insulin): dosage adjustment of the antidiabetic medicine may be required.

Other antihypertensive medication: additive effect or potentiation.

Cholestyramine and colestipol resins: absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract

by up to 85 and 43 %, respectively. FORTZAAR should therefore be administered one hour before the intake of the resin.

Corticosteroids, ACTH or glycyrrhizin (found in liquorice): intensified electrolyte depletion, particularly hypokalaemia.

Pressor amines (e.g. norepinephrine): possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants: response to non-depolarising agents may be increased.

Lithium: should not be given with FORTZAAR. Diuretic medicines reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with FORTZAAR (see section 4.3).

Non-steroidal anti-inflammatory drugs (NSAIDs) including cyclooxygenase-2 Inhibitors: the administration of these medicines can reduce the diuretic, natriuretic and antihypertensive effects of FORTZAAR.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing age should ensure effective contraception while on FORTZAAR.

Pregnancy

FORTZAAR is contraindicated for use during pregnancy (see section 4.3). When pregnancy is planned or confirmed, FORTZAAR should be discontinued. Medicines affecting the renin-

angiotensin system, such as FORTZAAR, can cause foetal and neonatal morbidity and mortality when administered to pregnant women.

Breastfeeding

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. Women taking FORTZAAR should not breastfeed their infants (see section 4.3).

Fertility N/A

4.7 Effects on ability to drive and use machines

No studies on the reactions on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occur when taking antihypertensive therapy, in particular during initiation of treatment or when the dose is increased.

4.8 Undesirable effects

Adverse reactions from clinical trials

In controlled clinical trials for essential hypertension, the following adverse experiences were reported in patients treated with FORTZAAR and are shown in decreasing order of frequency within body system:

Very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1 000, < 1/100) and rare (≥ 1/10 000, < 1/1 000)

Nervous system disorders

Common: dizziness

General disorders and administration site conditions

Common: asthenia/fatigue.

Losartan

In controlled clinical trials for essential hypertension, the following adverse experiences were reported in patients treated with losartan potassium and are shown in decreasing order of frequency within body system:

Very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1 000, < 1/100) and rare (≥ 1/10 000, < 1/1 000)

Infections and infestations

Common: upper respiratory infection

Psychiatric disorders

Common: insomnia

Nervous system disorders

Very common: headache

Common: dizziness

Cardiac disorders

Common: palpitation, tachycardia

Vascular disorders

Uncommon: orthostatic hypotension

Respiratory, thoracic and mediastinal disorders

Common: cough, pharyngitis, nasal congestion, sinus disorder

Gastrointestinal disorders

Common: diarrhoea, nausea, abdominal pain, dyspepsia

Skin and subcutaneous tissue disorders

Uncommon: rash

Musculoskeletal, connective tissue and bone disorders

Common: back pain, muscle cramps

General disorders and administration site conditions

Common: asthenia/fatigue, oedema/swelling, chest pain

Investigations

Common: hyperkalaemia, elevations of ALT.

Hydrochlorothiazide

In controlled clinical trials for essential hypertension, the following adverse experiences were reported in patients treated with hydrochlorothiazide and are shown in decreasing order of frequency within body system:

Events are classified within body system categories and enumerated in order of decreasing frequency using the following definitions:

Common: (≥ 1/100, < 1/10), uncommon; (≥ 1/1 000, < 1/100), rare: (≥ 1/10 000, < 1/1 000), very rare: (> 1/10 000, including isolated reports)

Blood and the lymphatic system disorders

Rare: thrombocytopenia

Very rare: leukopenia; agranulocytosis; haemolytic anaemia

Metabolic and nutrition disorders

Uncommon: anorexia; hyperuricaemia

Rare: hyperglycaemia

Nervous system disorders

Rare: paraesthesia; headache

Vascular disorders

Uncommon: hypotension, (including orthostatic hypotension)

Respiratory, thoracic and mediastinal disorders

Very rare: respiratory distress including pneumonitis and pulmonary oedema

Gastrointestinal disorders

Uncommon: nausea; vomiting

Rare: diarrhoea; constipation

Very rare: pancreatitis

Hepatobiliary disorders

Rare: jaundice (intrahepatic cholestatic jaundice)

Skin and subcutaneous tissue disorders

Uncommon: rash; urticaria

Rare: photosensitivity

Very rare: necrotising angiitis (vasculitis and cutaneous vasculitis)

Renal and urinary disorders

Rare: glycosuria.

The following clinical trials side effects have been reported with the use of either losartan or hydrochlorothiazide, but the frequencies are unknown:

Infections and infestations

Sialadenitis

Blood and the lymphatic system disorders

Aplastic anaemia

Metabolic and nutrition disorders

Electrolyte imbalance including hyponatraemia and hypokalaemia

Psychiatric disorders

Restlessness

Eye disorders

Xanthopsia, transient blurred vision

Ear and labyrinth disorders

Vertigo

Vascular disorders

Hypotension and/or postural hypotension

Gastrointestinal disorders

Gastric irritation

Skin and subcutaneous tissue disorders

Purpura

Musculoskeletal, connective tissue and bone disorders

Cramping, muscle spasm

Renal and urinary disorders

Renal dysfunction, interstitial nephritis, renal failure

General disorders and administration site conditions

Fever, weakness.

Post-marketing experience

Adverse reactions from spontaneous reporting

The following adverse reactions have been reported in post-marketing experience; they are derived from spontaneous reports for which precise incidences cannot be determined therefore, the frequency is unknown:

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

Non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma).

Blood and the lymphatic system disorders

Thrombocytopenia, anaemia, aplastic anaemia, haemolytic anaemia, leukopenia, agranulocytosis

Immune system disorders

Anaphylactic reactions, including angioedema, swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue has been reported in patients treated with FORTZAAR; some of these patients previously experienced angioedema with other medicines including ACE inhibitors.

Metabolism and nutrition disorders

Anorexia, hyperglycaemia, hyperuricaemia, electrolyte imbalance including hyponatraemia and hypokalaemia

Psychiatric disorders

Insomnia, restlessness

Nervous system disorders

Dysgeusia, headache, migraine, paraesthesias

Eye disorders

Xanthopsia, transient blurred vision

Cardiac disorders

Palpitation, tachycardia

Vascular disorders

Dose-related orthostatic effects, necrotising angiitis (vasculitis) (cutaneous vasculitis)

Respiratory, thoracic and mediastinal disorders

Cough, nasal congestion, pharyngitis, sinus disorder, upper respiratory infection, respiratory distress (including pneumonitis and pulmonary oedema)

Gastrointestinal disorders

Dyspepsia, abdominal pain, gastric irritation, cramping, diarrhoea, constipation, nausea, vomiting pancreatitis, sialadenitis

Hepatobiliary disorders

Hepatitis, jaundice (intrahepatic cholestatic jaundice)

Skin and subcutaneous tissue disorders

Rash, pruritus, purpura (including Henoch-Schoenlein purpura), toxic epidermal necrolysis, urticaria, erythroderma, photosensitivity, cutaneous lupus erythematosus

Musculoskeletal, connective tissue and bone disorders

Back pain, muscle cramps, muscle spasm, myalgia, arthralgia

Renal and urinary disorders

Glycosuria, renal dysfunction, interstitial nephritis, renal failure

Reproductive system and breast disorders

Erectile dysfunction/impotence

General disorders and administration site conditions

Chest pain, oedema/swelling, malaise, fever, weakness

Investigations

Liver function abnormalities.

Description of Selected Side Effects

Non-melanoma skin cancer

Based on available data from epidemiological studies, a cumulative dose-dependent association between hydrochlorothiazide and non-melanoma skin cancer (BCC and SCC) has been observed.

The largest study included a population comprised of 71 533 cases of BCC and 8 629 cases of SCC matched to 1 430 833 and 172 462 population controls, respectively. High cumulative hydrochlorothiazide use (≥ 50 000 mg) was associated with an adjusted odds ratio (OR) of 1,29 (95 % CI: 1,23 to 1,35) for BCC and 3,98 (95 % CI: 3,68 to 4,31) for SCC. A cumulative dose-response relationship was observed for both BCC and SCC. Another study evaluated the association between lip cancer (SCC) and exposure to hydrochlorothiazide: 633 cases of lip cancer were matched with 63 067 population controls. A cumulative dose-response relationship was demonstrated with an adjusted OR of 2,1 (95 % CI: 1,7 to 2,6) for ever-use, increasing to an OR of 3,9 (95 % CI: 3,0 to 4,9) for high use (≥ 25 000 mg) and an OR of 7,7 (95 % CI: 5,7 to 10,5) for the highest cumulative dose (≥ 100 000 mg).

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 SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Losartan potassium

The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor the active metabolite can be removed by haemodialysis.

Hydrochlorothiazide

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digoxin has also been administered, hypokalaemia may accentuate cardiac dysrhythmias. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

5 PHARMACOLOGICAL PROPERTIES

A 7.1.3. Other hypotensives

5.1 Pharmacodynamic properties

Losartan potassium is an angiotensin II receptor (type AT_1) antagonist and hydrochlorothiazide is a diuretic.

Losartan

Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin-angiotensin system and a major determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT_1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation.

Losartan is a synthetic, orally active compound which binds selectively to the AT_1 receptor. Both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block the actions of angiotensin II, regardless of the source of synthesis.

Hydrochlorothiazide

The mechanism of the antihypertensive effect of thiazides is unknown.

Hydrochlorothiazide, when used as a diuretic affects the distal renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by loss of potassium, magnesium and bicarbonate.

Losartan potassium-hydrochlorothiazide

Losartan and hydrochlorothiazide are additive in their antihypertensive efficacy.

5.2 Pharmacokinetic properties

Losartan

Absorption

Following oral administration, losartan undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33 %. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3 to 4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when losartan was administered with a standardised meal.

Distribution

Both losartan and its active metabolite are 99 % and more bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Metabolism

About 14 % of an intravenously or orally administered dose of losartan is converted to its active metabolite.

Elimination

Plasma clearance of losartan and its active metabolite is about 600 mL/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 mL/min and 26 mL/min, respectively. When losartan potassium is administered orally, about 4 % of the dose is excreted unchanged in the urine and about 6 % of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6 to 9 hours, respectively.

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of ^{14}C-labelled losartan in man, about 35 % of radioactivity is recovered in the urine and 58 % in the faeces.

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1,7-fold greater than those seen in young male volunteers.

Neither losartan nor the metabolite can be removed by haemodialysis.

Hydrochlorothiazide

When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5,6 and 14,8 hours. Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney. At least 61 % of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

Losartan potassium-hydrochlorothiazide

In a pharmacokinetic interaction study, hydrochlorothiazide 12,5 mg did not alter the pharmacokinetics of losartan 50 mg and vice versa.

5.3 Preclinical safety data

N/A

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive Ingredients: carnauba wax, hydroxypropyl cellulose, microcrystalline cellulose, hypromellose, lactose hydrous, magnesium stearate, pregelatinised starch, quinolone yellow aluminium lake, titanium dioxide.

6.2 Incompatibilities

N/A

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

FORTZAAR Tablets are supplied in blister packs of 30.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Organon South Africa (Pty) Ltd

Spaces, 1st Floor, 22 Magwa Crescent, Gateway West

Waterfall City, Midrand, 2090

South Africa

8 REGISTRATION NUMBER(S)

34/7.1.3/0281

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