PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

RANEPRES 8 mg

RANEPRES 16 mg

RANEPRES 32 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RANEPRES 8 mg

Each tablet contains 8 mg candesartan cilexetil.

Contains sugar (lactose monohydrate)

RANEPRES 8 mg contains sugar (lactose monohydrate 86.25 mg)

RANEPRES 16 mg

Each tablet contains 16 mg candesartan cilexetil.

Contains sugar (lactose monohydrate)

RANEPRES 16 mg contains sugar (lactose monohydrate 78.15 mg).

RANEPRES 32 mg

Each tablet contains 32 mg candesartan cilexetil

Contains sugar (lactose monohydrate):

RANEPRES 32 mg contains sugar (lactose monohydrate 156.30 mg)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

RANEPRES 8 mg:

Light pink circular, biconvex, uncoated tablets, debossed with “ML 53” on one side and breakline on other side.

RANEPRES 16 mg:

Pink, circular, biconvex, uncoated tablets, debossed with “ML 54” on one side and breakline on other side.

RANEPRES 32 mg:

Pink, circular, biconvex, uncoated tablets, debossed with “ML 55” on one side and breakline on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RANEPRES is indicated for mild to moderate hypertension.

RANEPRES can be used as monotherapy or in combination with other antihypertensive medicines such as thiazide diuretics and dihydropyridine calcium antagonists, for enhanced efficacy.

Heart failure

Treatment with **RANEPRES** reduces mortality, reduces hospitalisation due to heart failure, and improves symptoms in patients with left ventricular systolic dysfunction (LVEF ≤ 40 %.)

4.2 Posology and method of administration

Posology

Dosage in hypertension:

The recommended initial dose of **RANEPRES** is 8 mg once daily. The usual maintenance dose is 8 mg to 16 mg once daily.

The maximal antihypertensive effect is attained within 4 weeks of initiation of treatment.

Some patients may receive an additional benefit by increasing the dose to 32 mg once daily.

Special populations

Elderly population

No initial dosage adjustment is necessary for elderly patients with normal renal and hepatic function.

Renal impairment

No initial dosage adjustment is necessary in patients with mild to moderate renal impairment (i.e. creatinine clearance ≥ 30 mL/min/1,73m2 BSA). In patients with more severe renal impairment (i.e. creatinine clearance < 15 - 30 mL/min/1,73m2 BSA), the clinical experience is limited and a lower initial dose of 4 mg should be used.

Hepatic impairment

No initial dosage adjustment is necessary in patients with mild to moderate hepatic impairment. There is no experience available in patients with severe hepatic impairment and/or cholestasis (see section 4.3).

Concomitant therapy

RANEPRES can be used as monotherapy or in combination with other antihypertensive medicines, such as thiazide diuretics and dihydropyridine calcium antagonists, e.g. amlodipine, for enhanced efficacy.

Use in black patients

The antihypertensive effect of **RANEPRES** is less in black than non-black (Caucasian, Asian and other) patients. Consequently, up-titration of **RANEPRES** and concomitant therapy (such as thiazide diuretics) may be more frequently needed for blood pressure control in black than non-black patients.

Dosage in heart failure

The usual recommended initial dose of **RANEPRES** is 4 mg once daily. Up-titration to the target dose of 32 mg once daily or the highest tolerated dose is done by doubling the dose at intervals of at least 2 weeks (see section 4.4).

Special patient populations

No initial dose adjustment is necessary for elderly patients or in patients with renal or mild to moderate hepatic impairment.

Concomitant therapy

RANEPRES can be administered with other heart failure treatment, including ACE inhibitors, beta-blockers, diuretics and digoxin or a combination of these medicinal products (see section 5.1.)

Paediatric population

The safety and efficacy of **RANEPRES** has not been established in children.

Method of administration

For oral use

RANEPRES should be taken once daily with or without food.

4.3 Contraindications

- Hypersensitivity to candesartan cilexetil or to any of the excipients of **RANEPRES** listed in section 6.1.
- 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 hepatic impairment / cholestasis
- Severe renal function impairment (creatinine clearance less than 30 mL/min).
- 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, amiloride. (see section 4.5)
- Concomitant use of fluoroquinolones with ACE inhibitors/Angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment (creatinine clearance less than 30mL/min) and in elderly patients.
- Porphyria
- Lithium therapy: Concomitant administration with **RANEPRES** may lead to toxic blood concentrations of lithium. (see section 4.5)
- Pregnancy and lactation. (see section 4.6)
- The concomitant use of **RANEPRES** with aliskiren-containing products is contraindicated. (see section 4.4 and 4.5)

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving **RANEPRES**, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (See section 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 or aliskiren- containing medicines increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren-containing medicines is therefore not recommended (see Section 4.5).

RANEPRES should not be used concomitantly with aliskiren- containing medicines (see section 4.3)

ACE inhibitors and angiotensin II receptor blockers (ARBs) should not be used concomitantly in patients with diabetic nephropathy.

Renal impairment

Changes in renal function may be anticipated in susceptible patients treated with candesartan cilexetil. When **RANEPRES** is used in hypertensive patients with renal impairment, periodic monitoring of serum potassium and creatinine levels is recommended. There is limited experience in patients with very severe or end-stage renal impairment (CIcr < 15 mL / min). In these patients, Candesartan cilexetil should be carefully titrated with thorough monitoring of blood pressure.

Evaluation of patients with heart failure should include periodic assessments of renal function, especially in elderly patients 75 years or older, and patients with impaired renal function. During dose titration of **RANEPRES**, monitoring of serum creatinine and potassium is recommended. Clinical trials in heart failure did not include patients with serum creatinine > 265 µmoL / L (> 3 mg / dL).

Concomitant therapy with an ACE inhibitor in heart failure

The risk of adverse reactions, especially hypotension, hyperkalaemia and decreased renal function (including acute renal failure), may increase when candesartan is used in combination with an ACE-inhibitor. Co-therapy of **RANEPRES** and an ACE-inhibitor should be under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Haemodialysis

During dialysis the blood pressure may be particularly sensitive to AT1-receptor blockade as a result of reduced plasma volume and activation of the renin-angiotensin-aldosterone system. Therefore, **RANEPRES** should be carefully titrated with thorough monitoring of blood pressure in patients on haemodialysis.

Renal artery stenosis

Medicinal products that affect the renin-angiotensin-aldosterone system, including angiotensin II receptor blockers(ARBs), may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Kidney transplantation

There is limited clinical evidence regarding candesartan cilexetil use in patients who have undergone renal transplant.

Hypotension

Hypotension may occur during treatment with **RANEPRES** in heart failure patients. It may also occur in hypertensive patients with intravascular volume depletion such as those receiving high dose diuretics. Caution should be observed when initiating therapy and correction of hypovolemia should be attempted.

Anaesthesia and surgery

Hypotension may occur during anaesthesia and surgery in patients treated with angiotensin II blockers due to blockade of the renin-angiotensin system. Hypotension may be severe such that it may warrant the use of intravenous fluids and/or vasopressors.

Aortic and mitral valve stenosis (obstructive hypertrophic cardiomyopathy)

Special caution is indicated in patients suffering from haemodynamically relevant aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy when taking **RANEPRES**.

Primary hyperaldosteronism

Patients with primary hyperaldosteronism will not generally respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin-aldosterone system. Therefore, the use of **RANEPRES** is not recommended in this population.

Hyperkalaemia

Concomitant use of **RANEPRES** with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (e.g. heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole) may lead to increases in serum potassium in hypertensive patients. Monitoring of potassium should be undertaken as appropriate.

In heart failure patients treated with **RANEPRES**, hyperkalaemia may occur. Periodic monitoring of serum potassium is recommended. The combination of an ACE inhibitor, a potassium-sparing diuretic (e.g. spironolactone) and **RANEPRES** is not recommended.

General

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with other medicinal products that affect this system has been associated with acute hypotension, uraemia, oliguria or, acute renal failure. The possibility of similar effects cannot be excluded with ARBs. Excessive blood pressure decrease in patients with ischaemic cardiopathy or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.

The antihypertensive effect of candesartan in **RANEPRES** may be enhanced by other medicinal products with blood pressure lowering properties, whether prescribed as an antihypertensive or prescribed for other indications.

Paediatric population, including paediatric patients with renal impairment

Candesartan Cilexetil has not been studied in children with a glomerular filtration rate less than 30 mL / min / 1,73 m2. (see section 4.2)

Excipients: lactose intolerance

RANEPRES contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take **RANEPRES**.

4.5 Interaction with other medicines and other forms of interaction

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-containing medicines 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 medicine (see Sections 4.3, 4.4 and 5.1).

Compounds which have been investigated in clinical pharmacokinetic studies include hydrochlorothiazide, warfarin, digoxin, oral contraceptives (i.e. ethinylestradiol/levonorgestrel), glibenclamide, nifedipine and enalapril. No clinically significant pharmacokinetic interactions with these medicinal products have been identified with candesartan cilexetil.

Concomitant use of **RANEPRES** and potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products (e.g. heparin) may increase potassium levels. Monitoring of potassium should be undertaken as appropriate during this co-therapy. (see section 4.4).

Concomitant use of **RANEPRES** and lithium is not recommended. Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors and a similar effect may occur with candesartan cilexetil. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Concomitant use of **RANEPRES** and non-steroidal anti-inflammatory drugs (NSAIDs) (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g / day) and non-selective NSAIDs), may cause attenuation of the antihypertensive effect.

Concomitant use of candesartan cilexetil and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially

in patients with poor pre-existing renal function. Co-therapy of **RANEPRES** and ACE-inhibitors should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing age should ensure effective contraception.

Pregnancy

Safety in pregnancy has not been established .RANEPRES is contraindicated during pregnancy (see section 4.3). When pregnancy is planned or confirmed RANEPRES should be discontinued.

Medicines affecting the renin-angiotensin system, such as RANEPRES, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.

Breastfeeding

Safety in lactation has not been established. RANEPRES is contraindicated in lactation (see section 4.3)

Candesartan is excreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, breastfeeding should be discontinued if the use of RANEPRES is considered essential.

Fertility

No fertility data is available.

4.7 Effects on ability to drive and use machines

No studies on the effects of candesartan on the ability to drive and use machines have been performed. However, it should be taken into account that dizziness or weariness may occur during treatment with Candesartan cilexetil.

4.8 Undesirable effects

System Organ Class	Frequency		
	Frequent	Less Frequent	Not known
Infections and infestations	Respiratory infection		
Blood and lymphatic system disorders		Leukopenia, neutropenia and agranulocytosis	
Metabolism and nutrition disorders		Hyperkalaemia, hyponatraemia	
Immune system disorders		Angioedema	
Nervous system disorders	Dizziness/vertigo, headache		
Respiratory, thoracic and mediastinal disorders		Cough	
Gastrointestinal disorders		Nausea	Diarrhoea
Hepatobiliary disorders		Increased liver enzymes, abnormal hepatic function or hepatitis	
Skin and subcutaneous tissue disorders		Rash, urticaria, pruritus	
Musculoskeletal and connective tissue disorders		Back pain, arthralgia, myalgia	
Renal and urinary		Renal impairment,	

disorders		including renal failure in susceptible patients (see section 4.4)	

Laboratory findings

Small decreases in haemoglobin have been seen. Significant increases in creatinine, urea or potassium have been observed. In patients with severe renal impairment, periodic monitoring of serum potassium and creatinine levels is recommended.

Treatment of Heart Failure

The most commonly reported adverse reactions were hyperkalaemia, hypotension and renal impairment. These events were more common in patients over 70 years of age, diabetics, or subjects who received other medicinal products, which affect the renin-angiotensin-aldosterone system, in particular an ACE inhibitor and/or spironolactone.

System Organ Class	Frequency		
	Frequent	Less Frequent	Not known
Blood and lymphatic system disorders		Leukopenia, neutropenia and agranulocytosis	
Metabolism and nutrition disorders	Hyperkalaemia	Hyponatraemia	
Nervous system disorders		Dizziness, headache	
Vascular disorders	Hypotension		
Respiratory, thoracic and mediastinal disorders		Cough	
Gastrointestinal disorders		Nausea	Diarrhoea

Hepatobiliary disorders		Increased liver enzymes, abnormal hepatic function or hepatitis	
Skin and subcutaneous tissue disorders		Angioedema, rash, urticaria, pruritus	
Musculoskeletal and connective tissue disorders		Back pain, arthralgia, myalgia	
Renal and urinary disorders	Renal impairment, including renal failure in susceptible patients (see section 4.4)		

Laboratory findings

Hyperkalaemia and renal impairment are common in patients treated with Candesartan cilexetil for the indication of heart failure. Periodic monitoring of serum creatinine and potassium is recommended (see section 4.4).

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

Symptoms

Based on pharmacological considerations, the main manifestation of an overdose is likely to be symptomatic hypotension and dizziness. In individual case reports of overdose (of up to 672 mg candesartan cilexetil) in an adult patient recovery was uneventful.

Treatment

If symptomatic hypotension should occur, symptomatic treatment should be instituted and vital signs monitored. The patient should be placed supine with the legs elevated. If this is not sufficient, plasma volume should be increased by infusion of, for example, isotonic saline solution. Sympathomimetic medicinal products may be administered if the above-mentioned measures are not sufficient.
Candesartan is not removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A 7.1.3 Other hypotensives

Pharmacotherapeutic group: Angiotensin II antagonists, plain

ATC Code: C09CA06

Candesartan cilexetil is a prodrug. After oral administration it is converted to the active medicine, candesartan, by ester hydrolysis during absorption from the gastrointestinal tract. Candesartan is an angiotensin II receptor blocker, selective for AT1 receptors, with tight binding to and slow dissociation from the receptor. It has no agonist activity.

The major physiological effects of angiotensin II, such as vasoconstriction, aldosterone stimulation, regulation of salt and water homeostasis and stimulation of cell growth, are mediated via the type I (AT1) receptor.

The antagonism of the angiotensin II(AT1) receptors results in dose related increases in plasma renin levels, angiotensin I and angiotensin II levels, and a decrease in plasma aldosterone concentration.

Hypertension

In hypertension **RANEPRES** causes a dose-related sustained reduction in arterial blood pressure over the dosage interval. The antihypertensive action is due to decreased systemic peripheral resistance, while heart rate, stroke volume and cardiac output are not affected.

After administration of a single dose of **RANEPRES**, onset of antihypertensive effect generally begins within 2 hours. With continuous treatment, the maximum reduction in blood pressure is generally attained within 4 weeks and is sustained during long-term treatment. Candesartan has a peak to trough ratio of peak versus trough effects of close to 1.

RANEPRES increases renal blood flow and either has no effect on; or increases glomerular filtration rate while renal vascular resistance and filtration fraction are reduced.

RANEPRES also reduces urinary albumin excretion in patients with type II diabetes mellitus, hypertension and microalbuminuria.

Candesartan cilexetil had an additional blood pressure lowering effect when added to hydrochlorothiazide.

Heart failure

In patients with chronic heart failure (CHF) and depressed left ventricular systolic function (left ventricular ejection fraction, LVEF ≤ 40 %), **RANEPRES** decreases systemic vascular resistance and pulmonary capillary wedge pressure, increases plasma renin activity and angiotensin II concentration, and decreases aldosterone levels.

Treatment with **RANEPRES** reduces mortality due to cardiovascular events and hospitalisation due to CHF in patients with a left ventricular ejection fraction (LVEF) of ≤ 40 % and improves symptoms in these patients as shown in the Candesartan in Heart failure – Assessment of Reduction in Mortality and morbidity (CHARM) programme.

There was no benefit of **RANEPRES** in patients with a LVEF of more than 40 %.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, candesartan cilexetil is converted to the active medicine, candesartan.

The mean peak serum concentration (CMAX) is reached 3 - 4 hours following tablet intake.
The candesartan serum concentration increases linearly with increasing doses in the therapeutic dose range.

No gender related differences in the pharmacokinetics of candesartan have been observed. The area under the serum concentration versus time curve (AUC) of candesartan is not significantly affected by food.

Candesartan is highly bound to plasma protein (more than 99 %). The apparent volume of distribution of candesartan is 0, 1 L / kg.

Biotransformation and Elimination

Candesartan is mainly eliminated unchanged via urine and bile and only to a minor extent eliminated by hepatic metabolism (CYP2C9). Available interaction studies indicate no effect on CYP2C9 and CYP3A4. Based on in vitro data, no interaction would be expected to occur in vivo with medicines whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4. The terminal half-life (T½) of candesartan is approximately 9 hours. There is no accumulation following multiple doses.

Total plasma clearance of candesartan is about 0, 37 mL / min / kg, with a renal clearance of about 0, 19 mL / min / kg. Following an oral dose of 14C labelled candesartan cilexetil, the active candesartan, and its inactive metabolites are excreted via the urine (30 %) and to a larger extent (70 %) via the faeces.

Special population

In elderly subjects (over 65 years), Cmax and AUC of candesartan are increased by approximately 50 % and 80 %, respectively in comparison to young adults.

In patients with mild (Ccr 60- 90 mL/ min) and moderate (Ccr 30- 60 mL/min) to severe (Ccr 15- 30 mL/ min) renal impairment, Cmax and AUC of candesartan increased during repeated dosing. The

terminal t½ of candesartan in patients with severe renal impairment was approximately doubled compared to patients with normal renal function.
In patients with mild to moderate renal impairment AUC was approximately doubled, while in severe renal impairment the AUC was further increased.
Candesartan has not been studied in patients with more severe renal failure (Ccr ≤ 15 mL/min).

In patients with mild hepatic impairment, there was an increase in the AUC of candesartan, of approximately 30 %. In patients with moderate hepatic impairment, the increase in the AUC of candesartan was approximately 145 %.
There is no experience in patients with severe hepatic impairment and/or cholestasis.

5.3 Preclinical safety data

There was no evidence of abnormal systemic or target organ toxicity at clinically relevant doses. In preclinical safety studies candesartan had effects on the kidneys and on red cell parameters at high doses in mice, rats, dogs and monkeys. Candesartan caused a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit).
Effects on the kidneys (such as interstitial nephritis, tubular distension, basophilic tubules; increased plasma concentrations of urea and creatinine) were induced by candesartan which could be secondary to the hypotensive effect leading to alterations of renal perfusion. Furthermore,
candesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells. These changes were considered to be caused by the pharmacological action of candesartan. For therapeutic doses of candesartan in humans, the hyperplasia/hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

Foetotoxicity has been observed in late pregnancy (see section 4.6).
Data from in vitro and in vivo mutagenicity testing indicates that candesartan will not exert mutagenic or clastogenic activities under conditions of clinical use. There was no evidence of carcinogenicity.

The renin-angiotensin-aldosterone system plays a critical role in kidney development in utero. Renin-angiotensin-aldosterone system blockade has been shown to lead to abnormal kidney development in very young mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Corn starch,

lactose monohydrate,

red ferric oxide,

hydroxypropyl cellulose,

glycerin/glycerol,

carboxymethylcellulose calcium,

magnesium stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months from the manufacturing date.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Keep the blisters in the carton until required for use.

Keep the HDPE container tightly closed.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Blister Pack:

Tablets are packed in clear film PVC/PVdC 250 µm/90 with 90 gsm PVDC as the forming material and 25 µm aluminium foil with 6-8 gsm heat seal lacquer as the lidding material, packed in pre-printed carton.

Pack size include 14 or 28 tablets.

Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

Office block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBER

RANEPRES 8 mg tablets: 48/7.1.3/0472

RANEPRES 16 mg tablets: 48/7.1.3/0473

RANEPRES 32 mg tablets: 48/7.1.3/0474

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated by the Authority upon authorisation.

10. DATE OF REVISION OF THE TEXT

To be allocated by the Authority