SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

INSPRA® 25 Tablets

INSPRA® 50 Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

INSPRA 25: Each tablet contains 25 mg eplerenone.

INSPRA 50: Each tablet contains 50 mg eplerenone.

Contains sugar:

Each INSPRA 25 tablet contains 35,7 mg lactose monohydrate.

Each INSPRA 50 tablet contains 71,4 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

INSPRA 25: A yellow, debossed, arc diamond, film-coated tablet, stylised “Pfizer” on one side of the tablet and “NSR” over “25” on the other side of the tablet.

INSPRA 50: A yellow, debossed, arc diamond, film-coated tablet, stylised “Pfizer” on one side of the tablet and “NSR” over “50” on the other side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

INSPRA is indicated to reduce the risk of cardiovascular death in stable patients with left ventricular dysfunction (ejection fraction ≤ 40 %) and clinical evidence of heart failure after an acute myocardial infarction.

4.2 Posology and method of administration

Posology

INSPRA is usually administered in combination with standard therapies. The recommended maintenance dose of INSPRA is 50 mg once daily. The maximum dose is 50 mg daily for heart failure. Treatment should be initiated at 25 mg once daily and titrated in one step to the target dose of 50 mg once daily preferably within 4 weeks, as tolerated by the patient, taking into account the serum potassium level (see Table 1). After initiation, the dose should be adjusted based on the serum potassium level as shown in Table 1.

Table 1. Dose adjustment table in heart failure – post MI

Serum potassium (mmol/L or mEq/L)	**Action**	**Dose adjustment**
< 5,0	Increase	25 mg EOD to 25 mg OD 25 mg OD to 50 mg OD
5,0 – 5,4	Maintain	No dose adjustment
5,5 – 5,9	Decrease	50 mg OD to 25 mg OD 25 mg OD to 25 mg EOD 25 mg EOD to withhold
≥ 6,0	Withhold	N/A
EOD (every other day), OD (once daily)		

Following withholding INSPRA due to serum potassium ≥ 6,0 mmol/L (or > 6,0 mEq/L), INSPRA can be re-started at a dose of 25 mg every other day when potassium levels have fallen below 5,0 mmol/L (or 5,0 mEq/L).

Special populations

Elderly population

No dose adjustment is required in the elderly.

Renal impairment

No initial dose adjustment is required in patients with mild renal impairment (see section 4.4). The rates of hyperkalaemia increase with declining renal function. Periodic monitoring of serum potassium with dose adjustment according to Table 1 is recommended (see section 4.4).

Hepatic impairment

No initial dosage adjustment is necessary for patients with mild to moderate hepatic impairment.

Paediatric population

There are insufficient data to recommend the use of INSPRA in the paediatric population, and therefore, use in this age group is not recommended.

Method of administration

For oral use.

INSPRA may be administered with or without food.

4.3 Contraindications

INSPRA is contraindicated in patients with the following:

- Hypersensitivity to eplerenone or to any of the excipients of INSPRA.
- Clinically significant hyperkalaemia or with conditions associated with hyperkalaemia.
- Serum potassium level > 5,0 mmol/L (mEq/L) at initiation.
- Moderate to severe renal impairment (creatinine clearance < 50 mL/min).
- Severe hepatic impairment (Child-Pugh Class C).
- Concomitant use with potassium-sparing diuretics or strong inhibitors of CYP3A4 such as ketoconazole, itraconazole and ritonavir (see section 4.5).

4.4 Special warnings and precautions for use

Hyperkalaemia

Hyperkalaemia may occur with INSPRA. Serum potassium levels should be monitored in all patients at initiation of treatment and with a change in dosage. Thereafter, periodic monitoring is recommended in patients at risk for the development of hyperkalaemia. Dose reduction of INSPRA has been shown to decrease serum potassium levels. In one study, the addition of hydrochlorothiazide to INSPRA therapy has been shown to offset increases in serum potassium. The risk of hyperkalaemia may increase when INSPRA is used in combination with an angiotensin converting enzyme (ACE) inhibitor and/or an angiotensin receptor blocker (ARB).

Impaired renal function

Potassium levels should be monitored regularly in patients with impaired renal function, including patients with diabetic microalbuminuria. Patients who have serum creatinine levels > 221 µmol/L (>

2,5 mg/dL) or creatinine clearance < 50 mL/min should be treated with caution. INSPRA should be used with caution in patients with type 2 diabetes mellitus (see section 4.3).

Impaired hepatic function

No elevations of serum potassium above 5,5 mmol/L were observed in patients with mild to moderate hepatic impairment. Electrolyte levels should be monitored in patients with mild to moderate hepatic impairment. The use of INSPRA in patients with severe hepatic impairment (Child-Pugh Class C) has not been evaluated and is therefore contraindicated (see section 4.3).

Non-steroidal anti-inflammatory drugs (NSAIDS)

The administration of other potassium-sparing medicines with NSAIDs has been shown to result in hyperkalaemia in patients with impaired renal function (see section 4.5).

Lithium

Lithium toxicity has been reported in patients receiving lithium concomitantly with diuretics and ACE inhibitors. Serum lithium levels should be monitored frequently if INSPRA is administered concomitantly with lithium (see section 4.5).

CYP3A4 inducers

Co-administration of INSPRA with potent CYP3A4 inducers is not recommended (see section 4.5).

General considerations

Potassium

Serum potassium should be measured before initiating INSPRA therapy, within the first week and at one month after the start of treatment or dose adjustment. Serum potassium should be assessed periodically thereafter.

Elderly

Due to age-related decline in renal function, the risk of hyperkalaemia is increased in elderly patients. Periodic monitoring of serum potassium is recommended.

Information about the excipients of INSPRA

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Potassium-sparing diuretics

INSPRA should not be administered to patients receiving other potassium-sparing diuretics (see section 4.3).

ACE inhibitors, angiotensin receptor blockers (ARB)

The risk of hyperkalaemia may increase when INSPRA is used in combination with an angiotensin converting enzyme (ACE) inhibitor and/or an angiotensin receptor blocker (ARB). Close monitoring of serum potassium and renal function is recommended, especially in patients at risk for impaired renal function e.g. the elderly.

CYP3A4 inhibitors

Significant drug-drug pharmacokinetic interactions may occur when INSPRA is administered concomitantly with medicines that inhibit the CYP3A4 enzyme. Significant drug-drug pharmacokinetic interactions have been observed with ketoconazole, erythromycin, saquinavir, verapamil, fluconazole and ritonavir (see section 4.3).

INSPRA dosing should therefore not exceed 25 mg when mild to moderate inhibitors of CYP3A4 are co-administered with INSPRA.

CYP3A4 substrates

Results of pharmacokinetic studies with CYP3A4 probe-substrates i.e. midazolam and cisapride, showed no significant pharmacokinetic interactions when these medicines were co-administered with INSPRA.

CYP3A4 inducers

Co-administration of St John's Wort (a potent CYP3A4 inducer) with INSPRA caused a 30 % decrease in eplerenone AUC. A more pronounced decrease in eplerenone AUC may occur with more potent CYP3A4 inducers and the concomitant use of potent CYP3A4 inducers with INSPRA is not recommended (see section 4.4).

No clinically significant drug-drug pharmacokinetic interactions have been found with digoxin or warfarin.

Medicine interaction studies of INSPRA have not been conducted with NSAIDs. The administration of other potassium-sparing medicines with NSAIDs has been shown to result in severe hyperkalaemia in patients with impaired renal function (see section 4.4).

Medicine interaction studies of INSPRA have not been conducted with lithium. Lithium toxicity has been reported in patients receiving lithium concomitantly with diuretics and ACE inhibitors (see section 4.4).

In vitro studies indicate that INSPRA is not an inhibitor of CYP1A2, CYP2C19, CYP2C9 or CYP2D6 isozymes. INSPRA is not a substrate or an inhibitor of P-glycoprotein.

4.6 Fertility, pregnancy and lactation

Safety and efficacy of INSPRA have not been demonstrated in pregnancy and lactation.

Pregnancy

INSPRA should not be used during pregnancy.

Breastfeeding

INSPRA should not be used during lactation. INSPRA is excreted in animal breast milk. Mothers on INSPRA should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

No studies on the effect of INSPRA on the ability to drive or use machines have been performed. INSPRA does not cause drowsiness or impairment of cognitive function but when driving vehicles or operating machines it should be taken into account that dizziness and syncope may occur during treatment. Caution is advised when driving or operating machinery until the response to initial treatment has been determined.

4.8 Undesirable effects

Summary of the safety profile

INSPRA has been evaluated for safety in 3 307 patients treated for heart failure post-myocardial infarction (see section 5.1).

In the INSPRA post-acute myocardial infarction heart failure efficacy and survival study (EPHESUS), the overall incidence of adverse events reported with INSPRA (78,9 %) was similar to placebo (79,5 %).

The discontinuation rate due to adverse events in these studies was 4,4 % for patients receiving

INSPRA and for 4,3 % patients receiving placebo.

Tabulated summary of adverse reactions

Adverse events reported below are those with suspected relationship to treatment and in excess of placebo, taken from EPHESUS. Adverse events are listed according to the system organ class and absolute frequency. Frequencies are defined as: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000).

MedDRA System organ class	**Frequency**	**Adverse drug reactions**
Infections and infestations	Common	Infection
	Uncommon	Pharyngitis
Blood and lymphatic system disorders	Uncommon	Eosinophilia
Endocrine disorders	Uncommon	Hypothyroidism
Metabolism and nutrition disorders	Common	Hyperkalaemia, dehydration
	Uncommon	Hypercholesterolaemia, hypertriglyceridaemia, hyponatraemia
Psychiatric disorders	Uncommon	Insomnia
Nervous system disorders	Common	Dizziness, syncope
	Uncommon	Hypoaesthesia, headache
Cardiac disorders	Common	Myocardial infarction
	Uncommon	Left ventricular failure, atrial fibrillation
Vascular disorders	Common	Hypotension
	Uncommon	Postural hypotension
Respiratory, thoracic and mediastinal disorders	Common	Cough
Gastrointestinal disorders	Common	Diarrhoea, nausea, constipation
	Uncommon	Flatulence, vomiting
Hepatobiliary disorders	Uncommon	Cholecystitis
Skin and subcutaneous tissue	Common	Pruritus

disorders	Uncommon	Increased sweating
Musculoskeletal and connective tissue disorders	Common	Muscle spasms, musculoskeletal pain
	Uncommon	Back pain, leg cramps
Renal and urinary disorders	Common	Renal impairment
General disorders and administration site conditions	Uncommon	Asthenia, malaise
Investigations	Common	Increased blood urea nitrogen (BUN)
	Uncommon	Increased blood creatinine, decreased epidermal growth factor receptor, increased blood glucose

Post-marketing side effects

MedDRA System organ class	**Adverse drug reactions**
Skin and subcutaneous tissue disorders	Angioedema, rash

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

No cases of human overdosage with INSPRA have been reported.

The most likely manifestation of human overdosage would be anticipated to be hypotension or hyperkalaemia.

INSPRA cannot be removed by haemodialysis.

INSPRA has been shown to bind extensively to charcoal.

If symptomatic hypotension should occur, supportive treatment should be initiated. If hyperkalaemia develops, standard treatment should be initiated.

5. PHARMACEUTICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 6.4 Cardiac medicines – Others

Eplerenone prevents the binding of aldosterone and has relative selectivity in binding to recombinant human mineralocorticoid receptors compared to its binding to recombinant human glucocorticoid, progesterone and androgen receptors.

Eplerenone produces sustained increases in plasma renin and serum aldosterone, consistent with inhibition of the negative regulatory feedback of aldosterone on renin secretion.

Eplerenone was studied in the eplerenone post-acute myocardial infarction heart failure efficacy and survival study (EPHESUS). EPHESUS was a large multi-centre, double-blind, placebo-controlled study in 6 632 patients with acute myocardial infarction (MI), left ventricular dysfunction (as measured by left ventricular ejection fraction [LVEF] < 40 %), and clinical signs of heart failure. Patients were randomised into EPHESUS 3 to 14 days after the index MI; the average time to enrolment was 7 days. Because of the increased CV risk associated with diabetes, patients with diabetes and LV dysfunction were eligible for randomisation in the absence of symptoms of HF; 10 % of the population met this criterion. Patients received eplerenone or placebo in addition to standard therapies at an initial dose 25 mg once daily and titrated to the target dose of 50 mg once daily after 4 weeks if serum potassium was < 5,0 mEq/L. During the study patients received standard care including aspirin (92 %), ACE inhibitors (90 %), ß-blockers (83 %), nitrates (72 %), loop diuretics (66 %), or HMG CoA reductase inhibitors (60 %).

In EPHESUS, eplerenone reduced the risk of death from any cause by 15 % (RR 0,85; 95 % CI, 0,75 – 0,96; p=0,008). The most common cause of death was cardiovascular death (12,3 %), 4,9 % being attributed to sudden death. The risk of cardiovascular (CV) death or CV hospitalisation (cardiovascular hospitalisations were those due to stroke, AMI, ventricular arrhythmias, and heart failure) was reduced by 13 % with eplerenone (RR 0,87; 95 % CI, 0,79 – 0,95; p=0,002). NYHA functional classification improved or remained stable for a significantly greater proportion of patients receiving eplerenone compared to placebo.

In dose-ranging studies of chronic heart failure (NYHA classification II-IV), the addition of eplerenone to standard therapy resulted in dose-dependent increases in aldosterone.

Similarly, in a cardiorenal substudy of EPHESUS, therapy with eplerenone led to a significant increase in aldosterone. These results confirm the blockade of the mineralocorticoid receptor in these populations.

No consistent effects of eplerenone on heart rate, QRS duration, or PR or QT interval were observed in 147 normal subjects evaluated for electrocardiographic changes during pharmacokinetic studies.

5.2 Pharmacokinetic properties

Eplerenone is cleared predominantly by cytochrome P450 (CYP) 3A4 metabolism, with an elimination half-life of 4 to 6 hours. Steady state is reached within 2 days. Absorption is not affected by food. Inhibitors of CYP3A4 (e.g. ketoconazole, saquinavir) increase blood levels of eplerenone.

Absorption

The absolute bioavailability of eplerenone is 69 % following administration of a 100 mg oral tablet. Maximum plasma concentrations are reached after about 2 hours. Mean peak plasma concentrations of eplerenone are reached approximately 1,5 hours following oral administration. Both peak plasma levels (C_{max}) and area under the curve (AUC) are dose proportional for doses of 10 to 100 mg and less than proportional at doses above 100 mg.

Distribution

The plasma protein binding of eplerenone is about 50 % and is primarily bound to alpha 1-acid glycoproteins. The apparent volume of distribution at steady state is estimated at 50 (± 7) L. Eplerenone does not preferentially bind to red blood cells.

Metabolism

Eplerenone metabolism is primarily mediated via CYP3A4. No active metabolites of eplerenone have been identified in human plasma.

Excretion

Less than 5 % of an eplerenone dose is recovered as unchanged medicine in the urine and faeces. Following a single oral dose of radiolabelled medicine, approximately 32 % of the dose was excreted in the faeces and approximately 67 % was excreted in the urine. The elimination half-life of eplerenone is approximately 3 to 5 hours. The apparent plasma clearance is approximately 10 L/hr.

Special populations

Age, gender, and race

The pharmacokinetics of eplerenone at a dose of 100 mg once daily have been investigated in the elderly (≥ 65 years), in males and females, and in blacks. The pharmacokinetics of eplerenone did not differ significantly between males and females. At steady state, elderly subjects had increases in C_{max} (22 %) and AUC (45 %) compared with younger subjects (18 to 45 years). At steady state, C_{max} was 19 % lower and AUC was 26 % lower in blacks (see section 4.2).

Renal insufficiency

The pharmacokinetics of eplerenone were evaluated in patients with varying degrees of renal insufficiency and in patients undergoing haemodialysis. Compared with control subjects, steady state AUC and C_{max} were increased by 38 % and 24 %, respectively, in patients with severe renal impairment and were decreased by 26 % and 3 %, respectively, in patients undergoing haemodialysis. No correlation was observed between plasma clearance of eplerenone and creatinine clearance. Eplerenone is not removed by haemodialysis (see section 4.2).

Hepatic insufficiency

The pharmacokinetics of eplerenone 400 mg have been investigated in patients with moderate (Child-Pugh Class B) hepatic impairment and compared with normal subjects. Steady state C_{max} and AUC of eplerenone were increased by 3,6 % and 42 %, respectively (see section 4.2).

Heart failure

The pharmacokinetics of eplerenone 50 mg were evaluated in patients with heart failure (NYHA classification II-IV). Compared with healthy subjects matched according to age, weight and gender, steady state AUC and C_{max} in heart failure patients were 38 % and 30 % higher, respectively. Consistent with these results, a population pharmacokinetic analysis of eplerenone based on a subset of patients from EPHESUS indicates that clearance of eplerenone in patients with heart failure was similar to that in healthy elderly subjects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium

Hydroxypropyl methylcellulose

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Opadry Yellow

Sodium laurilsulfate

Talc (asbestos-free)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C in a cool dry place.

6.5 Nature and contents of the container

Cardboard cartons of 30, 60 or 90 tablets containing aluminium foil/opaque PVC blister strips each of 10 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Upjohn South Africa (Pty) Ltd

85 Bute Lane

Sandton

2196

South Africa

Tel.: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

Manufacturers: Neolpharma Inc., Caguas, Puerto Rico; Pfizer Pharmaceuticals LLC, Vega Baja, Puerto Rico.

8. REGISTRATION NUMBERS

INSPRA 25: A39/6.4/0106

INSPRA 50: A39/6.4/0107

9. DATE OF FIRST AUTHORISATION

17 February 2006

10. DATE OF REVISION OF THE TEXT

01 March 2022

NAMIBIA: NS2

INSPRA 25: Reg. No.: 06/6.4/0283

INSPRA 50: Reg. No.: 06/6.4/0282