SCHEDULING STATUS: S4

PROPRIETARY NAMES (AND DOSAGE FORMS):

INSPRA® 25 (Tablets)

INSPRA® 50 (Tablets)

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.

PHARMACOLOGICAL CLASSIFICATION:

A 6.4 Cardiac medicines – Others

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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

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 and distribution:

Mean peak plasma concentrations of eplerenone are reached approximately 1,5 hours following oral administration. The absolute bioavailability of eplerenone is unknown. Both peak plasma levels (C_{max}) and area under the curve (AUC) are dose proportional for doses of 25 to 100 mg and less than proportional at doses above 100 mg.

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 ranged from 43 to 90 L. Eplerenone does not preferentially bind to red blood cells.

Metabolism and excretion:

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

Less than 5 % of an eplerenone dose is recovered as unchanged drug in the urine and faeces. Following a single oral dose of radiolabelled drug, 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 4 to 6 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 (refer DOSAGE AND DIRECTIONS FOR USE).

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 (refer DOSAGE AND DIRECTIONS FOR USE).

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 (refer DOSAGE AND DIRECTIONS FOR USE).

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.

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.

CONTRAINDICATIONS:

Hypersensitivity to eplerenone or any of the excipients.

INPSRA should not be administered to patients with clinically significant hyperkalaemia or with conditions associated with hyperkalaemia.

INSPRA should not be co-administered to patients receiving potassium-sparing diuretics or strong inhibitors of CYP3A4 such as ketoconazole and itraconazole (refer to INTERACTIONS).

WARNINGS:

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.

Impaired renal function:

Potassium levels should be monitored regularly in patients with impaired renal function, including 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. While the data from EPHESUS in patients with type 2 diabetes and microalbuminuria is limited, an increased occurrence of hyperkalaemia was observed in this small number of patients. Therefore, these patients should be treated with caution.

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 has not been evaluated.

Non-steroidal anti-inflammatory drugs (NSAIDs):

The administration of other potassium-sparing agents with NSAIDs has been shown to result in hyperkalaemia in patients with impaired renal function (refer to INTERACTIONS).

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 (refer to INTERACTIONS).

INTERACTIONS:

INSPRA should not be administered to patients receiving other potassium-sparing diuretics (refer CONTRAINDICATIONS).

Significant drug-drug pharmacokinetic interactions may occur when INSPRA is administered concomitantly with drugs that inhibit the CYP3A4 enzyme. Significant drug-drug pharmacokinetic interactions have been observed with ketoconazole, erythromycin, saquinavir, verapamil, and fluconazole (refer CONTRAINDICATIONS).

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

Drug interaction studies of INSPRA have not been conducted with NSAIDs. The administration of other potassium-sparing agents with NSAIDs has been shown to result in severe hyperkalaemia in patients with impaired renal function (refer WARNINGS).

Drug 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 (refer WARNINGS).

PREGNANCY AND LACTATION:

Pregnancy:

There are no adequate data on use of INSPRA in pregnant women. Studies in rats and rabbits showed

no teratogenic effects, although decreased body weight in maternal rabbits and increased rabbit foetal resorptions and post-implantation loss were observed at the highest administered dosage. The potential risk for humans is unknown. INSPRA should not be used during pregnancy.

Lactation:

It is unknown if INSPRA is excreted in human breast milk after oral administration. However, preclinical data show that eplerenone and/or metabolites are present in rat breast milk and that rat pups exposed by this route developed normally. INSPRA should not be used during lactation.

DOSAGE AND DIRECTIONS FOR USE:

INSPRA is usually administered in combination with standard therapies. The recommended dose of INSPRA is 50 mg once daily. Treatment should be initiated at 25 mg once daily and titrated to the target dose of 50 mg once daily preferably within 4 weeks as tolerated by the patient.

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

No dose adjustment is required in the elderly.

No initial dose adjustment is required in patients with mild renal impairment (refer WARNINGS).

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

INSPRA may be administered with or without food.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

INSPRA has been evaluated for safety in 3 307 patients treated for heart failure post-myocardial infarction (refer PHARMACOLOGICAL ACTION, Pharmacodynamic properties).

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

The discontinuation rate due to adverse events in these studies was 4,4 % for patients receiving eplerenone and for 4,3 % patients receiving placebo.

Adverse events reported below are those with suspected relationship to treatment and in excess of placebo, taken from EPHESUS. Adverse events are listed by body system and absolute frequency. Frequencies are defined as: Common > 1 %, ≤ 10 %; Uncommon > 0,1 %, ≤ 1 %.

Common (> 1 %, ≤ 10 %):

Autonomic nervous system: Hypotension.

Central and peripheral nervous system: Dizziness.

Gastrointestinal system: Diarrhoea, nausea.

Metabolic and nutritional: Hyperkalaemia.

Urinary system: Renal function abnormal.

Uncommon (> 0,1 %, ≤ 1 %):

Autonomic nervous system: Hypotension postural.

Body as a whole – General: Asthenia, back pain, malaise.

Cardiovascular, general: Cardiac failure left.

Central and peripheral nervous system: Cramps legs, headache.

Gastrointestinal system: Flatulence, vomiting.

Heart rate and rhythm: Fibrillation atrial.

Metabolic and nutritional: Dehydration, hypercholesterolaemia, hypertriglyceridaemia, hyponatraemia.

Myo endo pericardial and valve: Myocardial infarction.

Psychiatric: Insomnia.

Respiratory system: Pharyngitis.

Skin and appendages: Pruritus, sweating increased.

Urinary system: Blood Urea Nitrogen (BUN) increased, creatinine increase.

White cell and reticuloendothelial system: Eosinophilia.

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 may occur during treatment.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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.

IDENTIFICATION:

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 tablet, “NSR” over “50” on the other side of tablet.

PRESENTATION:

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

STORAGE INSTRUCTIONS:

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

STORE ALL MEDICINES OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS:

INSPRA 25: A39/6.4/0106

INSPRA 50: A39/6.4/0107

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Upjohn South Africa (Pty) Ltd

85 Bute Lane

Sandton

2196

South Africa

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

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

19 August 2005

NAMIBIA: NS2

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INSPRA 50 – Reg. No. 06/6.4/0282