1.3.1 Summary of product characteristics (SmPC)

1. Name of the medicinal product

Valsartil 80 mg Tablet

2. Qualitative and quantitative composition

Each tablet contains Valsartan USP 80.000 mg.

3. Pharmaceutical form

Tablet

4. Clinical particulars

4.1 Therapeutic indications

Valsartan is indicated:

For hypertension

To reduce hospitalizations in patients with congestive heart failure

To reduce death in patients who developed congestive heart failure after myocardial infarction

4.2 Posology and method of administration

Hypertension:
The usual dose of Valsartan is 80 to 160 mg once daily. The maximum dose is 320 mg daily. Maximum blood pressure reduction occurs within 4 weeks.

Heart failure:
The usual dose is 40 mg twice daily and may be increased to 80-160 mg twice daily.

Post-Myocardial Infarction:
The initial dose after myocardial infarction is 20 mg twice daily. The dose should be increased with a target of 160 mg daily if tolerated without side effects.

Administration of Valsartan with food decreases the absorption of Valsartan by about 40 %, so it should be taken on an empty stomach. No initial dosage adjustment is required for elderly patients with mild to moderate renal and hepatic insufficiency.

Pediatric use: Safety and effectiveness in pediatric patients have not been established.

Geriatric use: No overall difference in the efficacy or safety without some exception.

4.3 Contraindications

Valsartan is contraindicated in patients who are hypersensitive to any component of this product.

4.4 Special warnings and precautions for use

Impaired Hepatic Function: As the majority of Valsartan is eliminated in the bile, care should be exercised in patients with mild to moderate hepatic impairment including biliary obstructive disorder.

Impaired Renal Function: Dosage reduction or discontinuation may be required with patients having pre-existing renal impairment.

Heart Failure and Myocardial Infarction: Caution should be exercised when initiating therapy in patients with heart failure and post-myocardial infarction patients.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended

- Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors. Due to the lack of experience with concomitant use of valsartan and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

- Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels

If a medicinal product that affects potassium levels is considered necessary in combination with valsartan, monitoring of potassium plasma levels is advised.

Caution required with concomitant use

- Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day), and non-selective NSAIDs

When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

4.6 Fertility, pregnancy and lactation

Pregnancy: Valsartan should not be used in pregnancy, as in 2nd and 3rd trimester it can cause injury and even death to fetus. When pregnancy is detected, Valsartan should be stopped as soon as possible.

Nursing mothers: It is not known whether Valsartan is excreted in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

Valsartan is generally well tolerated and side effects are rare. The most common side effects include headache, dizziness, fatigue, abdominal pain, cough, diarrhea and nausea. Patient may also experience hyperkalemia, impotency, reduced renal function, allergic reactions, dyspnea, constipation, back pain, muscle cramps, rash, anxiety, insomnia and vertigo. Hypotension may also occur if patient have been taking diuretics along with Valsartan

4.9 Overdose

Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia, bradycardia could occur from parasympathetic (vagal) stimulation. If excessive hypotension occurs, the patient should be placed in the supine position and if necessary, has to be given an intravenous infusion of normal saline.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Valsartan inhibits the pressor effect of angiotensin II infusions. An oral dose of 80 mg inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. No information on the effect of larger doses is available.

Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin and consequent rise in angiotensin II plasma concentration in hypertensive patients. Minimal decreases in plasma aldosterone were observed after administration of valsartan; very little effect on serum potassium was observed.

In multiple-dose studies in hypertensive patients with stable renal insufficiency and patients with renovascular hypertension, valsartan had no clinically significant effects on glomerular filtration rate, filtration fraction, creatinine clearance, or renal plasma flow.

In multiple-dose studies in hypertensive patients, valsartan had no notable effects on total cholesterol, fasting triglycerides, fasting serum glucose, or uric acid.

Mechanism of Action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT2 receptor found in many tissues, but AT2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT1 receptor than for the AT2 receptor. The increased plasma levels of angiotensin II following AT1 receptor blockade with valsartan may stimulate the unblocked AT2 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT1 receptor about one 200th that of valsartan itself.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because valsartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of valsartan on blood pressure.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as

measured by AUC) to valsartan by about 40% and peak plasma concentration (Cmax) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution

The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94-97%), mainly serum albumin.

Biotransformation

Valsartan is not biotransformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Excretion

Valsartan shows multiexponential decay kinetics (t½α <1 h and t½ß about 9 h). Valsartan is primarily eliminated by biliary excretion in faeces (about 83% of dose) and renally in urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential.

In rats, maternally toxic doses (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring. These doses in rats (600 mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

In non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised plasma urea, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are

approximately 6 and 18 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). In marmosets at similar doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy which included raised urea and creatinine. Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

6. Pharmaceutical particulars

6.1 List of excipients

-Microcrystalline Cellulose (Avicel 102)
-Crospovidone
- Colloidal Silicon Dioxide (Aerosil 200)
- Magnesium Stearate
- Opadry II 85G58977 White
- Purified Water

6.2 Incompatibilities

No information available.

6.3 Shelf life

24 months from the date of manufacturing.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Alu-Alu blister is used for packaging of the tablets. A printed carton contains the Alu-Alu blister pack.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorization holder

Incepta Pharmaceuticals Ltd

Plant Address: Dewan Idris Road, Bara Rangamatia, Zirabo, Savar, Dhaka, Bangladesh
Head Office Address: 40, Shahid Tajuddin Ahmed Sarani; Tejgaon I/A, Dhaka-1208; Bangladesh

8. Marketing authorization number(s)

DAR No. 116-577-022

9. Date of first authorization/renewal of the authorization

Date of first authorization: 03-06-2007
Date of next renewal: 02-06-2022

10. Date of revision of the text

01/01/2019