1. NAME OF THE MEDICINAL PRODUCT
Vacubassel 80 (Valsartan Film-Coated Tablets 80 mg)
Vacubassel 160 (Valsartan Film-Coated Tablets 160 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Vacubassel 80: One film-coated tablet contains 80 mg of valsartan.
Vacubassel 160: One film-coated tablet contains 160 mg of valsartan.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet.

Vacubassel 80: Pink coloured, round, film coated tablet with beveled edge debossed with 'V 80' on one side of the tablet and breakline on the other side.

Vacubassel 160: Grey-Orange coloured, Oval shaped, film coated tablet beveled edge debossed 'V160'on one side of the tablet and breakline on the other side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Hypertension
Treatment of hypertension.

Heart failure
Treatment of heart failure (NYHA class II-IV) in patients receiving usual therapy (such as diuretics, digitalis) who are intolerant to ACE inhibitors.
Vacubassel improves morbidity in these patients, primarily via reduction in hospitalization for heart failure. Valsartan also slows the progression of heart failure, improves NYHA functional class, ejection fraction and signs and symptoms of heart failure and improves quality of life versus placebo (see section PHARMACOLOGICAL PROPERTIES).

Post-myocardial infarction
Vacubassel is indicated to improve survival following myocardial infarction in clinically stable patients with signs, symptoms or radiological evidence of left ventricular failure and/or with left ventricular systolic dysfunction (see section PHARMACOLOGICAL PROPERTIES).

4.2 Posology and method of administration
Dosage
Adult Population
Hypertension
The recommended dose of Valsartan is 80 mg or 160 mg film-coated tablet once daily, irrespective of race, age, or gender. The antihypertensive effect is substantially present within 2 weeks and maximal effects are seen after 4 weeks. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to 320 mg film-coated tablet, or a diuretic may be added. Valsartan may also be administered with other antihypertensive agents.

Heart failure
The recommended starting dose of Valsartan is 40 mg film-coated tablet twice daily. Up-titration to 80 mg and 160 mg twice daily should be done to the highest dose tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses. Evaluation of patients with heart failure should always include assessment of renal function.

Post-myocardial infarction
Therapy may be initiated as early as 12 hours after a myocardial infarction. After an initial dose of 20 mg twice daily, valsartan therapy should be titrated to 40 mg, 80 mg, and 160 mg film-coated tablet twice daily over the next few weeks. The starting dose is provided by the 40 mg divisible tablet (not all dosage presentation is available locally).

The target maximum dose is 160 mg twice daily. In general, it is recommended that patients achieve a dose level of 80 mg twice daily by two weeks after treatment initiation and that the target maximum dose be achieved by three months, based on the patient's tolerability to valsartan during titration. If symptomatic hypotension or renal dysfunction occurs, consideration should be given to a dosage reduction.

Valsartan may be used in patients treated with other post-myocardial infarction therapies, e.g. thrombolytics, acetylsalicylic acid, beta-blockers or statins.

Evaluation of post-myocardial infarction patients should always include assessment of renal function.

Note for all indications
No dosage adjustment is required for patients with renal impairment or for patients with hepatic insufficiency of non-biliary origin and without cholestasis.

Use in children and adolescents
The safety and efficacy of Vacubassel have not been established in children and adolescents (below the age of 18 years).

Method of administration
Mode of administration: For oral use.
Vacubassel may be taken independently of a meal and should be administered with water.

4.3 Contraindications
Known hypersensitivity to valsartan or to any of the excipients.
Pregnancy (see section PREGNANCY AND LACTATION).
Concomitant use of angiotensin receptor antagonists (ARBs) - including Valsartan - or of angiotensin- converting-enzyme inhibitors (ACEIs) with aliskiren in patients with Type 2 diabetes (see section INTERACTIONS, subsection dual blockade of the RAS).

4.4 Special warnings and precautions for use
Patients with sodium- and/or volume-depletion
In severely sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of therapy with Vacubassel. Sodium and/or volume depletion should be corrected before starting treatment with Vacubassel, for example by reducing the diuretic dose.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an i.v. infusion of normal saline. Treatment can be continued once blood pressure has been stabilized.

Patients with renal artery stenosis
Short-term administration of valsartan to twelve patients with renovascular hypertension secondary to unilateral renal artery stenosis did not induce any significant changes in renal hemodynamics, serum creatinine, or blood urea nitrogen (BUN). However, since other drugs that affect the renin-angiotensin- aldosterone system (RAAS) may increase blood urea and serum creatinine in patients with bilateral or unilateral renal artery stenosis, monitoring of both parameters is recommended as a safety measure.

Patients with impaired renal function
No dosage adjustment is required for patients with renal impairment. However, no data is available for severe cases (creatinine clearance < 10 mL/min.), and caution is therefore advised.

The use of ARBs - including valsartan - or of ACEIs with aliskiren should be avoided in patients with severe renal impairment (GFR < 30 mL/min) (see section INTERACTIONS, subsection dual blockade of the RAS).

Patients with hepatic impairment
No dosage adjustment is required for patients with hepatic insufficiency. Valsartan is mostly eliminated unchanged in the bile, and patients with biliary obstructive disorders showed lower valsartan clearance (see section PHARMACOLOGICAL PROPERTIES). Particular caution should be exercised when administering valsartan to patients with biliary obstructive disorders.

Patients with heart failure/post-myocardial infarction
Use of Vacubassel in patients with heart failure or post-myocardial infarction commonly results in some reduction in blood pressure, but discontinuation of Vacubassel therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed.

Caution should be observed when initiating therapy in patients with heart failure or post-myocardial infarction (see section DOSAGE AND ADMINISTRATION).

As a consequence of the inhibition of the RAAS, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the RAAS, treatment with ACE inhibitors or angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

In patients with heart failure, caution should be observed with the triple combination of an ACE inhibitor, a beta-blocker and valsartan (see section PHARMACOLOGICAL PROPERTIES).

Angioedema
Angioedema, including 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 valsartan, some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vacubassel should be immediately discontinued in patients who develop angioedema, and Vacubassel should not be re-administered.

Dual Blockade of the Renin-Angiotensin System (RAS)
Caution is required while co-administering ARBs, including Vacubassel, with other agents blocking the RAS such as ACEIs or aliskiren (see section INTERACTIONS, subsection dual blockade of the RAS).

4.5 Interaction with other medicinal products and other forms of interaction
Dual blockade of the Renin-Angiotensin- System (RAS) with ARBs, ACEIs, or aliskiren
The concomitant use of ARBs, including Vacubassel, with other agents acting on the RAS is associated with an increased incidence of hypotension, hyperkalemia, and changes in renal function compared to monotherapy. It is recommended to monitor blood pressure, renal function and electrolytes in patients on Vacubassel and other agents that affect the RAS (see section WARNINGS AND PRECAUTIONS).

The concomitant use of ARBs - including Vacubassel - or of ACEIs with aliskiren, should be avoided in patients with severe renal impairment (GFR < 30 mL/min) (see section WARNINGS AND PRECAUTIONS).

The concomitant use of ARBs - including Vacubassel - or ACEIs with aliskiren is contraindicated in patients with Type 2 diabetes (see section CONTRAINDICATIONS).

Potassium
Concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium or other drugs that may increase potassium levels (heparin, etc.) may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine. If co-medication is considered necessary, monitoring of serum potassium is advisable.

Non-Steroidal Anti-Inflammatory Agents (NSAIDs) including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)
When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur.
Furthermore, in patients who are elderly, volume-depleted (including those on diuretic therapy), or have compromised renal function, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying the treatment in patients on valsartan who are taking NSAIDs concomitantly.

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists, including Vacubassel. Therefore, careful monitoring of serum lithium levels is recommended during concomitant use. If a diuretic is also used, the risk of lithium toxicity may presumably be increased further with Vacubassel.

Transporters
The results from an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (e.g. rifampin, ciclosporin) or efflux transporter (e.g. ritonavir) may increase the systemic exposure to valsartan.

No drug interactions of clinical significance have been found. Compounds which have been studied in clinical trials include cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine and glibenclamide.

As valsartan is not metabolized to a significant extent, clinically relevant drug-drug interactions in the form of metabolic induction or inhibition of the cytochrome P450 system are not expected with valsartan. Although valsartan is highly bound to plasma proteins, *in vitro* studies have not shown any interaction at this level with a range of molecules which are also highly protein bound, such as diclofenac, furosemide, and warfarin.

4.6 Pregnancy and lactation
Pregnancy
Risk summary
As for any drug that also acts directly on the RAAS, Vacubassel must not be used during pregnancy (see section CONTRAINDICATIONS). Due to the mechanism of action of angiotensin II antagonists, a risk for the fetus cannot be excluded. *In utero* exposure to ACE inhibitors (a specific class of drugs acting on the RAAS) during the second and third trimesters has been reported to cause injury and death to the developing fetus. In addition, in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects. There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction, when pregnant women have inadvertently taken valsartan. If pregnancy is detected during therapy, Vacubassel should be discontinued as soon as possible

Clinical considerations

Disease-associated maternal and/or embryo/fetal risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death.

Fetal/Neonatal Risk

Oligohydramnios in pregnant women who use drugs affecting the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension and death.

In case of accidental exposure to ARB therapy, appropriate fetal monitoring should be considered.
Infants whose mothers have taken ARB therapy should be closely observed for hypotension.

Animal data

In embryofetal development studies in mice, rats and rabbits, fetotoxicity was observed in association with maternal toxicity in rats at valsartan doses of 600 mg/kg/day approximately 6 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient) and in rabbits at doses of 10 mg/kg/day approximately 0.6 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). There was no evidence of maternal toxicity or fetotoxicity in mice up to a dose level of 600 mg/kg/day approximately 9 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

Breast-feeding

Risk summary

It is not known whether valsartan is excreted in human milk. Since valsartan was excreted in the milk of lactating rats, it is not advisable to use valsartan in breast-feeding mothers.

Females and males of reproductive potential

As for any drug that also acts directly on the RAAS, Vacubassel should not be used in women planning to become pregnant. Healthcare professionals prescribing any agents acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy.

Infertility

There is no information on the effects of Vacubassel on human fertility. Studies in rats did not show any effects of valsartan on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive have been performed. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects

In controlled clinical studies in adult patients with hypertension, the overall incidence of adverse reactions (ADRs) was comparable with placebo and is consistent with the pharmacology of valsartan. The incidence of ADRs did not appear to be related to dose or treatment duration and also showed no association with gender, age or race.

The ADRs reported from clinical studies, post-marketing experience and laboratory findings are listed below according to system organ class.

Adverse reactions are ranked by frequency, the most frequent first, using the following convention: 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), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

For all the ADRs reported from post-marketing experience and laboratory findings, it is not possible to apply any ADR frequency and therefore they are mentioned with a "not known" frequency.

Hypertension

Table 1: Adverse drug reaction in hypertension

Blood and lymphatic system disorders	
Not known	Hemoglobin decreased, hematocrit decreased, neutropenia, thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	

Not known	Blood potassium increased
Ear and labyrinth system disorders	
Uncommon	Vertigo
Vascular disorders	
Not known	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Abdominal pain
Hepato-biliary disorders	
Not known	Liver function test abnormal including blood bilirubin increase
Skin and subcutaneous tissue disorders	
Not known	Angioedema, dermatitis bullous, rash, pruritus
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Renal and urinary disorders	
Not known	Renal failure and impairment, blood creatinine increased
General disorders and administration site conditions	
Uncommon	Fatigue

The following events have also been observed during clinical trials in hypertensive patients irrespective of their causal association with the study drug: Arthralgia, asthenia, back pain, diarrhoea, dizziness, headache, insomnia, libido decrease, nausea, oedema, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral infections.

Heart failure and/or post-myocardial infarction

The safety profile seen in controlled-clinical studies in patients with heart failure and/or post- myocardial infarction varies from the overall safety profile seen in hypertensive patients. This may relate to the patients underlying disease. ADRs that occurred in heart failure and/or post-myocardial infarction patients are listed below.

Table 2: Adverse drug reactions in heart failure and/or post-myocardial infarction

Blood and lymphatic system disorders	
Not known	Thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Uncommon	Hyperkalaemia[#]
Nervous system disorders	
Common	Dizziness, postural dizziness
Uncommon	Syncope, headache
Ear and labyrinth system disorders	
Uncommon	Vertigo
Cardiac disorders	
Uncommon	Cardiac failure
Vascular disorders	
Common	Hypotension, orthostatic hypotension
Not known	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Nausea, diarrhea
Hepato-biliary disorders	
Not known	Liver function test abnormal
Skin and subcutaneous tissue disorders	
Uncommon	Angioedema
Not known	Dermatitis bullous, rash, pruritus
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Renal and urinary disorders	
Common	Renal failure and impairment
Uncommon	Acute renal failure, blood creatinine increased
Not known	Blood Urea Nitrogen increased

General disorders and administration site conditions	
Uncommon	Asthenia, fatigue

#Blood potassium increased (frequency unknown) – reported in post market reporting

The following events have also been observed during clinical trials in patients with heart failure and/or post-myocardial infarction irrespective of their causal association with the study drug: Arthralgia, abdominal pain, back pain, insomnia, libido decrease, neutropenia, oedema, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral infections.

4.9 Overdose
Overdosage with Vacubassel may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. If the ingestion is recent, vomiting should be induced. Otherwise, the usual treatment would be i.v. infusion of normal saline solution.

Valsartan is unlikely to be removed by hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
The active hormone of the RAAS is angiotensin II, which is formed from angiotensin I through ACE. Angiotensin II binds to specific receptors located in the cell membranes of various tissues. It has a wide variety of physiological effects, including in particular both direct and indirect involvement in the regulation of blood pressure. As a potent vasoconstrictor, angiotensin II exerts a direct pressor response. In addition, it promotes sodium retention and stimulation of aldosterone secretion.

Valsartan is an orally active, potent and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT1 receptor blockade with valsartan may stimulate the unblocked AT2 receptor, which appears to counterbalance the effect of the AT1 receptor. Valsartan does not exhibit any partial agonist activity at the AT1 receptor and has much (about 20,000 fold) greater affinity for the AT1 receptor than for the AT2 receptor.

Valsartan does not inhibit ACE, also known as kininase II, which converts Ang I to Ang II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with cough. In clinical trials where valsartan was compared with an ACE inhibitor, the incidence of dry cough was significantly ($P < 0.05$) lower in patients treated with valsartan than in those treated with an ACE inhibitor (2.6% versus 7.9% respectively). In a clinical trial of patients with a history of dry cough during ACE inhibitor therapy, 19.5% of trial subjects receiving valsartan and 19.0% of those receiving a thiazide diuretic experienced cough compared to 68.5% of those treated with an ACE inhibitor ($P < 0.05$). Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

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%. When valsartan is given with food, the area under the plasma concentration curve (AUC) of valsartan is reduced by 48%, although from about 8 hours post dosing, plasma valsartan concentrations are similar for the fed and fasted group. 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
Steady state volume of distribution of valsartan after intravenous administration is about 17 liters, indicating that valsartan is not distributed into tissues extensively. Valsartan is highly bound to serum protein (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.

Elimination
Valsartan shows multiexponential decay kinetics ($t½\ \alpha < 1$ h and $t½\ ß$ about 9 h). Valsartan is primarily eliminated in feces (about 83% of dose) and 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.

The pharmacokinetics of valsartan are linear in the dose range tested. There is no change in the kinetics of valsartan on repeated administration, and little accumulation when dosed once daily. Plasma concentrations were observed to be similar in males and females.

The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to that observed in healthy volunteers. AUC and Cmax values of valsartan increase linearly and are almost proportional with increasing dose over the clinical dosing range (40 to 160 mg twice a day). The average accumulation factor is about 1.7. The apparent clearance of valsartan following oral administration is approximately 4.5 L/h. Age does not affect the apparent clearance in heart failure patients.

Special populations

Geriatric patients (aged 65 years or above)

A somewhat higher systemic exposure to valsartan was observed in some elderly subjects compared to young subjects; however, this has not been shown to have any clinical significance.

Impaired renal function

As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan. Dose adjustment is therefore not required in patients with renal impairment. No studies have been performed in patients undergoing dialysis. However, valsartan is highly bound to plasma protein and is unlikely to be removed by dialysis.

Hepatic impairment

About 70% of the absorbed dose is excreted in the bile mainly as unchanged compound. Valsartan does not undergo extensive biotransformation, and, as expected, systemic exposure to valsartan is not correlated with the degree of liver dysfunction. No dose adjustment for valsartan is therefore necessary in patients with hepatic insufficiency of non-biliary origin and without cholestasis. The AUC with valsartan has been observed to approximately double in patients with biliary cirrhosis or biliary obstruction (see section WARNINGS AND PRECAUTIONS).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Lactose Monohydrate
Microcrystalline cellulose
Crospovidone
Povidone
Colloidal anhydrous silica
Magnesium stearate

Film-coat:

Hypromellose
Polyethylene glycol
Titanium dioxide
Red iron oxide
Black iron oxide
Yellow iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Storage

Do not store above 30^{o}C.

6.5 Pack Size

Available in blister packs of 14’s or 28’s film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7. PRODUCT REGISTRATION HOLDER
Dr. Reddy`s Laboratories Malaysia Sdn. Bhd.
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