# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF DRUG PRODUCT

Vacutro (Sacubitril + Valsartan) Tablets 49mg + 51mg

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Sacubitril...49mg
Valsartan...51mg
(as sacubitril valsartan sodium salt complex)

## 3. PHARMACEUTICAL FORM

Cream colored, oblong shaped, biconvex film coated tablet, plain on both sides.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Vacutro (Sacubitril + Valsartan) is indicated in adult patients for treatment of symptomatic chronic heart failure (NYHA Class II-IV) with reduced ejection fraction.
Vacutro (Sacubitril + Valsartan) is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.

### 4.2 Posology and Method of Administration

The recommended starting dose of Vacutro (Sacubitril + Valsartan) is one tablet of 49mg + 51mg twice daily.
The dose of Vacutro (Sacubitril + Valsartan) should be doubled after 2 to 4 weeks to the target maintenance dose of one tablet of 97mg + 103mg twice daily, as tolerated by the patient.
If patients experience tolerability issues (systolic blood pressure ≤95mmHg, symptomatic hypotension, hyperkalemia, renal dysfunction), consideration should be given to adjustment of concomitant medications or to temporary down–titration or discontinuation of Vacutro (Sacubitril + Valsartan).

***Starting dose of Vacutro of 24mg + 26mg for some populations***
A starting dose of Vacutro (Sacubitril + Valsartan) of one tablet of 24mg + 26mg taken twice daily is recommended for patients not currently taking an ACE inhibitor or an ARB, or patients previously taking low doses of these agents.
A starting dose of Vacutro (Sacubitril + Valsartan) of one tablet of 24mg + 26mg taken twice daily should be considered for patients who have risk factors for hypotension, including patients ≥ 75 years old and patients with low systolic blood pressure (SBP ≥100 to 110 mmHg). The dose of Vacutro (Sacubitril + Valsartan) should be doubled every 2-4 weeks to the target dose of one tablet of Vacutro (Sacubitril + Valsartan) 97mg + 103 mg twice daily, as tolerated by the patient.

***Renal impairment***
No dose adjustment is required in patients with mild renal impairment. A starting dose of 24mg + 26mg twice daily should be considered in patients with moderate renal impairment (eGFR 30-60 ml/min/1.73 $m^2$). Vacutro (Sacubitril + Valsartan) should be used with caution in patients with severe renal impairment and a starting dose of 24mg + 26mg twice daily is recommended. There is no experience in patients with end-stage renal disease (ESRD) and use of Vacutro (Sacubitril + Valsartan) is not recommended.

***Hepatic impairment***
No dose adjustment is required when administering Vacutro (Sacubitril + Valsartan) to patients with mild hepatic impairment (Child-Pugh A classification). Vacutro (Sacubitril + Valsartan) should be used with caution in patients with moderate hepatic impairment (Child-Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range and the recommended starting dose is 24mg + 26mg twice daily. Vacutro (Sacubitril + Valsartan) is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification).

***Pediatric population***
The safety and efficacy of Vacutro (Sacubitril + Valsartan) in children and adolescents aged below 18 years have not been established.

**4.3 Contraindications**

Vacutro (Sacubitril + Valsartan) is contraindicated in patients with:

- Hypersensitivity to the active substance, sacubitril, valsartan or to any of the excipient of the product.
- Concomitant use with ACE inhibitors. Sacubitril + Valsartan must not be administered until 36 hours after discontinuing ACE inhibitor therapy.
- Known history of angioedema related to previous ACE inhibitor or ARB therapy.
- Hereditary or idiopathic angioedema.
- Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 $m^2$).
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Second and third trimester of pregnancy.

**4.4 Special warnings and special precautions for use**

*Fetal Toxicity*
Sacubitril + valsartan can cause fetal harm when administered to a pregnant woman. When pregnancy is detected, consider alternative drug treatment and discontinue sacubitril + valsartan. However, if there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system, and if the drug is considered lifesaving for the mother, advise a pregnant woman of the potential risk to the fetus.
*Angioedema*

Sacubitril + valsartan may cause angioedema. If angioedema occurs, discontinue sacubitril + valsartan immediately, provide appropriate therapy, and monitor for airway compromise. Sacubitril + valsartan should not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy.

*Hypotension*
Sacubitril + valsartan lowers blood pressure and may cause symptomatic hypotension. Patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), are at greater risk. Correct volume or salt depletion prior to administration of sacubitril + valsartan or start at a lower dose. If hypotension occurs, consider dose adjustment of diuretics, concomitant antihypertensive drugs and treatment of other causes of hypotension (e.g., hypovolemia). If hypotension persists despite such measures, reduce the dosage or temporarily discontinue sacubitril + valsartan.

*Impaired Renal Function*
As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), decreases in renal function may be anticipated in susceptible individuals treated with sacubitril + valsartan. Closely monitor serum creatinine and down-titrate or interrupt sacubitril + valsartan in patients who develop a clinically significant decrease in renal function. As with all drugs that affect the RAAS, sacubitril + valsartan may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. In patients with renal artery stenosis, monitor renal function.

*Hyperkalemia*
Through its actions on the RAAS, hyperkalemia may occur with Sacubitril + Valsartan. Monitor serum potassium periodically and treat appropriately, especially in patients with risk factors for hyperkalemia such as severe renal impairment, diabetes, hypoaldosteronism or a high potassium diet. Dosage reduction or interruption of sacubitril + valsartan may be required.

*Patients with NYHA functional classification IV*
Caution should be exercised when initiating sacubitril + valsartan in patients with NYHA functional classification IV due to limited clinical experience in this population.

*B-type natriuretic peptide (BNP)*
BNP is not a suitable biomarker of heart failure in patients treated with sacubitril + valsartan because it is a neprilysin substrate.

*Patients with hepatic impairment*
There is limited clinical experience in patients with moderate hepatic impairment (Child-Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Caution is therefore recommended when using it in these patients.

**4.5 Interaction with other medicaments**

*Angiotensin Receptor Blockers*
Sacubitril + valsartan should not be co-administered with another ARB containing product.

*OATP1B1 and OATP1B3 substrates, e.g. statins*
Sacubitril inhibits OATP1B1 and OATP1B3 transporters. Therefore, it may increase the systemic exposure of OATP1B1 and OATP1B3 substrates such as statins. Caution should be exercised when co-administering sacubitril + valsartan with statins.

*PDE5 inhibitors including sildenafil*
Addition of a single dose of sildenafil to sacubitril + valsartan at steady state in patients with hypertension was associated with a significantly greater blood pressure reduction compared to administration of sacubitril + valsartan alone. Therefore, caution should be exercised when sildenafil or another PDE5 inhibitor is initiated in patients treated with sacubitril + valsartan.

*Potassium*
Concomitant use of potassium-sparing diuretics (triamterene, amiloride), mineralocorticoid antagonists (e.g. spironolactone, eplerenone), potassium supplements and salt substitutes containing potassium or other agents (such as heparin) may lead to increases in serum potassium, and to increases in serum creatinine. Monitoring of serum potassium is recommended if sacubitril + valsartan is co-administered with these agents.

*Non-steroidal anti-inflammatory agents (NSAIDs), including selective cyclooxygenase-2 (COX-2) inhibitors*
In elderly patients, volume-depleted patients (including those on diuretic therapy), or patients with compromised renal function, concomitant use of sacubitril + valsartan and NSAIDs may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying treatment in patients on sacubitril + 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. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased further.

*OATP and MRP2 transporters*
The active metabolite of sacubitril (LBQ657) and valsartan are OATP1B1, OATP1B3, OAT1 and OAT3 substrates; valsartan is also a MRP2 substrate. Therefore, co-administration of sacubitril + valsartan with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure of LBQ657 or valsartan.
Appropriate care should be exercised when initiating or ending concomitant treatment with such medicinal products.

*Metformin*
Co-administration of Sacubitril + Valsartan with metformin reduced both $C_{max}$ and AUC of metformin by 23%. Therefore, when initiating therapy with sacubitril + valsartan in patients receiving metformin, the clinical status of the patient should be evaluated.

**4.6 Pregnancy and Lactation**

It is not known whether sacubitril + valsartan is excreted in human milk. Because of the potential risk for adverse reactions in breast-fed newborns/infants, it is not recommended during breast-feeding. A decision should be made whether to abstain from breast-feeding or to discontinue sacubitril + valsartan while breast-feeding, taking into account the importance of sacubitril + valsartan to the mother.

**4.7 Effects on ability to drive and use machine**

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or fatigue may occur.

**4.8 Undesirable effects**

*Very Common*
Hyperkalemia, hypotension and renal impairment.

*Common*
Anemia, hypokalemia, hypoglycemia, dizziness, headache, syncope, vertigo, orthostatic hypotension, cough, diarrhea, nausea, gastritis, renal failure (renal failure, acute renal failure), fatigue and asthenia.

*Uncommon*
Hypersensitivity, dizziness postural, pruritus, rash and angioedema.

**Overdosage**

In healthy volunteers, a single dose of 583mg sacubitril + 617mg valsartan, and multiple doses of 437mg sacubitril + 463mg valsartan (14 days) have been studied and were well tolerated.
Hypotension is the most likely result of overdosage due to the blood pressure lowering effects of Vacutro (Sacubitril + Valsartan). Symptomatic treatment should be provided. Vacutro (Sacubitril + Valsartan) is unlikely to be removed by hemodialysis because of high protein binding.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

**Mechanism of Action**

Sacubitril + valsartan inhibits neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril and blocks the angiotensin II type-1 (AT1) receptor via valsartan. The cardiovascular and renal effects of sacubitril + valsartan in heart failure patients are attributed to the increased levels of peptides that are degraded by neprilysin, such as natriuretic peptides, by LBQ657 and the simultaneous inhibition of the effects of angiotensin II by valsartan. NPs exert their effects by activating membrane bound guanylyl cyclase coupled receptors, resulting in increased concentrations of the second messenger cyclic guanosine monophosphate (cGMP), which could result in vasodilation, natriuresis and diuresis, increased glomerular filtration rate and renal blood flow, inhibition of renin and aldosterone release, reduction of sympathetic activity and antihypertrophic and antifibrotic effects. Valsartan inhibits the effects of angiotensin II by selectively blocking the AT1 receptor, and also inhibits angiotensin II-dependent aldosterone release. This prevents sustained activation of the renin-angiotensin-aldosterone system that would result in vasoconstriction, renal sodium and fluid retention, activation of cellular growth and proliferation and subsequent maladaptive cardiovascular remodeling.

### 5.2 Pharmacokinetic properties

**Absorption**

Following oral administration, this medicinal product dissociates into sacubitril and valsartan. Sacubitril is further metabolized to LBQ657. The peak plasma concentrations of sacubitril, LBQ657, and valsartan are reached in 2 hours, 1 hour, and 2 hours respectively. The oral absolute bioavailability of sacubitril and valsartan is estimated to be more than 60% and 23%, respectively.

Following twice-daily dosing of sacubitril + valsartan, steady state levels of sacubitril, LBQ657, and valsartan are reached in 3 days. At steady state, sacubitril and valsartan do not accumulate significantly, whereas LBQ657 accumulates by 1.6-fold. Administration with food has no clinically significant effect on the systemic exposures of sacubitril, LBQ657, or valsartan. Sacubitril + valsartan can be administered with or without food.

**Distribution**

Sacubitril, LBQ657 and valsartan are highly bound to plasma proteins (94% to 97%). Based on the comparison of plasma and CSF exposures, LBQ657 crosses the blood brain barrier to a limited extent (0.28%). The average apparent volumes of distribution of valsartan and sacubitril are 75L and 103L, respectively.

**Metabolism**

Sacubitril is readily converted to LBQ657 by esterases; LBQ657 is not further metabolized to a significant extent. Valsartan is minimally metabolized; only about 20% of the dose is recovered

as metabolites. A hydroxyl metabolite has been identified in plasma at low concentrations (<10%).

**Elimination**
Following oral administration, 52% to 68% of sacubitril (primarily as LBQ657) and ~13% of valsartan and its metabolites are excreted in urine; 37% to 48% of sacubitril (primarily as LBQ657), and 86% of valsartan and its metabolites are excreted in feces. Sacubitril, LBQ657, and valsartan are eliminated from plasma with a mean elimination half-life ($T_{1/2}$) of approximately 1.4 hours, 11.5 hours, and 9.9 hours respectively.

**Special Populations**
*Elderly patients*
LBQ657 and valsartan exposure are increased in subjects over 65 years of age by 42% and 30% respectively, compared to younger subjects.

*Impaired renal function*
The exposure of LBQ657 in patients with moderate (30 ml/min/1.73 $m^2$ ≤ eGFR <60 ml/min/1.73 $m^2$) and severe renal impairment (15 ml/min/1.73 $m^2$ ≤ eGFR <30 ml/min/1.73 $m^2$) was 1.4-fold and 2.2-fold higher compared to patients with mild renal impairment (60 ml/min/1.73 $m^2$ ≤ eGFR <90 ml/min/1.73 $m^2$). The exposure of valsartan was similar in patients with moderate and severe renal impairment compared to patients with mild renal impairment.

*Impaired hepatic function*
In patients with mild to moderate hepatic impairment, the exposures of sacubitril increased by 1.5- and 3.4- fold, LBQ657 increased by 1.5- and 1.9-fold, and valsartan increased by 1.2-fold and 2.1-fold, respectively, compared to healthy subjects. However, in patients with mild to moderate hepatic impairment, the exposures of free concentrations of LBQ657 increased by 1.47- and 3.08-fold, respectively, and the exposures of free concentrations of valsartan increased by 1.09-fold and 2.20-fold, respectively, compared to healthy subjects. Sacubitril + valsartan has not been studied in patients with severe hepatic impairment.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of Excipients

Avicel PH-101 (Microcrystalline Cellulose), Low substituted hydroxypropyl cellulose (L-HPC), Crospovidone, Purified Talc, Aerosil 200 (Colloidal Anhydrous Silica), Magnesium Stearate and Opadry Yellow 03F620055.

### 6.2 Incompatibilities

None

### 6.3 Shelf-life

2 Years
The expiration date refers to the product correctly stored in the required conditions.

### 6.4 Special precautions for storage

Do not store above 30°C
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

### 6.5 Nature and contents of container

Vacutro (Sacubitril + Valsartan) Tablets 49mg + 51mg are available in Alu-Alu blister packs of 2 x 7's tablets in a unit carton along with a package insert.

### 6.6 Instructions for use/handling

- Keep out of reach of children.
- To be sold on prescription of a registered medical practitioner only.

## 7. MARKETING AUTHORISATION HOLDER

Getz Pharma (Private) Limited
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## 8. PRODUCT REGISTRATION NUMBER

006196-EX

## 9. DATE OF PRODUCT REGISTRATION ISSUED

March 15, 2017