SACUVAL®

SACUBITRIL / VALSARTAN
50, 100 & 200 mg

Ceux QUI VALENT, POUR LE coeur

PHILADELPHIA PHARMA
Health Priority

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINE

SACUVAL 50 mg tablet, film-coated tablets, pack of 30.

SACUVAL 100 mg tablet, film-coated tablets, pack of 60.

SACUVAL 200 mg tablet, film-coated tablets, pack of 60.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SACUVAL 24 mg / 26 mg or 50 mg, film-coated tablets

Each film-coated tablet contains 24.3 mg of sacubitril and 25.7 mg of valsartan (in the form of sacubitril valsartan sodium complex).
SACUVAL 49 mg / 51 mg or 100 mg, film-coated tablets

Each film-coated tablet contains 48.6 mg of sacubitril and 51.4 mg of valsartan (in the form of sacubitril valsartan sodium complex).
SACUVAL 97 mg / 103 mg or 200 mg, film-coated tablets

Each film-coated tablet contains 97.2 mg of sacubitril and 102.8 mg of valsartan (in the form of sacubitril valsartan sodium complex).

For a full list of excipients, (see section 6.1).

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL DATA

4.1. Therapeutic indications

SACUVAL is indicated to reduce the risk of cardiovascular mortality and morbidity in adult patients with systolic heart failure (NYHA class II-IV, LVEF ≤ 40%). SACUVAL is administered in appropriate combination with other heart failure treatments (e.g., beta-blockers, diuretics, and mineralocorticoid receptor antagonists) instead of an ACE inhibitor or an ARB.

4.2. Dosage and administration

Dosage :

The recommended initial dose of SACUVAL is one tablet of 49 mg/51 mg twice a day, except in the situations described below. The dose of SACUVAL should be doubled every 2 to 4 weeks until reaching the target dose of 97 mg/103 mg twice a day, based on the patient's tolerance. (See section 5.1).
In case of tolerance issues (systolic blood pressure [SBP] ≤ 95 mmHg, symptomatic hypotension, hyperkalemia, impaired kidney function), dosage adjustment of concomitant treatments, temporary dose reduction, or discontinuation of SACUVAL is recommended. (See section 4.4).
In the PARADIGM-HF study, SACUVAL was administered as a replacement for an ACE inhibitor or other ARBs and in combination with other heart failure therapies (see section 5.1). Due to limited experience in patients not currently treated with an ACE inhibitor or an ARB, or those taking these medications at a low dose, an initial dose of 24 mg/26 mg twice a day of SACUVAL and a slow dose escalation (doubling the dosage every 2-4 weeks) are recommended in these patients (see section 5.1: "Titration").

The treatment should not be initiated in patients with serum potassium levels >5.4 mmol/L or SBP <100 mmHg (See section 4.4). An initial dose of 24 mg/26 mg twice a day should be considered in patients with SBP between 100 and 110 mmHg.
SACUVAL should not be administered concomitantly with an ACE inhibitor or an ARB. Due to the potential risk of angioedema when administered concurrently with an ACE inhibitor, SACUVAL should be initiated at least 36 hours after discontinuing ACE inhibitor treatment (See sections 4.3, 4.4, and 4.5).
The valsartan contained in SACUVAL has better bioequivalence than valsartan contained in other marketed tablet formulations (See section 5.2).
In case of missing a dose of SACUVAL, the patient should take the next dose at the usual time.

Special populations :

Elderly patients :

The dosage should be adjusted based on the elderly patient's renal function.

Renal insufficiency :

No dosage adjustment is necessary for patients with mild renal impairment (glomerular filtration rate [GFR] of 60-90 ml/min/1.73 m^2).

An initial dose of 24 mg/26 mg twice a day should be considered for patients with moderate renal impairment (GFR of 30-60 ml/min/1.73 m^2). Clinical experience is very limited in patients with severe renal impairment (GFR < 30 ml/min/1.73 m^2), so SACUVAL should be administered with caution, and an initial dose of 24 mg/26 mg twice a day is recommended.

There is no experience in patients with end-stage renal disease, and the administration of SACUVAL is not recommended.

Hepatic insufficiency:

No dosage adjustment is necessary for patients with mild hepatic impairment (Child-Pugh class A). Due to limited experience in patients with moderate hepatic impairment (Child-Pugh class B) or with AST/ALT values twice the upper limit of normal, SACUVAL should be used with caution in these patients, and the recommended initial dose is 24 mg/26 mg twice a day. **(See sections 4.4 and 5.2).**

SACUVAL is contraindicated in patients with severe hepatic impairment, biliary cirrhosis, or cholestasis (Child-Pugh class C).

Pediatric population:

The safety and efficacy of SACUVAL in children and adolescents under 18 years of age have not yet been established. No data are available.

Mode of administration :

Oral route.

SACUVAL can be administered during or outside of meals. The tablets should be swallowed with a glass of water.

4.3. Contraindications

- Hypersensitivity to the active substances or any of the excipients mentioned in **section 6.1.**
- Concomitant use of ACE inhibitors **(sections 4.4 and 4.5).**
- SACUVAL should only be administered 36 hours after discontinuing an ACE inhibitor.
- History of angioedema related to previous treatment with ACE inhibitors or ARBs **(see section 4.4).**
- Hereditary or idiopathic angioedema **(see section 4.4).**
- Concomitant use of medicines containing aliskiren in patients with diabetes or renal impairment (GFR < 60 ml/min/1.73 m^2) **(see sections 4.4 and 4.5).**
- Severe hepatic impairment, biliary cirrhosis, or cholestasis **(see section 4.2).**
- Second and third trimesters of pregnancy **(see section 4.6).**

4.4. Special warnings and precautions for use.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS):

- The combination of SACUVAL with an ACE inhibitor is contraindicated due to an increased risk of angioedema **(see section 4.3).** SACUVAL should only be initiated 36 hours after the last dose of an ACE inhibitor. If switching from SACUVAL to an ACE inhibitor, the ACE inhibitor should be initiated 36 hours after the last dose of SACUVAL **(see sections 4.2, 4.3, and 4.5).**
- The combination of SACUVAL with direct renin inhibitors, such as aliskiren, is not recommended **(see section 4.5).** The combination of SACUVAL with products containing aliskiren is contraindicated in patients with diabetes or renal impairment (GFR < 60 ml/min/1.73 m^2) **(see sections 4.3 and 4.5)**
- SACUVAL contains valsartan and should not be administered with a product containing another ARB **(see sections 4.2 and 4.5).**

Hypotension :

Le The treatment should not be initiated unless the systolic blood pressure (SBP) is ≥100 mmHg. Patients with SBP <100 mmHg have not been studied **(see section 5.1)**. Cases of symptomatic hypotension have been reported in patients treated with SACUVAL during clinical trials **(see section 4.8)**, especially in patients ≥65 years of age, those with kidney disease, and those with low SBP (<112 mmHg). Blood pressure should be routinely monitored when initiating or adjusting the dose of SACUVAL. In case of hypotension, a dose reduction or temporary discontinuation of SACUVAL is recommended **(see section 4.2).**

Adjustment of the dosage of diuretics, concurrent antihypertensive treatments, and treatment of other causes of hypotension (e.g., hypovolemia) should be considered. Symptomatic hypotension is more likely to occur in cases of hypovolemia, such as following diuretic treatment, a low-sodium diet, diarrhea, or vomiting. Sodium and/or volume depletion should be corrected before initiating SACUVAL treatment, although these measures should be carefully evaluated considering the risk of volume overload.

Renal insufficiency :

The renal function of patients with heart failure should always be evaluated. Patients with mild and moderate renal insufficiency are at increased risk of developing hypotension **(see section 4.2).** Clinical experience is limited in patients with severe renal insufficiency (GFR < 30 ml/min/1.73 m^2), and they may be more susceptible to the risk of hypotension **(see section 4.2).**
There is no experience in patients with end-stage renal disease, and the administration of SACUVAL is not recommended.

Degradation of renal function:

The administration of SACUVAL may be associated with a deterioration of renal function. This risk may be increased by dehydration or concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) **(see section 4.5).** A dose reduction should be considered in patients who develop a clinically significant decrease in renal function.

Hyperkalemia:

The treatment should not be initiated if serum potassium is >5.4 mmol/L. The administration of SACUVAL may be associated with an increased risk of hyperkalemia, although hypokalemia may also occur **(see section 4.8)**. Serum potassium levels should be monitored, especially in patients with risk factors such as renal impairment, diabetes, hypoaldosteronism, or those on a high-potassium diet or taking mineralocorticoid receptor antagonists **(see section 4.2)**. In case of clinically significant hyperkalemia, adjustment of concomitant treatments, dose reduction, or discontinuation is recommended. SACUVAL should be considered for discontinuation if serum potassium levels are >5.4 mmol/L

Angioedema:

Cases of angioedema have occurred in patients treated with SACUVAL. In case of angioedema, SACUVAL treatment should be immediately stopped. Appropriate treatment and monitoring should be implemented until signs and symptoms completely and durably disappear. SACUVAL should not be re-administered. In confirmed cases of angioedema where swelling was limited to the face and lips, it generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema can be fatal. In cases involving the tongue, glottis, or larynx, potentially leading to airway obstruction, appropriate treatment, such as an injection of 1 mg/ml adrenaline solution (0.3 ml to 0.5 ml), and/or measures to clear the airway should be administered rapidly. The administration of SACUVAL in patients with a known history of angioedema has not been studied. As these patients may be at higher risk of angioedema, SACUVAL should be administered with caution. SACUVAL is contraindicated in patients with a history of angioedema related to previous treatment with ACE inhibitors or ARBs or in those with hereditary or idiopathic angioedema **(see section 4.3)**.

Black patients are at increased risk of developing angioedema **(see section 4.8).**

Renal artery stenosis :

SACUVAL may increase uremia and creatinine levels in patients with unilateral or bilateral renal artery stenosis. Particular caution is advised in cases of renal artery stenosis, and renal function should be monitored.

Dyspnea of NYHA functional class IV:

Due to limited clinical experience in patients with NYHA functional class IV, the initiation of SACUVAL treatment should be done cautiously in these patients.

B-type natriuretic peptide (BNP) :

BNP is not an appropriate biomarker in heart failure patients treated with SACUVAL because it is a substrate of neprilysin **(see section 5.1).**

Hepatic insufficiency:

Clinical experience is limited in patients with moderate hepatic impairment (Child-Pugh class B) or with AST/ALT values twice the upper limit of normal. In these patients, exposure may be increased, and safety has not been established. Therefore, caution is recommended when administering to these patients **(see sections 4.2 and 5.2)**. SACUVAL is contraindicated in patients with severe hepatic impairment, biliary cirrhosis, or cholestasis (Child-Pugh class C) **(see section 4.3)**.

4.5. Interactions with other medicinal products and other forms of interaction

Interactions leading to contraindication:

ACE inhibitors (IECs):

The concomitant use of SACUVAL with ACE inhibitors is contraindicated because simultaneous inhibition of neprilysin and angiotensin-converting enzyme can increase the risk of angioedema.

Treatment with SACUVAL should only be initiated 36 hours after the last dose of an ACE inhibitor. Treatment with an ACE inhibitor should only be initiated 36 hours after the last dose of SACUVAL **(see sections 4.2 and 4.3).**

Aliskiren

The concomitant use of SACUVAL with medicines containing aliskiren is contraindicated in patients with diabetes or renal impairment (GFR < 60 ml/min/1.73 m^2) **(see section 4.3)**. The combination of SACUVAL with direct renin inhibitors such as aliskiren is not recommended **(see section 4.4)**. The combination of SACUVAL with aliskiren is potentially associated with a higher frequency of adverse events such as hypotension, hyperkalemia, and impairment of renal function (including acute renal failure) **(see sections 4.3 and 4.4).**

Interactions en raison desquelles l'utilisation concomitante est déconseillée :

VALSARTAN

SACUVAL contains valsartan and should not be administered with another angiotensin II receptor antagonist (ARB) **(see section 4.4).**

Interactions requiring precautions :

OATP1B1 and OATP1B3 Substrates, such as statins:

In vitro data indicate that sacubitril has an inhibitory effect on OATP1B1 and OATP1B3 transporters. Therefore, SACUVAL may increase the systemic exposure to OATP1B1 and OATP1B3 substrates, such as statins. Concomitant administration of SACUVAL increases the Cmax of atorvastatin and its metabolites up to 2 times and the AUC up to 1.3 times. Particular caution is advised when administering SACUVAL with statins. No clinically significant drug interactions have been observed with concomitant administration of SACUVAL and simvastatin.

Phosphodiesterase type 5 (PDE5) inhibitors, including sildenafil:

At steady state, the addition of a single dose of sildenafil to SACUVAL treatment in hypertensive patients was associated with a significantly greater decrease in blood pressure than that observed with SACUVAL alone. Therefore, particular caution is required when administering sildenafil or other PDE5 inhibitors to patients treated with SACUVAL.

Potassium

Concomitant use of antikaliuretic diuretics (triamterene, amiloride), mineralocorticoid receptor antagonists (e.g., spironolactone, eplerenone), potassium supplements, potassium-containing salt substitutes, or other products (such as heparin) may lead to an increase in potassium levels and an increase in creatinine levels. When SACUVAL is used concomitantly with these medications, monitoring of potassium levels is recommended **(see section 4.4).**

Nonsteroidal anti-inflammatory drugs (NSAIDs), including selective COX-2 inhibitors:

In elderly patients, patients with volume depletion (including those on diuretic therapy), or patients with impaired renal function, concomitant use of SACUVAL and NSAIDs may result in an increased risk of deterioration of renal function. Therefore, renal function should be monitored when initiating or modifying treatment in patients treated with SACUVAL who are taking NSAIDs concurrently **(see section 4.4).**

Lithium

Reversible increases in lithium levels and its toxicity have been observed with concurrent administration of lithium with ACE inhibitors or angiotensin II receptor antagonists. The risk of interaction between SACUVAL and lithium has not been studied. Therefore, this combination is not recommended. If such combination is necessary, strict monitoring of lithium levels is recommended. If a diuretic is also administered, the risk of lithium toxicity may be even greater.

Furosemide

Concomitant administration of SACUVAL and furosemide had no effect on the pharmacokinetics of SACUVAL but decreased the Cmax and AUC of furosemide by 50% and 28%, respectively. Although the urinary volume was not significantly altered, urinary sodium excretion was decreased within 4 and 24 hours following their concomitant administration. The average daily dose of furosemide was not modified compared to the initial dose until the end of the PARADIGM-HF study in patients treated with SACUVAL.

Nitrates, such as nitroglycerin:

There was no drug interaction between SACUVAL and intravenously administered nitroglycerin concerning blood pressure reduction. Concurrent administration of nitroglycerin and SACUVAL was associated with a difference in heart rate of 5 bpm compared to nitroglycerin alone. A similar effect on heart rate may occur when SACUVAL is administered concomitantly with nitrates administered sublingually, orally, or transdermally. In general, dose adjustment is not necessary.

OATP and MRP2 transporters

The active metabolite of sacubitril (LBQ657) and valsartan are substrates of OATP1B1, OATP1B3, OAT1, and OAT3; valsartan is also a substrate of MRP2. Therefore, concurrent administration of SACUVAL with inhibitors of OATP1B1, OATP1B3, or OAT3 (such as rifampicin or cyclosporine), OAT1 (such as tenofovir, cidofovir), or MRP2 (such as ritonavir) may increase the systemic exposure of LBQ657 or valsartan. Appropriate monitoring should be done when initiating or discontinuing treatment with such medications.

Metformin:

Concurrent administration of SACUVAL and metformin decreased the Cmax and AUC of metformin by 23%. The clinical significance of these results is not known. Therefore, the patient's clinical condition should be assessed when initiating SACUVAL treatment in patients receiving metformin.

Non-significant interaction :

No clinically significant drug interactions have been observed with concurrent administration of SACUVAL and digoxin, warfarin, hydrochlorothiazide, amlodipine, omeprazole, carvedilol, or a combination of levonorgestrel/ethinylestradiol.

Interactions with CYP 450 :

In vitro studies of metabolism indicate that the potential risk of drug interaction between drugs involving CYP 450 and SACUVAL is low, as the metabolism of SACUVAL by CYP 450 enzymes is limited. SACUVAL does not have an inducing or inhibiting effect on CYP 450 enzymes.

4.6. Fertility, pregnancy, and lactation

Pregnancy :

The use of SACUVAL is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy **(see section 4.3)**.

Valsartan

Epidemiological data regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy are inconclusive; however, a slight increase in risk cannot be excluded. While there are no controlled epidemiological data on the risk with ARBs, similar risks may exist with this class of drugs. Unless treatment with ARBs is considered essential, pregnant women should be prescribed alternative antihypertensive treatments with established safety profiles for use in pregnant women. When pregnancy is confirmed, ARB treatment should be discontinued immediately, and if needed, alternative treatment should be initiated. Exposure to ARBs during the second and third trimesters of pregnancy can lead to fetal toxicity in humans (decreased renal function, oligohydramnios, delayed cranial ossification) and neonatal toxicity (renal failure, hypotension, hyperkalemia). If exposure to ARBs occurs from the second trimester of pregnancy, monitoring of renal function and cranial ultrasound is recommended. Infants born to women who have taken ARBs should be closely observed for hypotension **(see section 4.3)**.

Sacubitril

There are no data regarding the administration of sacubitril in pregnant women. Animal studies have shown reproductive toxicity **(see section 5.3)**.

SACUVAL

There are no data regarding the administration of SACUVAL in pregnant women. Animal studies with SACUVAL have shown reproductive toxicity **(see section 5.3)**.

Lactation :

It is not known whether SACUVAL is excreted in human breast milk. The components of SACUVAL, sacubitril, and valsartan, have been excreted in the milk of lactating rats **(see section 5.3)**. Due to the potential risk of adverse effects in breastfed newborns/infants, the use of SACUVAL is not recommended during breastfeeding. The decision should be made to either discontinue breastfeeding or discontinue treatment with SACUVAL, taking into account the importance of SACUVAL treatment for the mother.

Fertility :

are no available data on the effect of SACUVAL on human fertility. No alterations in fertility have been observed in studies conducted in male and female rats **(see section 5.3)**.

4.7. Effects on the ability to drive and use machines:

SACUVAL has only a minor influence on the ability to drive vehicles and use machines. Occasional occurrences of dizziness or fatigue should be taken into consideration when driving vehicles or using machines.

4.8. Adverse Effects

Summary of the tolerance profile :

The most commonly reported adverse effects during SACUVAL treatment were hypotension, hyperkalemia, and impaired renal function **(see section 4.4).**

Angioedema has been reported in patients treated with SACUVAL **(see specific adverse effects section).**

The safety of SACUVAL in patients with chronic heart failure was evaluated in **the pivotal phase III PARADIGM-HF study**, which compared patients treated with Sacubitril-valsartan 97 mg/103 mg twice daily **(n = 4,203)** to enalapril 10 mg twice daily **(n = 4,229)**. Patients randomized in Group C were treated for a median duration of 24 months; 3,271 patients were treated for more than one year.

In the PARADIGM-HF study, patients were previously treated with ACE inhibitors and/or ARBs and had to complete sequential run-in periods with enalapril and Sacubitril-valsartan (average exposure duration of 15 and 29 days, respectively) before being randomized in the double-blind treatment period. During the run-in period with enalapril, 1,102 patients (10.5%) permanently discontinued the study, of which 5.6% were due to the occurrence of an adverse effect, with the most frequent being renal dysfunction (1.7%), hyperkalemia (1.7%), and hypotension (1.4%). During the run-in period with Sacubitril-valsartan, 10.4% of patients permanently discontinued the study, with 5.9% due to the occurrence of an adverse effect, with the most frequent being renal dysfunction (1.8%), hypotension (1.7%), and hyperkalemia (1.3%).

Due to study discontinuations during the run-in period, the frequencies of adverse effects presented in the table below may be lower than the expected frequencies in clinical practice.

During the double-blind treatment period, treatment was interrupted due to an adverse effect in 450 (10.7%) patients treated with SACUVAL and 516 (12.2%) patients treated with enalapril.

Summary table of adverse effects :

Adverse effects are classified according to the organ system classification and within each class in descending order of frequency, according to the following convention: Very Frequent (≥ 1/10), Frequent (≥ 1/100, <1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), very rare (< 1/10,000). Within each frequency category, adverse effects are ranked in descending order of severity.

Table 1 List of Adverse Reactions in Clinical Studies.

Organ System Class.	**Preferred Term**	**Frequency**
Hematological and lymphatic system disorders	Anemia	Frequent
Immune system disorders	Hypersensitivity	Uncommon
Metabolism and nutrition disorders	Hyperkalemia*	Very frequent
	Hypokalemia	Frequent
	Hypoglycemia	Frequent
Nervous system disorders	Dizziness	Frequent
	Headache	Frequent
	Syncope	Frequent
	Postural dizziness	Uncommon
Ear and labyrinth disorders	Vertigo	Frequent
Vascular disorders	Hypotension*	Very frequent
	Orthostatic hypotension	Frequent
Respiratory, thoracic, and mediastinal disorders	Cough	Frequent

Gastrointestinal disorders	Diarrhea	Frequent
	Nausea	Frequent
	Gastritis	Frequent
Skin and subcutaneous tissue disorders	Pruritus (itching)	Uncommon
	Rash	Uncommon
	Angioedema*	Uncommon
Renal and urinary disorders	Impairment of renal function*	Very frequent
	Renal failure (renal insufficiency, acute renal failure)	Frequent
General disorders and administration site conditions	Fatigue	Frequent
	Asthenia	Frequent

* See description of specific side effects

Description of specific side effects:

Angioedema:

Cases of angioedema have been reported in patients treated with SACUVAL. In PARADIGM-HF, angioedema was reported in 0.5% of patients treated with Sacubitril-valsartan compared to 0.2% of patients treated with enalapril. A higher incidence of angioedema was observed in black patients treated with Sacubitril-valsartan (2.4%) and enalapril (0.5%) **(See section 4.4)**.

Hyperkalemia and Potassium Levels:

In the PARADIGM-HF study, hyperkalemia and potassium levels >5.4 mmol/l were reported in 11.6% and 19.7% of patients treated with SACUVAL, and in 14.0% and 21.1% of patients treated with enalapril, respectively.

Blood Pressure:

In PARADIGM-HF, hypotension and clinically significant decreases in systolic blood pressure (<90 mmHg and decrease of >20 mmHg from baseline) were reported in 17.6% and 4.76% of patients treated with SACUVAL, compared to 11.9% and 2.67% of patients treated with enalapril, respectively.

Renal Impairment:

In PARADIGM-HF, renal function impairment was reported in 10.1% of patients treated with SACUVAL and 11.5% of patients treated with enalapril.

Reporting of Suspected Adverse Reactions:

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continuous monitoring of the benefit/risk balance of the drug. Healthcare professionals are encouraged to report any suspected adverse reactions via the national reporting system.

4.9. Overdose

The available data on overdose in humans are limited. Single doses of 583 mg sacubitril/617 mg valsartan and multiple doses of 437 mg sacubitril/463 mg valsartan (14 days) have been studied in healthy volunteers and were well tolerated.

The most likely symptom of overdose is hypotension due to the antihypertensive effect of SACUVAL. Symptomatic treatment should be administered.

It is unlikely that this medication can be removed by hemodialysis due to its strong binding to plasma proteins

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5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Therapeutic class: Drugs acting on the renin-angiotensin system, angiotensin II antagonists, other combinations

ATC code: C09DX04.

Mechanism of action :

SACUVAL has the mechanism of action of an angiotensin receptor and neprilysin inhibitor by inhibiting both neprilysin (neutral endopeptidase, NEP) through LBQ657, the active metabolite of the prodrug sacubitril, and blocking the type 1 angiotensin II receptor (AT1) through valsartan. The complementary cardiovascular effects of SACUVAL in patients with heart failure are attributed to the increase in peptides that are degraded by neprilysin, such as natriuretic peptides (NP) by LBQ657, and the simultaneous inhibition of the effects of angiotensin II by valsartan. Natriuretic peptides exert their physiological effects by activating membrane receptors with guanylate cyclase activity, leading to an increase in the concentrations of the hormonal second messenger, cyclic guanosine monophosphate (cGMP). This can result in vasodilation, natriuresis and diuresis, increased glomerular filtration and renal blood flow, inhibition of renin and aldosterone release, as well as a decrease in sympathetic activity, and anti-hypertrophic and anti-fibrotic effects.

Valsartan prevents the adverse cardiovascular and renal effects of angiotensin II by selectively blocking AT1 receptors and angiotensin II-dependent aldosterone release. This prevents the continuous activation of the renin-angiotensin-aldosterone system and causes vasoconstriction, fluid and sodium retention, and activation of cell growth and proliferation leading to maladaptive cardiovascular remodeling.

Pharmacodynamic effects :

The pharmacodynamic effects of SACUVAL have been evaluated after single and multiple doses in healthy subjects and in patients with heart failure, and are consistent with simultaneous inhibition of neprilysin and the renin-angiotensin-aldosterone system (RAAS). In a 7-day study conducted in patients with heart failure with reduced ejection fraction (HFrEF), administration of Sacubitril-valsartan led to an initial increase in natriuresis, increased urinary cGMP levels, and decreased plasma levels of mid-regional pro-atrial natriuretic peptide (MR-proANP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), compared to valsartan.

In a 21-day study in the same patients with HFrEF, SACUVAL significantly increased urinary levels of atrial natriuretic peptide (ANP) and cGMP, and plasma cGMP levels, and decreased plasma levels of NT-proBNP, aldosterone, and endothelin-1, compared to baseline. The AT1 receptor was also blocked, as evidenced by increased plasma renin activity and plasma renin concentrations. In the PARADIGM-HF study, Sacubitril-valsartan reduced NT-proBNP levels and increased plasma B-type natriuretic peptide (BNP) levels, as well as urinary cGMP levels, to a greater extent than enalapril. BNP is not an appropriate biomarker in heart failure patients treated with SACUVAL as it is a neprilysin substrate (see section 4.4). NT-proBNP, being a non-neprilysin substrate, is a more suitable biomarker.

In an in-depth QTc interval clinical study conducted in healthy male subjects, single doses of 194 mg sacubitril/206 mg valsartan and 583 mg sacubitril/617 mg valsartan had no effect on cardiac repolarization.

Neprilysin is one of the enzymes involved in the clearance of β-amyloid (Aβ) peptide from the brain and cerebrospinal fluid (CSF). Administration of SACUVAL to healthy subjects at a dose of 194 mg sacubitril/206 mg valsartan once daily for two weeks resulted in an increase in Aβ1-38 concentration in the CSF compared to placebo; the concentrations of Aβ1-40 and Aβ1-42 in the CSF were not affected. The clinical significance of these observations is not known **(see section 5.3)**.

Efficacy and Clinical Safety :

The dosages of 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg correspond to 50 mg, 100 mg, and 200 mg, respectively, in some publications.

PARADIGM-HF

--- PARADIGM-HF was a multinational, randomized, double-blind study comparing SACUVAL to enalapril in 8,442 patients, both administered in addition to other heart failure treatments, in adult patients with chronic heart failure of NYHA class II-IV with reduced ejection fraction (left ventricular ejection fraction [LVEF] ≤ 40%, later amended to ≤ 35%).

The primary endpoint was a composite endpoint of cardiovascular death or heart failure hospitalizations. Patients with systolic blood pressure <100 mmHg, severe renal impairment (eGFR <30 ml/min/1.73 m²), and severe hepatic impairment were excluded at the time of screening and were therefore not studied.

Before inclusion in the study, patients were optimally treated with a standard treatment, including ACE inhibitors/ARBs (>99%), beta-blockers (94%), aldosterone antagonists (58%), and diuretics (82%). The median duration of follow-up was 27 months, and patients were treated for a maximum period of 4.3 years.

Patients had to discontinue their ACE inhibitor or ARB treatment to enter a single-blind run-in period during which they received enalapril 10 mg twice daily followed by a single-blind treatment with SACUVAL 100 mg twice daily, increased to 200 mg twice daily (see section 4.8 for discontinuations during this period). Patients were then randomized to the double-blind period of the study to receive SACUVAL 200 mg or enalapril 10 mg twice daily [SACUVAL (n=4,209); enalapril (n=4,233)].

The mean age of the studied population was 64 years, and 19% were aged 75 years or older. At randomization, 70% of patients were in NYHA class II, 24% in class III, and 0.7% in class IV. The mean LVEF was 29%, and 963 (11.4%) patients had an initial LVEF >35% and ≤ 40%.

In the SACUVAL group, 76% of patients remained on the target dose of 200 mg twice daily until the end of the study (mean daily dose of 375 mg). In the enalapril group, 75% of patients remained on the target dose of 10 mg twice daily until the end of the study (mean daily dose of 18.9 mg).

SACUVAL was superior to enalapril in reducing the risk of cardiovascular death or heart failure hospitalizations by 21.8% compared to 26.5% with enalapril. The absolute risk reductions were 4.7% for the composite endpoint of cardiovascular death or heart failure hospitalizations, 3.1% for cardiovascular mortality alone, and 2.8% for the first heart failure hospitalization alone. The relative risk reduction was 20% compared to enalapril (see Table 2). This effect was observed early and maintained throughout the trial (see Figure 1). Both components of the endpoint contributed to the risk reduction. Sudden death contributed to 45% of cardiovascular deaths and was reduced by 20% in patients treated with SACUVAL compared to patients treated with enalapril (HR: 0.80, p=0.0082). Heart failure contributed to 26% of cardiovascular deaths and was reduced by 21% in patients treated with SACUVAL compared to patients treated with enalapril (HR: 0.79, p=0.0338).

This risk reduction was consistently and homogeneously observed in all subgroups, including sex, age, ethnic origin, geographic location, NYHA class (II/III), ejection fraction, renal function, history of diabetes or hypertension, prior heart failure treatment, and atrial fibrillation.

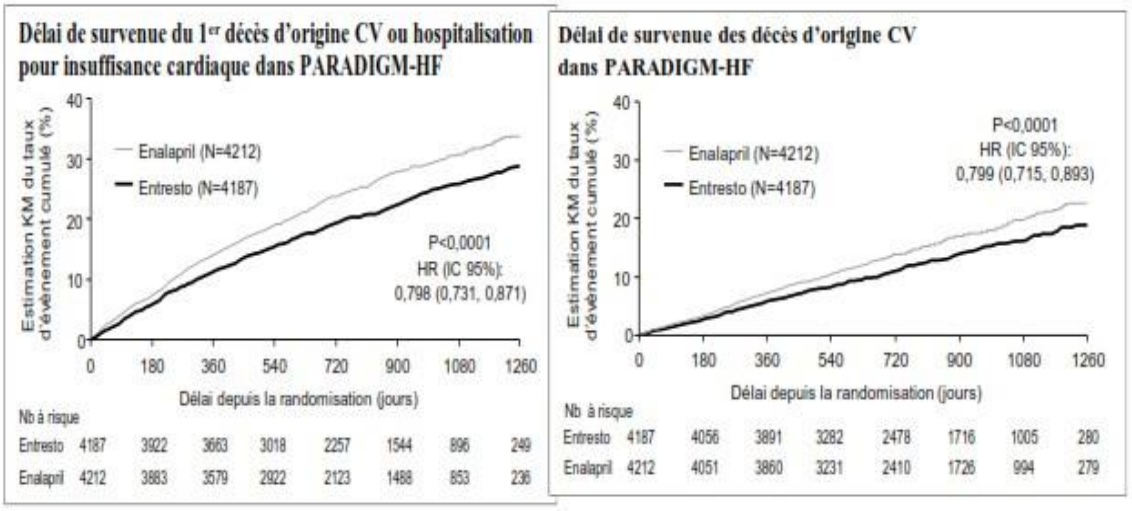
SACUVAL improved survival by significantly reducing all-cause mortality by 2.8% (SACUVAL 17%, enalapril 19.8%). The relative risk reduction was 16% compared to enalapril **(see Table 2).**

Table 2 Effect of treatment on the primary composite endpoint, its components, and all-cause mortality during the average follow-up period of 27 months:

	SACUVAL N = 4 187♯ n (%)	**Enalapril N = 4 212♯ n (%)**	**Hazard ratio (IC 95%)**	**Relative Risk Reduction**	**p-value *****
Primary composite endpoint including cardiovascular mortality and hospitalizations for heart failure*	914 (21,83)	1117 (26,52)	0,80 (0,73, 0,87)	20%	0,0000002
Individual components of the primary composite endpoint					
Cardiovascular mortality**	558 (13,33)	693 (16,45)	0,80 (0,71, 0,89)	20%	0,00004
First hospitalization for heart failure	537 (12,83)	658 (15,62)	0,79 (0,71, 0,89)	21%	0,00004
Secondary endpoint					
All-cause mortality	711 (16,98)	835 (19,82)	0,84 (0,76, 0,93)	16%	0,0005

*The primary endpoint was defined as the time to the first occurrence of CV death or hospitalization for heart failure.
** CV deaths include all patients who died up to the cut-off date, whether hospitalized or not.
*** One-sided p-value.
♯ Full Analysis Set (FAS)

Figure 1: Kaplan-Meier curves for the composite primary endpoint and cardiovascular mortality.



TITRATION

TITRATION was a 12-week tolerance study conducted in 538 patients with chronic heart failure (NYHA class II-IV) and reduced systolic function (left ventricular ejection fraction ≤ 35%) who had either never received an ACE inhibitor or ARB treatment or were receiving variable doses of ACE inhibitors or ARBs before inclusion in the study. Patients started their treatment with a dose of 50 mg twice daily of SACUVAL, which was increased to 100 mg twice daily and then up to the target dose of 200 mg either over a period of 3 weeks or 6 weeks.

The proportion of patients who had never received ACE inhibitors or ARBs or were receiving low doses (equivalent to ≤ 10 mg of enalapril per day), and were able to achieve and maintain the dose of 200 mg of SACUVAL, was higher when the dose was increased over 6 weeks (84.8%) compared to 3 weeks (73.6%). Overall, 76% of patients were able to achieve and maintain the target dose of 200 mg of SACUVAL twice daily without any interruption or dose reduction during the 12 weeks.

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Pharmacokinetic properties

The European Medicines Agency has deferred the obligation to submit the results of studies in one or more subsets of the pediatric population for the treatment of heart failure (see section 4.2 for information on pediatric use).

5.2. Propriétés pharmacocinétiques

The valsartan in SACUVAL has higher bioavailability than valsartan in other tablet formulations on the market; 51 mg and 103 mg of valsartan in SACUVAL are equivalent to 80 mg and 160 mg of valsartan in other tablet formulations on the market.

Absorption :

After oral administration, SACUVAL dissociates into valsartan and the prodrug sacubitril. Sacubitril is then metabolized into an active metabolite, LBQ657. These molecules reach peak concentrations at 2 hours, 1 hour, and 2 hours, respectively. The absolute bioavailability of orally administered sacubitril and valsartan is estimated to be over 60% and 23%, respectively.

After twice-daily administration of SACUVAL, steady-state levels of sacubitril, LBQ657, and valsartan are reached within three days. At steady state, sacubitril and valsartan do not accumulate significantly, while the accumulation of LBQ657 is multiplied by 1.6. Administration with food did not have a significant impact on the exposure to sacubitril, LBQ657, and valsartan. SACUVAL can be administered with or without food.

Distribution :

Sacubitril, LBQ657, and valsartan are highly bound to plasma proteins (94% - 97%). By comparing the exposure levels in plasma and in the cerebrospinal fluid (CSF), SACUVAL does not significantly cross the blood-brain barrier (0.28%). The mean apparent volume of distribution of valsartan and sacubitril was between 75 liters and 103 liters, respectively.

Biotransformation :

Sacubitril is rapidly transformed into LBQ657 by carboxylesterases 1b and 1; LBQ657 is not further metabolized to a significant extent. Valsartan is minimally metabolized, with only 20% of the dose recovered as metabolites. A hydroxyl metabolite of valsartan has been identified in the plasma at low concentrations (<10%).

Since sacubitril and valsartan are minimally metabolized by CYP450 enzymes, their concomitant administration with drugs that act on these enzymes should not affect their pharmacokinetics. CYP3A4 is the main isoenzyme responsible for the metabolism of ticagrelor and the formation of the active metabolite, and its interactions with other CYP3A substrates range from activation to inhibition.

Elimination :

After oral administration, 52-68% of sacubitril (mainly as LBQ657) and approximately 13% of valsartan and its metabolites are excreted in the urine; 37-48% of sacubitril (mainly as LBQ657) and 86% of valsartan and its metabolites are excreted in the feces.

Sacubitril, LBQ657, and valsartan are eliminated from plasma with an average elimination half-life (T1/2) of approximately 1.43 hours, 11.48 hours, and 9.90 hours, respectively.

Linearity/Non-linearity:

The pharmacokinetics of sacubitril, LBQ657, and valsartan were approximately linear over the SACUVAL dose range from 24 mg sacubitril/26 mg valsartan to 97 mg sacubitril/103 mg valsartan.

Special Populations :

Elderly Patients:

Exposure to LBQ657 and valsartan is higher by 42% and 30%, respectively, in patients over 65 years of age compared to younger patients.

Renal Impairment:

A correlation has been observed between renal function and systemic exposure to LBQ657 in patients with mild to severe renal impairment. Exposure to LBQ657 in patients with moderate renal impairment (30 mL/min/1.73 m2 ≤ eGFR < 60 mL/min/1.73 m2) and severe renal impairment (15 mL/min/1.73 m2 ≤ eGFR < 30 mL/min/1.73 m2) was 1.4 times and 2.2 times higher, respectively, than in patients with mild renal impairment (60 mL/min/1.73 m2 ≤ eGFR < 90 mL/min/1.73 m2), the largest group included in PARADIGM-HF. Exposure to valsartan was similar in patients with moderate and severe renal impairment and in those with mild renal impairment. No studies have been conducted in dialysis patients. However, LBQ657 and valsartan are highly bound to plasma proteins and are therefore unlikely to be eliminated by dialysis.

Hepatic Impairment:

In patients with mild to moderate hepatic impairment, exposure to sacubitril was increased by 1.5 and 3.4 times, LBQ657 by 1.5 and 1.9 times, and valsartan by 1.2 and 2.1 times, respectively, compared to matched healthy subjects. Nevertheless, in patients with mild to moderate hepatic impairment, exposure to free concentrations of LBQ657 increased by 1.47 and 3.08 times, respectively, and exposure to free concentrations of valsartan increased by 1.09 and 2.20 times, respectively, compared to matched healthy subjects. SACUVAL has not been studied in patients with severe hepatic impairment, biliary cirrhosis, or cholestasis (see sections 4.3 and 4.4).

Effect of Gender:

The pharmacokinetics of SACUVAL (sacubitril, LBQ657, and valsartan) are similar in men and women.

5.3 Efficacy and Clinical Safety

Non-clinical data (including studies with the components, sacubitril and valsartan, and/or with SACUVAL) from conventional safety pharmacology, repeated dose toxicology, genotoxicity, carcinogenicity, and fertility studies did not reveal any specific risks for humans.

Fertility, Reproduction, and Development:

Treatment with SACUVAL during organogenesis led to increased embryonic and fetal mortality in rats at doses ≥49 mg sacubitril/51 mg valsartan/kg/day (≤0.72 times the maximum recommended human dose based on AUC) and in rabbits at doses ≥4.9 mg sacubitril/5.1 mg valsartan/kg/day (2 times and 0.03 times the maximum recommended human dose based on AUC of valsartan and LBQ657, respectively). It is teratogenic due to a low incidence of fetal hydrocephaly, associated with toxic doses in the mother, which was observed in rabbits at doses of SACUVAL ≥4.9 mg sacubitril/5.1 mg valsartan/kg/day.

Cardiovascular anomalies (mainly cardiomegaly) were observed in rabbit fetuses at a non-toxic maternal dose (1.46 mg sacubitril/1.54 mg valsartan/kg/day). A slight increase in two fetal skeletal variations (sternal deformities, bipartite sternal ossification) was observed in rabbits at a dose of SACUVAL 4.9 mg sacubitril/5.1 mg valsartan/kg/day). The adverse effects of SACUVAL on embryo-fetal development are likely related to the antagonistic activity on the angiotensin receptor (see section 4.6).

In rabbits, treatment with sacubitril during organogenesis resulted in embryo-fetal lethality and embryo-fetal toxicity (reduced fetal body weight and skeletal malformations) at doses associated with maternal toxicity (500 mg/kg/day; 5.7 times the maximum recommended human dose based on AUC of LBQ657). A slight generalized delay in ossification was observed at doses >50 mg/kg/day. This observation is not considered adverse. No evidence of embryo-fetal toxicity or teratogenicity was observed in rats treated with sacubitril. The No Observed Adverse Effect Level (NOAEL) for embryo-fetal development was at least 750 mg/kg/day in rats and 200 mg/kg/day in rabbits (2.2 times the maximum recommended human dose based on AUC of LBQ657).

Pre- and post-natal development studies conducted in rats with sacubitril at doses up to 750 mg/kg/day (2.2 times the maximum recommended human dose based on AUC) and with valsartan at doses up to 600 mg/kg/day (0.86 times the maximum recommended human dose based on AUC) show that treatment with SACUVAL during organogenesis, pregnancy, and lactation could have an effect on the development and survival of offspring.

Other Preclinical Results :

SACUVAL

Les effets de S---- The effects of SACUVAL on β-amyloid peptide concentrations in cerebrospinal fluid (CSF) and brain tissue were evaluated in young cynomolgus monkeys (aged 2 to 4 years) treated with SACUVAL (at a dose of 24 mg sacubitril/26 mg valsartan per kg body weight) for 2 weeks. In this study, the clearance of Aβ in the CSF of cynomolgus monkeys was reduced, leading to increased levels of Aβ1-40, 1-42, and 1-38 in the CSF; however, no corresponding increase in Aβ levels was observed in the brain. Increases in Aβ1-40 and 1-42 levels in the CSF were not observed in a 2-week study conducted in healthy human subjects (see section 5.1). Furthermore, in a toxicology study conducted in cynomolgus monkeys treated with SACUVAL at a dose of 146 mg sacubitril/154 mg valsartan per kg body weight for 39 weeks, no amyloid plaques were observed in the brain. However, the presence of amyloid was not quantitatively measured in this study.

Sacubitril

In young rats treated with sacubitril (7 to 70 days postnatal), there was a decrease in age-related bone mass development and bone elongation. An adult rat study showed only a minimal and transient inhibitory effect on bone mineral density but no effect on other criteria related to bone growth, suggesting the absence of sacubitril's effect on bones in adult patient populations under normal conditions. However, a slight and transient interference of sacubitril during the early phase of fracture consolidation cannot be excluded in adults.

Valsartan

In young rats treated with valsartan (7 to 70 days postnatal), doses as low as 1 mg/kg/day resulted in persistent and irreversible renal modifications of tubular nephropathy (sometimes accompanied by tubular epithelial necrosis) and pelvic dilation. These renal modifications represent an expected pharmacological effect of angiotensin-converting enzyme inhibitors and type 1 angiotensin II receptor antagonists in rats when treated during their first 13 days of life. This period corresponds to 36 weeks of gestation in humans, which can occasionally be extended to 44 weeks after conception in humans.

6. PHARMACEUTICAL DATA

6.1. List of excipients

Microcrystalline cellulose 102, hydroxypropyl cellulose (low-substituted LH11), crospovidone XL, colloidal anhydrous silica, talc, magnesium stearate, sepifilm 5361 pink (hypromellose, macrogol 6000, glycerol, magnesium stearate, titanium dioxide anatase, red iron oxide).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years.

6.4. Special precautions for storage

Store below 30°C, protect from moisture.

6.5. Nature and contents of the outer packaging

Blister packs (Aluminium Formpack/Aluminium).

6.6. Special precautions for disposal and handling

Not applicable.

7. MARKETING AUTHORIZATION HOLDER

Laboratoires PHILADELPHIA PHARMA, Route de Tunis km 16 Sidi Salah Sfax.

8. MARKETING AUTHORIZATION NUMBERS

Authorized Medication No.:

SACUVAL 50 MG film-coated tablets, Box of 30 tablets: 9353291

SACUVAL 100 MG film-coated tablets, Box of 60 tablets: 9353292

SACUVAL 200 MG film-coated tablets, Box of 60 tablets: 9353293

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

17/07/2023.

10. DATE OF TEXT UPDATE

Not applicable.

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR THE PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

13. CONDITIONS FOR PRESCRIPTION AND DELIVERY

Table A – (List I)