ARNISTO 50/100/200

Sacubitril & Valsartan Tablets

Quantitative composition:
ARNISTO 50 : Each film-coated tablet contains : Sacubitril 24.3mg and Valsartan 25.7mg (as Sacubitril Valsartan sodium salt complex)
ARNISTO 100 : Each film-coated tablet contains : Sacubitril 48.6mg and Valsartan 51.4mg (as Sacubitril Valsartan sodium salt complex)
ARNISTO 200 : Each film-coated tablet contains sacubitril 97.2mg and valsartan 102.8mg (as Sacubitril Valsartan sodium salt complex)
Pharmaceutical form: Film-coated tablets
ARNISTO 50: Peach coloured, oval shaped, Flat face beveled edge (FFBE), film coated tablet having one side break line and other side plain.
ARNISTO 100: Yellow coloured, oval shaped, flat face beveled edge (FFBE), film coated tablet having one side break line and other side plain.
ARNISTO 200: Brick red, oval shaped, biconvex, film coated tablets having both sides plain
Pharmacology:
Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; angiotensin II receptor blockers (ARBs), other combinations, ATC code: C09DX04
Mechanism of action: Sacubitril/valsartan exhibits the mechanism of action of an angiotensin receptor neprilysin inhibitor by simultaneously inhibiting neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and by blocking the angiotensin II type-1 (AT1) receptor via valsartan. The complementary cardiovascular benefits of sacubitril/valsartan in heart failure patients are attributed to the enhancement of 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 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 anti-hypertrophic and anti-fibrotic effects.
Pharmacokinetics:
Absorption: Following oral administration, sacubitril/valsartan dissociates into valsartan and the prodrug sacubitril. Sacubitril is further metabolised to the active metabolite, Sacubitrilat. These reach peak plasma concentrations 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, Sacubitrilat and valsartan are reached in three days. At steady state, sacubitril and valsartan do not accumulate significantly, while Sacubitrilat accumulates 1.6-fold. Administration with food has no clinically significant impact on the systemic exposures of sacubitril, Sacubitrilat and valsartan. Sacubitril/valsartan can be administered with or without food.
Distribution: Sacubitril, Sacubitrilat and valsartan are highly bound to plasma proteins (94-97%). Based on the comparison of plasma and CSF exposures, Sacubitrilat crosses the blood brain barrier to a limited extent (0.28%). The average apparent volume of distribution of valsartan and sacubitril were 75 litres to 103 litres, respectively.
Biotransformation: Sacubitril is readily converted to Sacubitrilat by carboxylesterases 1b and 1c; Sacubitrilat is not further metabolised to a significant extent. Valsartan is minimally metabolised, as only about 20% of the dose is recovered as metabolites. A hydroxyl metabolite of valsartan has been identified in plasma at low concentrations (<10%). Since CYP450-enzyme-mediated metabolism of sacubitril and valsartan is minimal, co-administration with medicinal products that impact CYP450 enzymes is not expected to impact the pharmacokinetics.
Elimination: 52-68% of sacubitril (primarily as Sacubitrilat) and ~13% of valsartan and its metabolites are excreted in urine; 37-48% of sacubitril (primarily as Sacubitrilat) and 86% of valsartan and its metabolites are excreted in faeces. Sacubitril, Sacubitrilat and valsartan are eliminated from plasma with a mean elimination half-life (T½) of approximately 1.43 hours, 11.48 hours, and 9.90 hours, respectively.
Indications:
Arnisto is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction and in paediatric heart failure in children and adolescents aged one year or older for treatment of symptomatic chronic heart failure with left ventricular systolic dysfunction.
Posology and method of administration:
Adult heart failure:
The recommended starting dose of Arnisto is one tablet of 49 mg/51 mg twice daily, except in the situations described below. The dose should be doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient
If patients experience tolerability issues (systolic blood pressure [SBP] ≤95 mmHg, symptomatic hypotension, hyperkalaemia, renal dysfunction), adjustment of concomitant medicinal products, temporary down–titration or discontinuation of Arnisto is recommended.
In PARADIGM-HF study, Arnistowas administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB. There is limited experience in patients not currently taking an ACE inhibitor or an ARB or taking low doses of these medicinal products, therefore a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3-4 weeks) are recommended in these patients. Treatment should not be initiated in patients with serum potassium level >5.4 mmol/l or with SBP <100 mmHg. A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥ 100 to 110 mmHg.
Paediatric heart failure: The recommended dose should be taken orally twice daily. The dose should be increased every 2-4 weeks to the target dose, as tolerated by the patient. Arnisto film-coated tablets are not suitable for children weighing less than 40 kg.
Table 1 Recommended dose titration

Patient weight	To be given twice daily			
	Half the starting dose	Starting dose	Intermediate dose	Target dose
Paediatric patients less than 40 kg	0.8 mg/kg	1.6 mg/kg	2.3 mg/kg	3.1 mg/kg
Paediatric patients at least 40 kg, less than 50 kg	0.8 mg/kg	24 mg/26 mg	49 mg/51 mg	72 mg/78 mg
Paediatric patients at least 50 kg	24 mg/26 mg	49 mg/51 mg	72 mg/78 mg	97 mg/103 mg

Half the starting dose is recommended in patients who have not been taking an ACE inhibitor or an ARB or have been taking low doses of these medicinal products, patients who have renal impairment (estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m2) and patients who have moderate hepatic impairment.
0.8 mg/kg, 1.6 mg/kg, 2.3 mg/kg and 3.1 mg/kg refer to the combined amount of sacubitril and valsartan and are to be given using granules.
In patients not currently taking an ACE inhibitor or an ARB or taking low doses of these medicinal products, half of the starting dose is recommended. For paediatric patients weighing 40 kg to less than 50 kg, a starting dose of 0.8 mg/kg twice daily (given as granules) is recommended. After initiation, the dose should be increased to the standard starting dose following the recommended dose titration in Table 1 and adjusted every 3-4 weeks. Treatment should not be initiated in patients with serum potassium level >5.3 mmol/l or with SBP <5th percentile for the age of the patient. If patients experience tolerability issues (SBP <5th percentile for the age of the patient, symptomatic hypotension, hyperkalaemia, renal dysfunction), adjustment of concomitant medicinal products, temporary down-titration or discontinuation of Arnisto is recommended.
Special populations
Elderly: The dose should be in line with the renal function of the elderly patient.
Renal impairment: No dose adjustment is required in patients with mild (eGFR 60-90 ml/min/1.73 m2) renal impairment. Half of the starting dose should be considered in patients with moderate renal impairment (eGFR 30-60 ml/min/1.73 m2).
Hepatic impairment : No dose adjustment is required when administering Arnisto to patients with mild hepatic impairment. Arnisto is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis
Method of administration
Oral use.
Sacubitril and Valsartan Tablets may be administered with or without food. The tablets must be swallowed with a glass of water.
Contraindications:
• Hypersensitivity to the active substances or to any of the excipients, • Concomitant use with ACE inhibitors, • Known history of angioedema related to previous ACE inhibitor or ARB therapy, • Hereditary or idiopathic angioedema and Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2).
Also contraindicated in patient with severe hepatic impairment, biliary cirrhosis, cholestasis, second and third trimesters of pregnancy.
Special warnings and precautions for use:
Dual blockade of the renin-angiotensin-aldosterone system (RAAS): The combination of sacubitril/valsartan with an ACE inhibitor is contraindicated due to the increased risk of angioedema. Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with sacubitril/valsartan is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan.
• The combination of sacubitril/valsartan with direct renin inhibitors such as aliskiren is not recommended. The combination of sacubitril/valsartan with aliskiren-containing medicinal products is contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2).
• Sacubitril and Valsartan Tablets contains valsartan, and therefore should not be co-administered with another ARB containing medicinal product.
Hypotension: Treatment should not be initiated unless SBP is ≥100 mmHg. Patients with SBP <100 mmHg were not studied. Cases of symptomatic hypotension have been reported in patients treated with sacubitril/valsartan during clinical studies. especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112 mmHg). When initiating therapy or during dose titration with sacubitril/valsartan, blood pressure should be monitored routinely. If hypotension occurs, temporary down-titration or discontinuation of sacubitril/valsartan is recommended. Dose adjustment of diuretics, concomitant antihypertensives and treatment of other causes of hypotension (e.g. hypovolaemia) should be considered. Symptomatic hypotension is more likely to occur if the patient has been volume-depleted, e.g. by diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Sodium and/or volume depletion should be corrected before starting treatment with sacubitril/valsartan, however, such corrective action must be carefully weighed against the risk of volume overload.
Impaired renal function: Evaluation of patients with heart failure should always include assessment of renal function. Patients with mild and moderate renal impairment are more at risk of developing hypotension. There is very limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m2) and these patients may be at greatest risk of hypotension. There is no experience in patients with end-stage renal disease and use of sacubitril/valsartan is not recommended.
Worsening renal function: Use of sacubitril/valsartan may be associated with decreased renal function. The risk may be further increased by dehydration or concomitant use of non-steroidal anti-inflammatory agents (NSAIDs). Down-titration should be considered in patients who develop a clinically significant decrease in renal function.
Hyperkalaemia: Treatment should not be initiated if the serum potassium level is >5.4 mmol/l. Use of sacubitril/valsartan may be associated with an increased risk of hyperkalaemia, although hypokalaemia may also occur. Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists. If patients experience clinically significant hyperkalaemia adjustment of concomitant medicinal products, or temporary down–titration or discontinuation is recommended. If serum potassium level is >5.4 mmol/l discontinuation should be considered.
Angioedema has been reported in patients treated with sacubitril/valsartan. If angioedema occurs, sacubitril/valsartan should be immediately discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. It must not be re-administered. In cases of confirmed angioedema where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms.
Patients with renal artery stenosis: Sacubitril/valsartan may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. Caution is required in patients with renal artery stenosis and monitoring of renal function is recommended.
Interaction with other medicinal products and other forms of interaction:
ACE inhibitors. The concomitant use of sacubitril/valsartan with ACE inhibitors is contraindicated, as the concomitant inhibition of neprilysin (NEP) and ACE may increase the risk of angioedema.
Aliskiren: The concomitant use of sacubitril/valsartan with aliskiren-containing medicinal products is contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m2).
OATP1B1 and OATP1B3 substrates, e.g. Statins:
In vitro data indicate that Sacubitril inhibits OATP1B1 and OATP1B3 transporters. Arnisto may increase the systemic exposure of OATP1B1 and OATP1B3 substrates such as statins.
PDE5 inhibitors including Sildenafil. Co-administration 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-sparing diuretics (triamterene, amiloride), mineralocorticoid antagonists (e.g. spironolactone, eplerenone), potassium supplements, salt substitutes containing potassium or other agents (such as heparin): May lead to increases in serum potassium, and to increases in serum creatinine hence close monitoring of serum potassium is recommended.
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
There was no drug-drug interaction between sacubitril/valsartan and intravenously administered nitroglycerin with regard to blood pressure reduction.
Co-administration of nitroglycerin and sacubitril/valsartan was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerine alone. A similar effect on the heart rate may occur when sacubitril/valsartan is co-administered with sublingual, oral or transdermal nitrates. In general, no dose adjustment is required.
Co-administration of sacubitril/valsartan with metformin reduced both Cmax and AUC of Metformin by 23%. The clinical relevance of these findings is unknown. Therefore, when initiating therapy with sacubitril/valsartan in patients receiving metformin, the clinical status of the patient should be evaluated.
No clinically meaningful drug-drug interaction was observed when sacubitril/valsartan was co-administered with digoxin, warfarin, hydrochlorothiazide, amlodipine, omeprazole, carvedilol or a combination of levonorgestrel/ethinyl estradiol.
Pregnancy, lactation and fertility:
Pregnancy: The use of sacubitril/valsartan is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy. Valsartan, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.
When pregnancy is diagnosed, treatment with ARBs should be stopped immediately and, if appropriate, alternative therapy should be started.
Sacubitril /valsartan: There are no data from the use of sacubitril/valsartan in pregnant women. Animal studies with sacubitril/valsartan have shown reproductive toxicity.
Breast-feeding: 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 and Valsartan Tablets while breast-feeding, taking into account the importance of sacubitril/valsartan to the mother.
Fertility: There are no available data on the effect of sacubitril/valsartan on human fertility. No impairment of fertility was demonstrated in studies with it in male and female rats.
Effects on ability to drive and use machines:
Sacubitril/valsartan has a minor influence on the ability to drive and use machines. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or fatigue may occur.
Adverse reactions:
Stop taking Arnisto and seek immediate medical attention if there are any swelling on the face, lips, tongue and or through which many cause difficulties in breathing or swallowing. These may be signs of angioedema. Other common adverse effects may includes low blood pressure, high level of potassium in the blood, decreased renal function, cough, dizziness, diarrhoea, low level of red blood cell, tiredness, renal failure, low level of potassium in the blood,headach,fainting weakness, nausea low blood pressure,gastritis,spinning sensation low level of sugar in the blood.
Uncommon adverse effects include Allergic reaction with rash and itching, dizziness and angioedema.
Overdose and Treatment:
Hypotension is the most likely symptom of overdose due to the blood pressure lowering effects of sacubitril/valsartan. Symptomatic treatment should be provided. The medicinal product is unlikely to be removed by haemodialysis due to high protein binding.
Presentation: Blister Pack of 3x10's, packed in printed unit carton along with literature insert.
Shelf life: 2 years from the date of manufacture.
Storage: Do not store above 30°C. Protect from direct sunlight. Keep all medicines out of reach of children.
Distribution category: Prescription only medicine (POM).

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