UPERIO

50, 100, 200 mg film-coated tablets

LEAFLET

DISETUJUI OLEH BPOM: 06/03/2023

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Trade name

UPERIO 50 mg film-coated tablets sacubitril valsartan sodium hydrate

UPERIO 100 mg film-coated tablets sacubitril valsartan sodium hydrate

UPERIO 200 mg film-coated tablets sacubitril valsartan sodium hydrate

Description and composition

Pharmaceutical form

Film-coated tablets.

50 mg: Violet white ovaloid biconvex film-coated tablet with beveled edges, unscored, debossed with “NVR” on one side and “LZ” on the other side.

100 mg: Pale yellow ovaloid biconvex film-coated tablet with beveled edges, unscored, debossed with “NVR” on one side and “L1” on the other side.

200 mg: Light pink ovaloid biconvex film-coated tablet with beveled edges, unscored, debossed with “NVR” on one side and “L11” on the other side.

Active substances

Sacubitril valsartan sodium hydrate.

UPERIO contains a salt complex of the anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:2.5 respectively. Following oral administration, UPERIO dissociates into sacubitril (which is further metabolized to LBQ657 [sacubitrilat]) and valsartan.

UPERIO 50 mg film-coated tablets

Each film-coated tablet contains 24.3 mg sacubitril and 25.7 mg valsartan (as Sacubitril valsartan sodium hydrate).

UPERIO 100 mg film-coated tablets

Each film-coated tablet contains 48.6 mg sacubitril and 51.4 mg valsartan (as Sacubitril valsartan sodium hydrate).

UPERIO 200 mg film-coated tablets

Each film-coated tablet contains 97.2 mg sacubitril and 102.8 mg valsartan (as Sacubitril valsartan sodium hydrate).

Excipients

Microcrystalline cellulose, low-substituted hydroxypropylcellulose, crospovidone, magnesium stearate (vegetable origin), talc and colloidal silicon dioxide.

Excipients of film coating:

hypromellose, titanium dioxide (E 171), Macrogol 4000, talc, iron oxide red (E 172).

For 50 and 200 mg: iron oxide black (E 172). For 100 mg: iron oxide yellow (E 172).

Indications

UPERIO is indicated for the treatment of heart failure (NYHA class II-IV) in patients with reduced ejection fraction (LVEF ≤40%).

Dosage and administration

The target dose of UPERIO is 200 mg twice daily.

The recommended starting dose of UPERIO is 100 mg twice daily. A starting dose of 50 mg twice daily is recommended for patients not currently taking an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB), and should be considered for patients previously taking low doses of these agents (see section Clinical Trials).

The dose of UPERIO should be doubled every 2-4 weeks to the target dose of 200 mg twice daily, as tolerated by the patient.

Due to the potential risk of angioedema when used concomitantly with an ACE inhibitor, UPERIO must not be started until 36 hours after discontinuing ACE inhibitor therapy (see section Contraindications).

Treatment should not be initiated in patients with serum potassium level >5.4 mmol/l or with SBP <100 mmHg (see section Warnings and precautions). A starting dose of 50 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg.

UPERIO should not be co-administered with an ARB due to the angiotensin II receptor blocking activity of UPERIO (see section Warnings and Precautions and section Drug Interactions).

If patients experience tolerability issues (symptomatic hypotension, hyperkalemia, renal dysfunction), consideration should be given to adjustment of concomitant medications, or to temporary down–titration of UPERIO.

Special populations

Renal impairment

A starting dose of 50 mg twice daily should be considered in patients with moderate renal impairment (eGFR 30-60 mL/min/1.73 m^2). As there is very limited clinical experience in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) (see section Pharmacodynamics (PD)) UPERIO should be used with caution and a starting dose of 50 mg twice daily is recommended. There is no experience in patients with end-stage renal disease and use of UPERIO is not recommended.

No dose adjustment is required in patients with mild (Estimated Glomerular Filtration Rate [eGFR] 60-90 mL/min/1.73 m^2) renal impairment.

Hepatic impairment

No dose adjustment is required when administering UPERIO to patients with mild hepatic impairment (Child-Pugh A classification). 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. UPERIO should be used with caution in these patients and the recommended starting dose is 50 mg twice daily (see sections Warnings and precautions and Pharmacokinetics (PK)). UPERIO is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification) (see section Contraindications).

Pediatric patients

The safety and efficacy of UPERIO in pediatric patients aged below 18 years has not been established.

Geriatric patients (older than 65 years)

No dosage adjustment is required in patients over 65 years.

Method of administration

For oral use. UPERIO may be administered with or without food (see section Clinical Pharmacology). The tablets must be swallowed with a glass of water.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Concomitant use with ACE inhibitors (see section Warnings and Precautions, section Dosage and Administration, and section Interactions). UPERIO 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 angiodema (see section Warnings and precautions).
- Concomitant use with aliskiren in patients with Type 2 diabetes or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2) (see section Warnings and Precautions, and section Interactions).
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Pregnancy. (see section Females of child-bearing potential, pregnancy, breast-feeding and fertility).

Warnings and precautions

Dual blockade of the Renin-Angiotensin-Aldosterone System (RAAS)

- UPERIO is contraindicated with an ACE inhibitor due to the risk of angioedema. UPERIO must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with UPERIO is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of UPERIO (see section Contraindications, section Dosage and Administration, and section Interactions).

- The combination of UPERIO with direct renin inhibitors such as aliskiren is not recommended (see section Interactions). The combination of UPERIO with aliskiren-containing products is contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2) (see sections Contraindications and Interactions).
- UPERIO should not be co-administered with an ARB due to the angiotensin II receptor blocking activity of UPERIO (see section Dosage and Administration, and section Interactions).

Hypotension

Treatment should not be initiated unless SBP is ≥100 mmHg. Patients with SBP <100 mmHg were not studied (see section Pharmacodynamics (PD)). Cases of symptomatic hypotension have been reported in patients treated with UPERIO during clinical studies (see section Adverse drug reactions), 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 UPERIO, blood pressure should be monitored routinely. If hypotension occurs, temporary down-titration or discontinuation of UPERIO is recommended (see section Dosage and administration). 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, diarrhea or vomiting. Sodium and/or volume depletion should be corrected before starting treatment with UPERIO, 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 (see section Dosage and administration).

There is very limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m^2) and these patients may be at greatest risk of hypotension (see section Dosage and administration). There is no experience in patients with end-stage renal disease and use of UPERIO is not recommended.

Worsening renal function

Use of UPERIO 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) (see section Interactions).

Down-titration should be considered in patients who develop a clinically significant decrease in renal function.

Hyperkalemia

Treatment should not be initiated if the serum potassium level is >5.4 mmol/l. As for any drug that acts on the renin-angiotensin-aldosterone system, use of UPERIO may be associated with an increased risk of hyperkalemia, although hypokalaemia may also occur (see section Adverse drug reactions). In PARADIGM-HF, the incidence of clinically relevant hyperkalemia was low, resulting in treatment discontinuation in 0.26% of UPERIO treated patients compared to 0.35% of enalapril treated patients. Medications known to raise potassium levels (e.g. potassium-sparing diuretics, potassium supplements) should be used with caution when co-administered with UPERIO. If clinically significant hyperkalemia occurs, measures such as reducing dietary potassium, or adjusting the dose of concomitant medications should be considered. Monitoring of serum potassium is recommended especially in patients with risk factors such as severe renal impairment, diabetes mellitus, hypoaldosteronism or receiving a high potassium diet or on mineralocorticoid antagonists (see section Dosage and administration). 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

Angioedema has been reported in patients treated with UPERIO. If angioedema occurs, UPERIO should be immediately discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. UPERIO 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.

Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine/adrenaline solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly administered.

Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if UPERIO is used in these patients. UPERIO is contraindicated in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy or with hereditary or idiopathic angioedema (see section Contraindications).

Black patients may have increased susceptibility to develop angioedema.

Patients with renal artery stenosis

Similar to other drugs that affect the renin-angiotensin-aldosterone system, UPERIO 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.

Patients with NYHA functional classification IV

Caution should be exercised when initiating UPERIO 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 UPERIO because it is a neprilysin substrate (see section Pharmacodynamics (PD)).

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. In these patients, exposure may be increased and safety is not established. Caution is therefore recommended when using it in these patients (see section Dosage and administration and Pharmacokinetics (PK)). UPERIO is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification) (see section Contraindications).

Adverse drug reactions

Summary of the safety profile

The most commonly reported adverse reactions during treatment with UPERIO were hypotension, hyperkalaemia and renal impairment (see section Warnings and precautions). Angioedema was reported in patients treated with UPERIO (see description of selected adverse reactions).

The safety of UPERIO in patients with chronic heart failure was evaluated in the pivotal phase 3 study PARADIGM-HF, which compared patients treated twice daily with UPERIO 200 mg (n= 4203) or enalapril 10 mg (n= 4229). Patients randomized to UPERIO received treatment for up to 4.3 years, with a median duration of exposure of 24 months; 3271 patients were treated for more than one year.

Discontinuation of therapy due to an AE in the double-blind period of the PARADIGM-HF trial occurred in 450 (10.71%) of UPERIO treated patients and 516 (12.20%) of patients receiving enalapril. The events most commonly associated with dosage adjustment or treatment interruption were hypotension, hyperkalemia and renal impairment.

The overall incidence of adverse drug reactions (ADRs) of UPERIO in heart failure patients was comparable to enalapril. The pattern of the ADRs is consistent with the pharmacology of UPERIO and the patients underlying conditions.

The overall frequency of adverse reactions was not related to gender, age, or race.

Adverse drug reactions are ranked by System Organ Class and then by frequency with 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.

Table 1 Adverse Drug Reactions in the PARADIGM-HF, Safety Set

Adverse drug reactions	**Uperio** 200mg twice daily (%)*	**Enalapril** 10 mg twice daily (%)*	**Frequency category**
Blood and lymphatic system disorders			
Anaemia	4.00	4.75	Common
Metabolism and nutrition disorders			
Hyperkalaemia	11.61	14.00	Very common
Hypokalaemia	3.31	2.53	Common
Hypoglycaemia	1.36	1.06	Common
Nervous system disorders			
Dizziness	6.33	4.87	Common
Dizziness postural	0.57	0.28	Uncommon
Headache	2.45	2.51	Common
Ear and labyrinth disorders			
Vertigo	1.45	1.40	Common
Vascular disorders			
Hypotension	17.61	11.97	Very common
Syncope	2.24	2.70	Common
Orthostatic hypotension	1.52	0.80	Common
Respiratory, thoracic and mediastinal disorders			
Cough	8.78	12.60	Common
Gastrointestinal disorders			
Diarrhoea	4.62	4.47	Common
Nausea	2.09	2.36	Common
Gastritis	1.48	1.66	Common
Skin and subcutaneous tissue disorders			
Angioedema	0.45	0.24	Uncommon
Renal and urinary disorders			
Renal impairment	10.14	11.52	Very Common
Renal failure (renal failure, acute renal failure)	4.76	5.30	Common
General disorders and administration site conditions			
Fatigue	2.97	3.05	Common
Asthenia	2.09	1.84	Common

* Safety analysis set

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with UPERIO via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency, which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA.

Table 2 Adverse Drug Reactions from spontaneous reports and literature cases (frequency not known)

Immune system disorders
Hypersensitivity (including rash, pruritus, and anaphylaxis)

Description of selected adverse reactions

Angioedema

Angioedema has been reported in patients treated with UPERIO. In PARADIGM-HF, angioedema was reported in 0.5% of patients treated with UPERIO, compared with 0.2% of patients treated with enalapril. A higher incidence of angioedema was observed in Black patients treated with UPERIO (2.4%) and enalapril (0.5%).

Hyperkalaemia and serum potassium

In PARADIGM-HF, hyperkalaemia and serum potassium concentrations >5.4 mmol/l were reported in 11.6% and 19.7% of Uperio-treated patients and 14.0% and 21.1% of enalapril-treated patients, respectively.

Blood pressure

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

Renal impairment

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Interactions

Anticipated interactions resulting in a contraindication

ACE inhibitors: The concomitant use of UPERIO with ACE inhibitors is contraindicated, as the concomitant inhibition of neprilysin (NEP) and ACE inhibitor therapy may increase the risk of angioedema. UPERIO must not be started until 36 hours after taking the last dose of ACE

inhibitor therapy. ACE inhibitor therapy must not be started until 36 hours after the last dose of UPERIO (see section Contraindications, and section Dosage and Administration).

Aliskiren: The concomitant use of UPERIO with aliskiren is contraindicated in patients with Type 2 diabetes or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2) (see section Contraindications).

The combination of UPERIO with direct renin inhibitors such as aliskiren is not recommended (see section Warnings and precautions). Combination of UPERIO with aliskiren is potentially associated with a higher frequency of adverse events such as hypotension hyperkalaemia and decreased renal function (including acute renal failure) (see sections Contraindications and Warnings and precautions).

Anticipated interactions resulting in concomitant use not being recommended

UPERIO should not be co-administered with an ARB due to the angiotensin II receptor blocking activity of UPERIO (see section Warnings and Precautions).

Observed interactions to be considered

Statins: *In vitro* data indicates that sacubitril inhibits OATP1B1 and OATP1B3 transporters. UPERIO may therefore increase the systemic exposure of OATP1B1 and OATP1B3 substrates such as statins. Co-administration of UPERIO increased the Cmax of atorvastatin and its metabolites by up to 2-fold and AUC by up to 1.3-fold. Caution should be exercised upon co-administration of UPERIO with statins. No clinically relevant drug-drug interaction was observed when simvastatin and Uperio were co-administered.

Sildenafil: Addition of a single dose of sildenafil to UPERIO at steady state in patients with hypertension was associated with greater BP reduction compared to administration of UPERIO alone. Therefore, caution should be exercised when sildenafil or another PDE-5 inhibitor is initiated in patients treated with UPERIO.

Anticipated interactions to be considered

Potassium: Concomitant use of potassium-sparing diuretics (e.g, triamterene, amiloride), mineralocorticoid antagonists (e.g. spironolactone, eplerenone), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium, and to increases in serum creatinine. Monitoring of serum potassium is recommended if UPERIO is co-administered with these agents (see section Warnings and Precautions).

Non-Steroidal Anti-Inflammatory Agents (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 Inhibitors): In elderly patients, volume-depleted patients (including those on diuretic therapy), or patients with compromised renal function, concomitant use of UPERIO 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 UPERIO who are taking NSAIDs concomitantly.

Lithium: The potential for a drug interaction between UPERIO and lithium has not been investigated. 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 during concomitant use with UPERIO. If a diuretic is also used, the risk of lithium toxicity may be increased further.

Furosemide: Co-administration of UPERIO and furosemide had no effect on the pharmacokinetics of UPERIO but reduced Cmax and AUC of furosemide by 50% and 28%, respectively. While there was no relevant change in urine volume, the urinary excretion of sodium was reduced within 4 hours and 24 hours after co-administration. The average daily dose of furosemide was unchanged from baseline until the end of the PARADIGM-HF study in patients treated with UPERIO.

Nitrates, e.g. nitroglycerine: There was no drug-drug interaction between UPERIO and intravenously administered nitroglycerin with regard to blood pressure reduction. Co-administration of nitroglycerin and UPERIO 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 UPERIO is co-administered with sublingual, oral or transdermal nitrates. In general no dose adjustment is required.

OATP and MRP2 Transporters: The active metabolite of sacubitril (sacubitrilat) and valsartan are OATP1B1, OATP1B3, OAT1 and OAT3 substrates; valsartan is also a MRP2 substrate. Therefore, co-administration of UPERIO with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampin, cyclosporine), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure to sacubitrilat or valsartan, respectively. Exercise appropriate care when initiating or ending concomitant treatment with such drugs.

Metformin: Co-administration of UPERIO with metformin reduced both Cmax and AUC of metformin by 23%. The clinical relevance of these findings is unknown. Therefore, when initiating therapy with UPERIO in patients receiving metformin, the clinical status of the patient should be evaluated.

No significant interactions

No clinically meaningful drug-drug interaction was observed upon co-administration of UPERIO and digoxin, warfarin, hydrochlorothiazide, amlodipine, omeprazole, carvedilol or a combination of levonorgestrel/ethinyl estradiol. No interaction is expected with atenolol, indomethacin, glyburide, or cimetidine.

CYP 450 Interactions: In vitro metabolism studies indicate that the potential for CYP 450 - based drug interactions is low since there is limited metabolism of UPERIO via the CYP450 enzymes. UPERIO does not induce or inhibit CYP450 enzymes.

Females of child-bearing potential, pregnancy, breast-feeding and fertility

Females of child-bearing potential (and contraceptive measures if applicable)

Female patients of child-bearing potential should be advised about the consequences of exposure to UPERIO during pregnancy and to use contraception during treatment with UPERIO and for 1 week after their last dose.

Pregnancy

As for other drugs that also act directly on the RAAS, UPERIO must not be used during pregnancy (see section Contraindications). UPERIO exerts its effects via angiotensin II antagonism. As a result, a risk to the fetus cannot be excluded. There have been reports of injury to the developing fetus (e.g. spontaneous abortion, oligohydramnios and newborn renal dysfunction), when pregnant women have taken valsartan. Patients should be advised to discontinue UPERIO as soon as pregnancies occur and to inform their physicians.

Breast-feeding

It is not known whether UPERIO is excreted in human milk. The components of UPERIO, sacubitril and valsartan, were excreted in the milk of lactating rats (see section Non-clinical). Because of the potential risk for adverse drug reactions in breastfed newborns/infants, UPERIO is not recommended during breastfeeding. A decision should be made whether to abstain from breast-feeding or to discontinue UPERIO while breast-feeding, taking into account the importance of UPERIO to the mother.

Fertility

There are no available data on the effect of UPERIO on human fertility. No impairment of fertility was demonstrated in studies with UPERIO in male and female rats (see section Non-clinical).

Effects on ability to drive and use machines

UPERIO 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.

Overdosage

Limited data are available with regards to overdosage in human subjects with UPERIO. In healthy volunteers, a single dose of UPERIO 1200 mg, and 900 mg multiple doses (14 days) have been studied and were well tolerated.

Hypotension is the most likely symptom of overdosage due to the blood pressure lowering effects of UPERIO. Symptomatic treatment should be provided.

UPERIO is unlikely to be removed by hemodialysis due to high protein binding.

Clinical pharmacology

Pharmacotherapeutic group, ATC

Agents acting on the renin-angiotensin system; angiotensin II antagonists, other combinations, ATC code: C09DX04

Mechanism of action (MOA)

UPERIO exhibits the novel mechanism of action of an angiotensin receptor neprilysin inhibitor (ARNI) by simultaneously inhibiting neprilysin (neutral endopeptidase; NEP) via sacubitrilat, the active metabolite of the prodrug sacubitril, and by blocking the angiotensin II type-1 (AT1) receptor via valsartan. The complementary cardiovascular benefits and renal effects of UPERIO in heart failure patients are attributed to the enhancement of peptides that are degraded by neprilysin, such as natriuretic peptides (NP), by sacubitrilat and the simultaneous inhibition of the deleterious 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), thereby promoting 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. Sustained activation of the renin-angiotensin-aldosterone system results in vasoconstriction, renal sodium and fluid retention, activation of cellular growth and proliferation, and subsequent maladaptive cardiovascular remodeling. Valsartan inhibits detrimental cardiovascular and renal effects of angiotensin II by selectively blocking the AT1 receptor, and also inhibits angiotensin II-dependent aldosterone release.

Pharmacodynamics (PD)

The pharmacodynamic effects of UPERIO were evaluated after single and multiple dose administrations in healthy subjects and in patients with heart failure, and are consistent with simultaneous neprilysin inhibition and RAAS blockade. In a 7-day valsartan-controlled study in patients with reduced ejection fraction (HFrEF), administration of UPERIO resulted in an initial increase in natriuresis, increased urine cGMP, and decreased plasma MR-proANP and NT-proBNP compared to valsartan. In a 21-day study in HFrEF patients, UPERIO significantly increased urine ANP and cGMP and plasma cGMP, and decreased plasma NT-proBNP, aldosterone and endothelin-1 compared to baseline. UPERIO also blocked the AT1-receptor as evidenced by increased plasma renin activity and plasma renin concentrations. In PARADIGM-HF, UPERIO decreased plasma NT-proBNP and increased plasma BNP and urine cGMP compared with enalapril. While BNP is a neprilysin substrate, NT-proBNP is not. Therefore, NT-proBNP (but not BNP) is a suitable biomarker for monitoring of heart failure patients treated with UPERIO.

In a thorough QTc clinical study in healthy male subjects, single doses of 400 mg and 1200 mg UPERIO had no effect on cardiac repolarization.

Neprilysin is one of multiple enzymes involved in the clearance of amyloid-beta (A-beta) from the brain and cerebrospinal fluid (CSF). Administration of UPERIO 400 mg once daily for 2 weeks to healthy subjects was associated with an increase in CSF A-beta 1-38 compared to placebo; there were no changes in concentrations of CSF A-beta 1-40 and 1-42. The clinical relevance of this finding is unknown (see section Nonclinical studies).

Pharmacokinetics (PK)

Absorption

Following oral administration, UPERIO dissociates into sacubitril, which is further metabolized to sacubitrilat, and valsartan, which reach peak plasma concentrations in 0.5 hours, 2 hours, and 1.5 hours, respectively. The oral absolute bioavailability of sacubitril and valsartan is estimated

to be ≥ 60% and 23%, respectively. The valsartan in Uperio is more bioavailable than the valsartan in other marketed tablet formulations.

Following twice daily dosing of UPERIO, steady state levels of sacubitril, sacubitrilat, and valsartan are reached in 3 days. At steady state, sacubitril and valsartan do not accumulate significantly, while sacubitrilat accumulates by 1.6-fold. UPERIO administration with food has no clinically significant impact on the systemic exposures of sacubitril, sacubitrilat and valsartan. Although there is a decrease in exposure to valsartan when UPERIO is administered with food, this decrease is not accompanied by a clinically significant reduction in the therapeutic effect. UPERIO can therefore be administered with or without food.

Distribution

UPERIO is highly bound to plasma proteins (94% - 97%). Based on the comparison of plasma and CSF exposures, sacubitrilat does cross the blood brain barrier to a limited extent (0.28%). UPERIO has an apparent volume of distribution ranging from 75 L to 103 L.

Biotransformation/metabolism

Sacubitril is readily converted to sacubitrilat by esterases; sacubitrilat is not further metabolized to a significant extent. Valsartan is minimally metabolized, as only about 20% of the dose is recovered as metabolites. A hydroxyl metabolite has been identified in plasma at low concentrations (<10%). Since CYP450 enzyme mediated metabolism of sacubitril and valsartan is minimal, co-administration with drugs that impact CYP450 enzymes is not expected to impact the pharmacokinetics.

Elimination

Following oral administration, 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 feces.

Sacubitril, sacubitrilat, and valsartan are eliminated from plasma with a mean 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, sacubitrilat, and valsartan are linear in the dose range tested (50 - 400 mg of UPERIO).

Special populations

Elderly patients (aged over 65 years)

The exposures of sacubitrilat and valsartan are increased in elderly subjects by 42% and 30%, respectively, compared to younger subjects. However, this is not associated with clinically relevant effects and therefore no dosage adjustment is necessary.

Pediatric patients (aged below 18 years)

UPERIO has not been studied in pediatric patients.

Impaired renal function

A correlation was observed between renal function and systemic exposure to sacubitrilat in patients with mild (60 ml/min/1.73 m^2 ≤ eGFR <90 ml/min/1.73 m^2) to severe renal impairment. The exposure of sacubitrilat 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 largest group of patients enrolled in PARADIGM-HF). The exposure of valsartan was similar in patients with moderate and severe renal impairment compared to patients with mild renal impairment.

No studies have been performed in patients undergoing dialysis. However, sacubitrilat and valsartan are highly bound to plasma protein and therefore unlikely to be effectively removed by dialysis.

Impaired hepatic function

In patients with mild to moderate hepatic impairment, the exposures of sacubitril increased by 1.5- and 3.4- fold, sacubitrilat increased by 1.5- and 1.9-fold, and valsartan increased by 1.2-fold and 2.1-fold, respectively, compared to matching healthy subjects. However, in patients with mild to moderate hepatic impairment, the exposures of free concentrations of sacubitrilat 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 matching healthy subjects. UPERIO 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 50 mg twice daily. UPERIO has not been studied in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (see sections Contraindications and Warnings and Precautions).

Ethnic groups

The pharmacokinetics of UPERIO (sacubitril, sacubitrilat and valsartan) are comparable across different race and ethnic groups (Caucasians, Blacks, Asians, Japanese and others).

Effect of gender

The pharmacokinetics of UPERIO (sacubitril, sacubitrilat and valsartan) are similar between male and female subjects.

Clinical studies

Dosing in clinical trials was based on the total amount of both components of Uperio, i.e., 24/26 mg, 49/51 mg and 97/103 mg were referred to as 50 mg, 100 mg, and 200 mg, respectively.

PARADIGM-HF

PARADIGM-HF was a multinational, randomized, double-blind study of 8,442 patients comparing UPERIO to enalapril, both given to adult patients with chronic heart failure, NYHA class II – IV, and systolic dysfunction (left ventricular ejection fraction ≤ 40%), in addition to

other heart failure therapy. The primary endpoint was the composite of cardiovascular (CV) death or hospitalization for heart failure (HF).

Prior to study participation, patients were well treated with standard of care therapy which included ACE inhibitors/ARBs (>99%), beta-blockers (94%), mineralocorticoid antagonists (58%), and diuretics (83%). The median follow- up duration was 27 months and patients were treated for up to 4.3 years.

Patients were required to discontinue their existing ACE inhibitor or ARB therapy and entered a sequential single-blind run-in period during which patients received treatment with enalapril 10 mg twice daily, followed by treatment with UPERIO 100 mg twice daily, increasing to 200 mg twice daily. Patients were then randomized to the double-blind period of the study to receive either UPERIO 200 mg or enalapril 10 mg twice daily [UPERIO (n= 4209); enalapril (n= 4233)].

The mean age of the population studied was 64 years of age and 19% were 75 years or older. At randomization, 70% of patients were NYHA Class II and 25% were Class III/IV.

In the UPERIO group, 76% of patients remained on the target dose of 200 mg twice daily at 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 at the end of the study (mean daily dose of 18.9 mg).

UPERIO demonstrated clinically relevant and statistically significant superiority to enalapril, reducing the risk of cardiovascular death or heart failure hospitalizations by 20% (hazard ratio (HR): 0.80, 95% CI [0.73; 0.87], 1-sided p =0.0000002) versus enalapril. This effect was observed early and was sustained throughout the duration of the trial. The absolute risk reduction was 4.69%. A statistically significant reduction for CV death and first HF hospitalization was observed (CV death, RRR 20%, HR 0.80; 95% CI [0.71, 0.89], 1-sided p= 0.00004; and hospitalization for heart failure RRR 21%; HR 0.79; 95% CI 0.71, 0.89], 1-sided p= 0.00004); see Table 2 and Figure 1. Sudden death accounted for 45% of cardiovascular deaths and was reduced by 20% in UPERIO treated patients compared to enalapril treated patients (HR 0.80, p= 0.0082). Pump failure accounted for 26% of cardiovascular deaths and was reduced by 21% in UPERIO treated patients compared to enalapril treated patients (HR 0.79, p = 0.0338).

This risk reduction was consistently observed across subgroups including: age, gender, race, geography, NYHA class, ejection fraction, renal function, history of diabetes or hypertension, prior heart failure therapy, and atrial fibrillation.

UPERIO also significantly reduced all-cause mortality by 16% compared with enalapril (RRR 16%, HR 0.84; 95% CI [0.76 to 0.93], 1-sided p=0.0005) (Table 2). The absolute risk reduction was 2.84%.

Table 3 Treatment effect for the primary composite endpoint, its components and all-cause mortality

	Uperio N = 4187# n (%)	**Enalapril** N = 4212# n (%)	**Hazard Ratio (95% CI)**	**Relative Risk Reduction**	**p-value** ***

Primary Composite Endpoint of CV Death and Heart Failure Hospitalizations*	914 (21.83)	1117 (26.52)	0.80 (0.73, 0.87)	20%	0.0000002
Individual Components of the primary composite endpoint					
CV Death **	558 (13.33)	693 (16.45)	0.80 (0.71, 0.89)	20%	0.00004
First Heart Failure Hospitalization	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 first event.

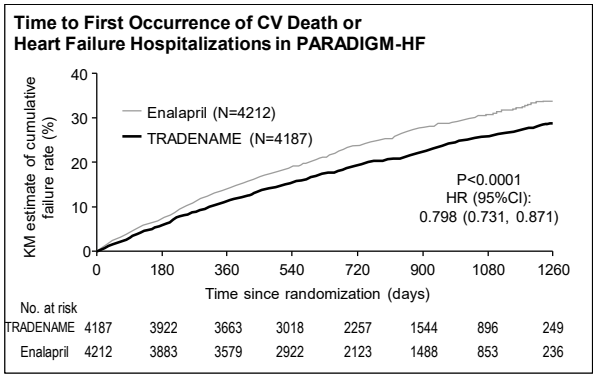
** CV death includes all patients who died up to the cut-off date irrespective of previous hospitalization.

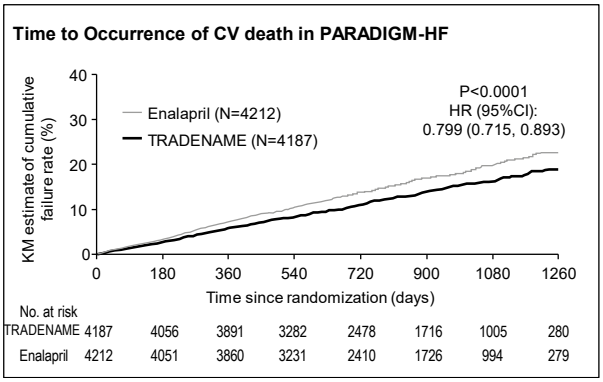
*** One-sided p-value.

♯ Full analysis set

The Kaplan-Meier presented in the figure below (left) shows time to first occurrence of the primary composite endpoint of CV death or heart failure hospitalization. UPERIO treatment effect was evident early and sustained for the duration of the study. The Kaplan-Meier figure presented below (right) shows the time to CV death endpoint.

Figure 1 Kaplan-Meier curves for the primary composite endpoint and the CV death component





Overall, there were fewer all cause hospital admissions in patients treated with UPERIO compared to enalapril, including a 12% relative risk reduction for the first hospitalization (HR 0.88 [95% CI: 0.82, 0.94], P<0.001), and a 16% relative rate reduction for total number of hospitalizations (RR 0.84 [95% CI: 0.78, 0.91], P<0.001).

UPERIO demonstrated a significantly better clinical summary score for the domains related to HF symptoms and physical limitations as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ), a self- administered questionnaire. More patients had improved NYHA functional class from baseline to Month 8 on UPERIO (16%) compared to enalapril (14%), and fewer patients had worsened NYHA functional class (10% vs 13%, respectively).

TITRATION

TITRATION was a 12 week safety and tolerability study in 538 patients with chronic heart failure (NYHA class II – IV) and systolic dysfunction (left ventricular ejection fraction ≤ 35%) naïve to ACE inhibitor or ARB therapy or on varying doses of ACE inhibitors or ARBs prior to study entry. Patients initiated UPERIO 50 mg twice daily, were uptitrated to 100 mg twice daily and then to the target dose of 200 mg twice daily with either a 3-week or 6-week regimen.

Overall, 76% of patients achieved and maintained the target dose of UPERIO 200 mg twice daily without any dose interruption or down-titration over 12-weeks. More patients who were naïve to previous ACE inhibitor or ARB therapy or on low dose therapy (equivalent to < 10 mg of enalapril/ day) were able to achieve and maintain UPERIO 200 mg when uptitrated over 6 weeks versus 3 weeks.

Non-clinical safety data

Non-clinical safety studies conducted with UPERIO included assessment of safety pharmacology, repeated dose toxicity genotoxicity carcinogenicity and reproductive and development toxicity UPERIO had no adverse effects on vital organ systems. Most findings seen in repeated toxicity studies were reversible and attributable to the pharmacology of AT_1 receptor blockade.

Carcinogenicity, mutagenesis and genetic toxicity

Carcinogenicity studies conducted in mice and rats with sacubitril and valsartan did not identify any carcinogenic potential for UPERIO. The doses of sacubitril studied (high dose of 1200 and 400 mg/kg/day in mice and rats, respectively) were about 29 and 19 times, respectively, the maximum recommended human dose (MRHD) on a mg/m^2 basis. The doses of valsartan studied (high dose of 160 and 200 mg/kg/day in mice and rats, respectively) were about 4 and 10 times, respectively, the maximum recommended human dose on a mg/m^2 basis.

Mutagenicity and clastogenicity studies conducted with UPERIO, sacubitril, and valsartan did not reveal any effects at either the gene or chromosome level.

Fertility, reproduction and development

UPERIO did not show any effects on fertility or early embryonic development in rats up to a dose of 150 mg/kg/day (≤1.0 fold and ≤0.18 fold the MRHD on the basis of valsartan and sacubitrilat AUC, respectively).

UPERIO treatment during organogenesis resulted in increased embryo-fetal lethality in rats at doses ≥100 mg/kg/day [≤0.72 fold the MRHD on the basis of AUC] and rabbits at doses ≥ 10 mg/kg/day [2 fold and 0.03 fold the MRHD on the basis of valsartan and sacubitrilat AUC, respectively]. UPERIO is teratogenic based on a low incidence of fetal hydrocephaly, associated with maternally toxic doses, which was observed in rabbits at a UPERIO dose of ≥ 10 mg/kg/day. The adverse embryo-fetal effects of UPERIO are attributed to the angiotensin receptor antagonist activity (see section Females of child-bearing potential, pregnancy, breast-feeding and fertility).

Pre- and postnatal development studies in rats conducted with sacubitril at doses up to 750 mg/kg/day [2.2 fold the MRHD on the basis of AUC] and valsartan at doses up to 600 mg/kg/day [0.86 fold the MRHD on the basis of AUC] indicate that treatment with UPERIO during organogenesis, gestation and lactation may affect pup development and survival.

Other preclinical findings

UPERIO

The effects of UPERIO on amyloid-beta concentrations in CSF and brain tissue were assessed in young (2 to 4 years old) cynomolgus monkeys treated with UPERIO (50 mg/kg/day) for two weeks. In this study CSF A-beta clearance in cynomolgus monkeys was reduced, increasing CSF A-beta 1-40, 1-42, and 1-38 levels; there was no corresponding increase in A-beta levels in the brain. Increases in CSF A-beta 1-40 and 1-42 were not observed in a two-week healthy volunteer study in humans. Additionally, in a toxicology study in cynomolgus monkeys treated with UPERIO at 300 mg/kg/day for 39-weeks, there was no evidence for the presence of amyloid plaques in the brain. Amyloid content was not, however, measured quantitatively in this study.

Sacubitril

In juvenile rats treated with sacubitril (postnatal days 7 to 70), there was a reduction in age-related bone mass development and bone elongation. A study in adult rats showed only a minimal transient inhibitory effect on bone mineral density but not on any other parameters relevant for bone growth, suggesting no relevant effect of sacubitril on bone in adult patient populations under normal conditions. However, a mild transient interference of sacubitril with the early phase of fracture healing in adults cannot be excluded.

Valsartan

In juvenile rats treated with valsartan (postnatal days 7 to 70), doses as low as 1 mg/kg/day produced persistent irreversible kidney changes consisting of tubular nephropathy (sometimes accompanied by tubular epithelial necrosis) and pelvic dilatation. These kidney changes represent an expected exaggerated pharmacological effect of angiotensin converting enzyme inhibitors and angiotensin II type 1 blockers; such effects are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after conception in humans.

Pharmaceutical information

Incompatibilities

Not applicable.

Special precautions for storage

Storage requirements: Do not store above 30°C. Store in the original package to protect from moisture.

UPERIO must be kept out of the reach and sight of children.

Shelf-life

The expiry date is indicated on the packaging.

Instructions for use and handling

Not applicable.

Special precautions for disposal

Not applicable.

Pack size

UPERIO 50 mg
Box, 2 blisters @ 14 film coated tablets, Reg. No.
UPERIO 100 mg
Box, 2 blisters @ 14 film coated tablets, Reg. No.
UPERIO 200 mg
Box, 4 blisters @ 7 film coated tablets, Reg. No.

HARUS DENGAN RESEP DOKTER

To be dispensed only on the prescription of a physician

Manufactured by Novartis Farma S.p.A, Torre Annunziata, Italy for Novartis Pharma AG, Basel, Switzerland.

Imported by PT Novartis Indonesia, Jakarta, Indonesia.

Based on CDS 10-Aug-2015 & 10-Jul-2017 (safety) and PUBS 148630

UPERIO®

(sacubitril valsartan sodium hydrate)

Tablet salut selaput 50, 100, 200 mg

Informasi Produk untuk Pasien

DISETUJUI OLEH BPOM: 06/03/2023

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EREG100005VR12200088

Mohon brosur dibaca dengan seksama sebelum Anda menggunakan obat ini

Mohon agar brosur ini disimpan. Anda mungkin akan membutuhkan brosur ini untuk dibaca kembali.

Jika Anda ingin bertanya lebih lanjut, mohon hubungi dokter atau apoteker Anda.

Obat ini diresepkan untuk Anda. Mohon jangan berikan obat ini kepada orang lain meskipun mereka memiliki gejala penyakit yang serupa dengan Anda.

Jika Anda mengalami efek samping yang berat, atau jika Anda mengalami efek samping yang tidak tertera pada brosur ini, mohon informasikan kepada dokter ataupun apoteker Anda.

Daftar Isi

1 Apakah UPERIO® dan apa kegunaanya

Apakah UPERIO®

UPERIO® merupakan penghambat reseptor angiotensin neprilisin/ *Angiotensin Receptor Neprilysin Inhibitor (ARNI)*, yang terdiri dari sacubitril (penghambat neprilisin), dan valsartan (penghambat reseptor angiotensin/*angiotensin receptor blocker* (ARB)). Kedua zat aktif tersebut membantu dalam pengobatan gagal jantung.

Apakah kegunaan UPERIO®

UPERIO® digunakan untuk pengobatan gagal jantung pada pasien dewasa.

Gagal jantung merupakan suatu kondisi dimana otot jantung tidak dapat memompa darah dengan kuat untuk mensuplai darah ke seluruh tubuh. Gejala gagal jantung yang sering terjadi adalah nafas pendek dan pembengkakan pada kaki dan lengan karena terjadinya penimbunan cairan tubuh.

Bagaimana cara kerja UPERIO®

UPERIO® bekerja dengan cara menghambat efek neprilisin melalui sacubitril dan reseptor angiotensin-II melalui valsartan. Sebagai dampaknya, pembuluh darah akan melebar dan timbunan air di dalam tubuh akan berkurang, yang mana mekanisme ini berguna dalam pengobatan gagal jantung.

Jika Anda memiliki pertanyaan terkait dengan cara kerja UPERIO® ataupun alasan mengapa Anda diresepkan obat ini, mohon konsultasikan kepada dokter atau apoteker Anda

2 Apa yang harus diketahui sebelum dan ketika mengkonsumsi UPERIO®

Ikuti semua petunjuk yang diberikan dokter dengan seksama. Petunjuk dokter tersebut mungkin dapat berbeda dengan informasi umum yang tercantum pada brosur ini.

Tidak diperbolehkan mengkonsumsi UPERIO®

- **Jika Anda mengalami** reaksi **alergi** secara tidak wajar terhadap sacubitril atau valsartan atau zat tambahan lain yang terkandung dalam obat (tertulis pada Bagian 6). Jika Anda berfikir bahwa Anda kemungkinan mengalami alergi, mohon agar meminta saran kepada dokter Anda
- **Jika Anda sedang menggunakan** obat-obatan lain untuk penanganan tekanan darah tinggi atau gagal jantung yang disebut sebagai *Angiotensin Converting Enzyme (ACE) Inhibitors*. Mohon untuk tidak mengkonsumsi UPERIO® selama 36 jam setelah penggunaan dosis terakhir dari kelompok obat-obatan ini (Lihat "Penggunaan Obat Lain")
- Jika Anda mengalami reaksi yang disebut sebagai angioedema (pembengkakan pada wajah, bibir, lidah dan/atau tenggorokan, kesulitan bernafas) ketika sedang mengkonsumsi *ACE inhibitor* atau *ARB*
- Jika Anda memiliki sejarah penyakit angioedema turunan di dalam keluarga Anda atau mengalami angioedema yang tidak diketahui penyebabnya
- Jika Anda menderita diabetes tipe 2 (kadar gula yang tinggi dalam darah) dan sedang mengkonsumsi obat yang mengandung zat aktif aliskiren untuk menurunkan tekanan darah (Lihat "Penggunaan Obat Lain") atau pada pasien mengalami gangguan ginjal (eGFR <60 ml/min/1.73 m^2)
- Jika Anda mengalami gangguan hati yang berat, sirosis biliari dan kolestasis
- Jika Anda sedang hamil.

Jika hal ini terjadi pada Anda, mohon untuk tidak mengkonsumsi UPERIO® dan beritahukan kepada dokter Anda.

Perhatian khusus dalam penggunaan UPERIO®

Jika hal ini terjadi pada Anda, mohon untuk memberitahukan kepada dokter atau apoteker Anda sebelum Anda mengkonsumsi UPERIO®:

- Jika Anda memiliki penyakit ginjal yang berat.
- Jika Anda memiliki penyakit hati.
- Jika Anda mengalami reaksi yang disebut sebagai *angioedema* (pembengkakan pada wajah, bibir, lidah dan/atau tenggorokan, kesulitan bernafas).
- Jika Anda mengalami pembengkakan pada lidah dan/atau tenggorokan dan kesulitan bernafas, **mohon agar menghentikan penggunaan UPERIO® dan segera hubungi dokter Anda.**

- Jika Anda sedang mengkonsumsi obat-obatan untuk penanganan tekanan darah tinggi atau gagal jantung yang disebut sebagai *ACE-inhibitor*, ARB, atau aliskiren.
- Jika Anda mengalami tekanan darah rendah atau sedang menggunakan obat-obatan untuk menurunkan tekanan darah (seperti diuretik) **atau** Anda sedang mengalami muntah atau diare.
- Jika Anda sedang mengkonsumsi obat-obatan untuk meningkatkan kadar kalium dalam darah (hiperkalemia). Obat-obatan tersebut termasuk suplemen kalium, pengganti garam yang mengandung kalium dan heparin. Sangatlah penting bagi dokter Anda untuk memeriksa kadar kalium dalam darah secara reguler selama pengobatan menggunakan UPERIO®.
- Jika arteri ginjal Anda menyempit.

Penggunaan Obat Lain

Sebelum Anda mengkonsumsi UPERIO®, mohon agar memberitahukan kepada dokter atau apoteker Anda jika Anda sedang ataupun baru saja mengkonsumsi obat-obatan lain termasuk penggunaan obat non-resep, karena obat-obat tersebut mungkin dapat berinteraksi dengan UPERIO®:

- Mohon untuk tidak mengkonsumsi UPERIO® secara bersamaan dengan *ACE inhibitors*. Jika Anda sedang mengkonsumsi *ACE inhibitor*, mohon untuk menunggu selama 36 jam setelah penggunaan dosis terakhir sebelum Anda menggunakan UPERIO® (Lihat "Tidak diperbolehkan mengkonsumsi UPERIO®"). Jika Anda menghentikan penggunaan UPERIO®, mohon untuk menunggu selama 36 jam setelah penggunaan dosis terakhir sebelum Anda mengkonsumsi *ACE inhibitor*.
- Obat-obatan lain yang digunakan untuk penanganan gagal jantung atau menurunkan tekanan darah tinggi seperti *ACE inhibitor*, ARB atau aliskiren.
- Obat-obatan yang digunakan untuk menurunkan kadar kolesterol yang disebut sebagai golongan 'statin' (contohnya: atorvastatin).
- Sildenafil, yaitu obat yang digunakan untuk pengobatan disfungsi ereksi atau hipertensi paru.
- Obat-obatan yang dapat meningkatkan kadar kalium dalam darah. Obat-obatan tersebut termasuk suplemen kalium, pengganti garam yang mengandung kalium dan heparin. Dokter Anda akan memeriksa kadar kalium dalam darah secara periodik selama pengobatan menggunakan UPERIO®.
- Beberapa jenis obat penghilang rasa nyeri yang disebut sebagai anti inflamasi non-steroid/ *non-steroidal anti-inflammatory medicines (NSAIDs)* atau *Selective Cyclooxygenase-2 Inhibitors (Cox-2 Inhibitors)*. Jika Anda sedang mengkonsumsi obat-obatan tersebut, dokter Anda mungkin akan memeriksa fungsi ginjal Anda sebelum memulai pengobatan dan melakukan penyesuaian dosis penggunaan.
- Lithium, yaitu obat yang digunakan untuk penanganan beberapa jenis depresi.
- Furosemide, yaitu obat diuretik yang digunakan untuk meningkatkan jumlah produksi urin.
- Nitrogliserin, obat untuk terapi angina

- Beberapa antibiotik (kelompok rifamisin), yaitu obat yang digunakan untuk perlindungan terhadap reaksi penolakan terhadap organ yang ditransplantasi (siklosporin) atau obat antiretroviral yang digunakan penanganan infeksi HIV/AIDS (ritonavir). Obat-obatan ini dapat meningkatkan efek dari valsartan.
- Metformin, obat untuk diabetes.

Mohon untuk menanyakan kepada dokter atau apoteker Anda jika Anda merasa tidak yakin bahwa obat yang sedang Anda gunakan saat ini termasuk dalam daftar obat-obatan yang disebutkan diatas.

Penggunaan UPERIO® bersama makanan

UPERIO® dapat dikonsumsi bersamaan atau tanpa makanan.

Pasien usia lanjut (usia 65 tahun keatas)

Jika Anda berusia 65 tahun keatas, Anda tetap dapat mengkonsumsi UPERIO® dengan dosis yang sama dengan dosis dewasa

Pasien anak dan remaja (kurang dari 18 tahun)

UPERIO® tidak dapat dikonsumsi untuk pasien anak dan remaja (dibawah 18 tahun).

Wanita yang mungkin mengalami kehamilan

Wanita yang mungkin mengalami kehamilan sebaiknya menggunakan kontrasepsi selama menggunakan UPERIO® dan selama 1 minggu setelah penggunaan dosis terakhir. Anda sebaiknya memberitahu dokter Anda tentang pilihan terapi jika Anda sedang merencanakan kehamilan.

Wanita hamil dan menyusui

Anda tidak diperbolehkan untuk mengkonsumsi UPERIO® jika Anda sedang hamil. Anda harus berhenti mengkonsumsi UPERIO® sesaat anda hamil ketika terapi sedang berjalan dan memberitahu dokter Anda.

Menyusui juga tidak direkomendasikan selama mengkonsumsi UPERIO®. Mohon untuk memberitahukan kepada dokter Anda jika Anda sedang dalam masa menyusui.

Mengemudi dan menggunakan mesin

Sebelum Anda mengemudi kendaraan, menggunakan alat atau mengoperasikan mesin, atau melakukan aktivitas yang membutuhkan konsentrasi, pastikan Anda mengetahui pengaruh UPERIO® terhadap Anda. Jika Anda mengalami pusing atau merasa terlalu lelah ketika Anda mengkonsumsi obat ini, jangan mengemudikan kendaraan, sepeda atau menggunakan alat atau mesin.

3 Bagaimana cara mengkonsumsi UPERIO®

Mohon untuk selalu mengkonsumsi obat ini sesuai dengan petunjuk dokter Anda. Mohon tanyakan kepada dokter atau apoteker Anda jika Anda merasa tidak yakin.

Mohon untuk tidak melebihi dosis yang direkomendasikan oleh dokter Anda.

UPERIO® diminum secara oral.

Berapa banyak UPERIO® yang dikonsumsi

Dosis umum yang direkomendasikan adalah 200 mg dua kali sehari (satu tablet pada pagi hari dan satu tablet pada sore hari).

Anda biasanya akan memulai dengan penggunaan dosis 50 mg atau 100 mg dua kali sehari (satu tablet pada pagi hari dan satu tablet pada sore hari). Dokter Anda akan menentukan dosis permulaan sesuai dengan obat yang Anda gunakan sebelumnya. Dokter Anda kemudian akan melakukan penyesuaian dosis sesuai dengan respon terhadap pengobatan sampai dengan tercapainya dosis optimal.

Jika Anda menggunakan obat-obatan *ACE inhibitor* sebelumnya, mohon untuk tidak mengkonsumsi UPERIO® selama 36 jam setelah penggunaan dosis terakhir *ACE inhibitor* tersebut. Jika Anda sedang menggunakan ARB, mohon untuk menghentikan pengobatan.

Kapan mengkonsumsi UPERIO®

Mengkonsumsi UPERIO® pada saat yang sama setiap hari akan memudahkan Anda untuk mengingat waktu penggunaannya

Bagaimana cara mengkonsumsi UPERIO®

Tablet UPERIO® ditelan melalui mulut.

Tablet salut selaput tersebut sebaiknya tidak dibelah atau dibagi dua.

Berapa lama UPERIO® dikonsumsi

Mohon untuk tetap mengkonsumsi UPERIO® selama dokter Anda masih menyarankan penggunaannya

Jika Anda memiliki pertanyaan mengenai berapa lama penggunaan UPERIO®, mohon konsultasikan pada dokter atau apoteker Anda.

Jika Anda mengkonsumsi UPERIO® lebih dari yang seharusnya

Jika Anda secara tidak sengaja mengkonsumsi dosis UPERIO® terlalu banyak, **mohon konsultasikan dengan dokter Anda.**

Jika Anda lupa mengkonsumsi UPERIO®

Jika Anda lupa dalam mengkonsumsi satu dosis, mohon agar sesegera mungkin mengkonsumsi satu dosis tersebut, lalu gunakan dosis berikutnya seperti biasanya. Jangan mengkonsumsi dosis ganda untuk menggantikan dosis yang terlupa.

Jika Anda berhenti mengkonsumsi UPERIO®

Penghentian penggunaan UPERIO® dapat menyebabkan penyakit yang Anda derita semakin memburuk. Mohon untuk tidak menghentikan penggunaan jika dokter Anda tidak menyarankannya.

Jika pengobatan menggunakan UPERIO® dihentikan dan Anda kemudian diresepkan obat *ACE-inhibitor*, mohon untuk tidak memulai penggunaan *ACE inhibitor* sampai dengan 36 jam setelah penggunaan dosis UPERIO® terakhir.

4 Efek samping yang mungkin terjadi

Seperti pada penggunaan semua obat, pasien yang menggunakan UPERIO® dapat mengalami efek samping, walaupun tidak semua pasien akan mengalaminya

Beberapa efek samping yang dapat menjadi serius

Mohon agar menghentikan penggunaan UPERIO® dan segera beritahukan kepada dokter Anda jika Anda mengalami beberapa gejala dibawah ini yang merupakan tanda-tanda reaksi alergi yang disebut "*angioedema*":

- Pembengkakan pada wajah, lidah atau tenggorokan;
- Kesulitan menelan;
- Gatal-gatal dan kesulitan bernafas.

Jika Anda mengalami efek samping yang serius, **mohon agar menghentikan penggunaan UPERIO® dan segera beritahukan kepada dokter Anda.**

Sering terjadi: *dapat terjadi pada lebih dari 1 dari setiap 10 pasien*

- Penurunan tekanan darah tinggi;
- Gangguan ginjal (tanda-tanda kegagalan ginjal);
- Kadar kalium yang tinggi dalam darah yang ditunjukkan pada saat tes darah.

Umum terjadi: *dapat terjadi hingga 1 dari setiap 10 pasien*

- Batuk
- Pusing
- Gangguan ginjal berat
- Kadar kalium yang rendah dalam darah yang ditunjukkan dari tes darah
- Diare
- Kelelahan
- Sakit kepala
- Kehilangan kesadaran secara tiba-tiba
- Mual
- Rasa lemah

- Tekanan darah rendah pada saat berganti posisi dari duduk atau berbaring ke posisi berdiri
- Sensasi berputar.
- Rendahnya jumlah sel darah merah (yang ditunjukkan dari hasil tes darah)
- Rendahnya kadar gula dalam darah (yang ditunjukkan dari hasil tes darah)
- Gastritis (nyeri perut, mual)

Jarang terjadi: *dapat terjadi hingga 1 pasien dari setiap 100 pasien*

- Rasa pusing pada saat berganti posisi dari duduk atau berbaring ke posisi berdiri (atau sebaliknya);
- Pembengkakan pada wajah dan tenggorokan (angioedema).
- Reaksi alergi ditandai dengan ruam dan gatal

Tidak diketahui: *frekuensi tidak dapat diestimasi dari data yang tersedia*

- Sulit bernapas atau menelan, kulit kemerahan, gatal-gatal, pusing (tanda-tanda hipersensitifitas, reaksi anafilaktik)

Jika Anda mengetahui adanya efek samping lain yang tidak tertera pada brosur ini, harap menginformasikannya dengan dokter atau apoteker atau praktisi kesehatan Anda.

5 Cara penyimpanan UPERIO®

- Kondisi penyimpanan: disimpan pada suhu tidak lebih dari 30°C
- Mohon untuk tidak menggunakan obat jika kemasannya rusak atau menunjukkan adanya cacat.
- Mohon untuk menjauhkan obat dari jangkauan dan penglihatan anak-anak.
- Mohon untuk menyimpan obat di dalam kemasannya.
- Mohon tidak menggunakan obat setelah tanggal kadaluarsa yang tercantum pada dus obat.

6 Isi dari kemasan dan informasi lain

Apakah isi dari UPERIO®

Zat aktif dari UPERIO® adalah *sacubitril valsartan sodium hydrate*.

Zat tambahan lain dari UPERIO® mikrokristalin selulosa, hidroksipropilselulosa, krospovidon, magnesium stearat (sumber dari tumbuhan), talk dan koloidal silicon dioksida. Zat tambahan salut selaput: hipromelosa, titanium dioksida (E 171), Makrogol 4000, talk, *iron oxide red* (E 172). Untuk salut selaput dari kekuatan 50 and 200 mg: *iron oxide black* (E 172). Untuk salut selaput dari kekuatan 100 mg: *iron oxide yellow* (E 172).

Bagaimana bentuk dari UPERIO® dan isi kemasannya

UPERIO® tersedia dalam bentuk tablet salut selaput dan 3 kekuatan 50 mg, 100 mg, atau 200 mg.

- 50 mg tablet salut selaput berwarna ungu putih ovaloid bikonveks dengan tepi yang miring, tidak bergaris tengah, tercetak “NVR” pada satu sisi dan “LZ” pada sisi yang lain.
- 100 mg tablet salut selaput berwarna kuning pucat ovaloid bikonveks dengan tepi yang miring, tidak bergaris tengah, tercetak “NVR” pada satu sisi dan “L1” pada sisi yang lain.
- 200 mg tablet salut selaput berwarna merah muda terang ovaloid bikonveks dengan tepi yang miring, tidak bergaris tengah, tercetak “NVR” pada satu sisi “L11” pada sisi yang lain.

Kemasan

Uperio 50 mg

Dus, 2 blister @ 14 tablet salut selaput, No. Reg:

Uperio 100 mg

Dus, 2 blister @ 14 tablet salut selaput, No. Reg:

Uperio 200 mg

Dus, 4 blister @ 7 tablet salut selaput, No. Reg:

HARUS DENGAN RESEP DOKTER

Pemegang Nomor Ijin Edar

PT Novartis Indonesia

Pabrik Pembuat

Novartis Farma S.p.A, Torre Annunziata, Italia untuk Novartis Pharma AG, Basel, Swiss

PIL based on BPL 10-Jul-2017 (safety) and PUBS 148630