NOVARTIS

Drug Regulatory Affairs

UPERIO®

50, 100, 200 mg film-coated tablets

Summary of Product Characteristics (SmPC)

Version 1.2

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Uperio®

Uperio® 50 mg film-coated tablets (sacubitril/valsartan)

Uperio® 100 mg film-coated tablets (sacubitril/valsartan.

Uperio® 200 mg film-coated tablets (sacubitril/ valsartan).

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 or local designated active substance name as applicable.

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.

Single dose strengths

Uperio film coated tablets contains 50 mg (sacubitril/valsartan)*.

Uperio film coated tablets contains 100 mg (sacubitril/valsartan)*.

Uperio film coated tablets contains 200 mg (sacubitril/valsartan)*.

* Certain dosage strengths may not be available in all countries.

Fixed dose strengths

Uperio 24 mg/26 mg film-coated tablets*

Each film-coated tablet contains 24.3 mg sacubitril and 25.7 mg

valsartan. Uperio 49 mg/51 mg film-coated tablets*

Each film-coated tablet contains 48.6 mg sacubitril and 51.4 mg

valsartan. Uperio 97 mg/103 mg film-coated tablets*

Each film-coated tablet contains 97.2 mg sacubitril and 102.8 mg valsartan.

*Information may differ in some countries

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 100mg: iron oxide yellow (E 172).

INDICATIONS

Uperio is indicated for the treatment of heart failure (NYHA class II-IV) in patients with systolic dysfunction. Uperio has been shown to reduce the rate of cardiovascular death and heart failure hospitalization compared to enalapril.

Uperio has also been shown to reduce the rate of all-cause mortality compared to enalapril.

Uperio is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or ARB.

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 STUDIES).

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).

Uperio should not be co-administered with an ARB due to the angiotensin II receptor blocking activity of Uperio (see sections WARNINGS AND PRECAUTIONS and 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 is recommended in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2). Caution is recommended when using Uperio in these patients due to limited data (see section CLINICAL PHARMACOLOGY).

No dose adjustment is required in patients with mild (eGFR 60-90 mL/min/1.73 m^2) to moderate (eGFR 30-60 mL/min/1.73 m^2) renal impairment.

Hepatic impairment

A starting dose of 50 mg twice daily is recommended for patients with moderate hepatic impairment (Child-Pugh B classification).

No dose adjustment is required when administering Uperio to patients with mild hepatic impairment (Child-Pugh A classification).

No studies have been conducted in patients with severe hepatic impairment (Child-Pugh C classification). Therefore use of Uperio in these patients is not recommended (see section CLINICAL PHARMACOLOGY).

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).

CONTRAINDICATIONS

- Hypersensitivity to the active substance, sacubitril, valsartan, or to any of the excipients.
- Concomitant use with ACE inhibitors (see sections WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION, and 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 angioedema
- Concomitant use with aliskiren in patients with Type 2 diabetes (see sections WARNINGS AND PRECAUTIONS and INTERACTIONS).
- 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 must not be administered 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 sections CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION, and INTERACTIONS).
- Caution is required while co-administering Uperio with direct renin inhibitors such as aliskiren (see sections CONTRAINDICATIONS and INTERACTIONS). Uperio must not be administered with aliskiren in patients with Type 2 diabetes (see section CONTRAINDICATIONS).
- Uperio should not be co-administered with an ARB due to the angiotensin II receptor blocking activity of Uperio (see sections DOSAGE AND ADMINISTRATION andINTERACTIONS).

Hypotension

Cases of symptomatic hypotension have been reported in patients treated with Uperio during clinical trials. If hypotension occurs, dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g. hypovolemia) should be considered. If hypotension persists despite such measures, the dosage of Uperio should be reduced or the product should be temporarily discontinued (see section DOSAGE AND ADMINISTRATION). Permanent discontinuation of therapy is usually not required**.** 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.

Impaired renal function

As for any drug that acts on the renin-angiotensin-aldosterone system, use of Uperio may be associated with decreased renal function. In PARADIGM-HF, the incidence of clinically relevant renal impairment was low and associated treatment discontinuation was observed less frequently in patients receiving Uperio (0.65%) compared to enalapril (1.28%). Down titration of Uperio should be considered in patients who develop a clinically significant decrease in renal function. Caution should be exercised when administering Uperio in patients with severe renal impairment (see sections DOSAGE AND ADMINISTRATION, and CLINICAL PHARMACOLOGY).

Hyperkalemia

As for any drug that acts on the renin-angiotensin-aldosterone system, use of Uperio may be associated with an increased risk of hyperkalemia. 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 (see section DOSAGE AND ADMINISTRATION).

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 must not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy, or in patients with hereditary 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.

ADVERSE DRUG REACTIONS

Summary of the safety profile

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= 4,203) or enalapril 10 mg (n= 4,229). 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**
Metabolism and nutrition disorders			
Hyperkalemia	11.61	14.00	Very common
Hypokalemia	3.31	2.53	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			
Diarrhea	4.62	4.47	Common
Nausea	2.09	2.36	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)

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 sections CONTRAINDICATIONS, and DOSAGE AND ADMINISTRATION).

Aliskiren: The concomitant use of Uperio with aliskiren is contraindicated in patients with Type 2 diabetes (see section CONTRAINDICATIONS).

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).

Concomitant use with aliskiren should be avoided in patients with renal impairment (eGFR < 60 mL/min/1.73 m^2) (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, 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.

Transporters: The active metabolite of sacubitril (sacubitrilat), and valsartan are OATP1B1, OATP1B3 and OAT3 substrates; valsartan is also a MRP2 substrate. Therefore, co- administration of Uperio with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampin, cyclosporine) 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.

No significant interactions

No clinically meaningful drug-drug interaction was observed upon co-administration of Uperio and furosemide, digoxin, warfarin, hydrochlorothiazide, amlodipine, metformin, omeprazole, carvedilol, intravenous nitroglycerin 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 SAFETY DATA). 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 SAFETY DATA).

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

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 a significant non-sustained 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 NON-CLINICAL SAFETY DATA).

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 75L 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 to 68% of sacubitril (primarily as sacubitrilat) and ~13% of valsartan and its metabolites are excreted in urine; 37 to 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 to 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 tosacubitrilat, but
not to valsartan. In patients with mild (60 mL/min/1.73 m^2 ≤eGFR<90 mL/min/1.73 m^2) to moderate (30 mL/min/1.73 m^2 ≤eGFR<60 mL/min/1.73 m^2) renal impairment, the AUC for sacubitrilat was up to 2-fold higher. No dosage adjustment is required in patients with mild or moderate renal impairment. A 2.7-fold higher AUC for sacubitrilat was observed in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2). A starting dose of 50 mg twice daily is recommended in patients with severe renal impairment. Caution is recommended when administering Uperio to these patients due to limited data.

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. No dosage adjustment is recommended when administering Uperio to patients with mild hepatic impairment (Child- Pugh A classification) including patients with biliary obstructive disorders. A starting dose of 50 mg twice daily is recommended in patients with moderate hepatic impairment (Child-Pugh B classification). Uperio has not been studied in patients with severe hepatic impairment. Therefore, its use is not recommended in patients with severe hepatic impairment.

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= 4,209); enalapril (n= 4,233)].

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%.

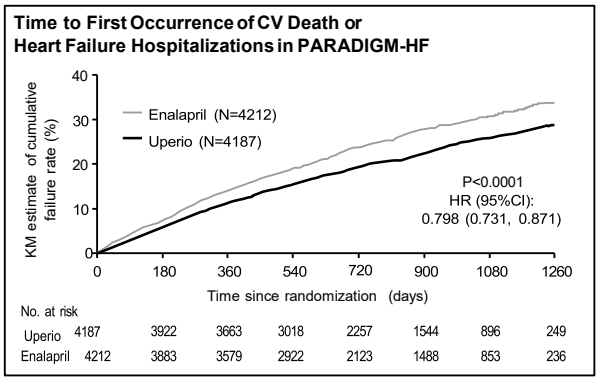
Table 2 Treatment effect for the primary composite endpoint, its components and all-cause mortality

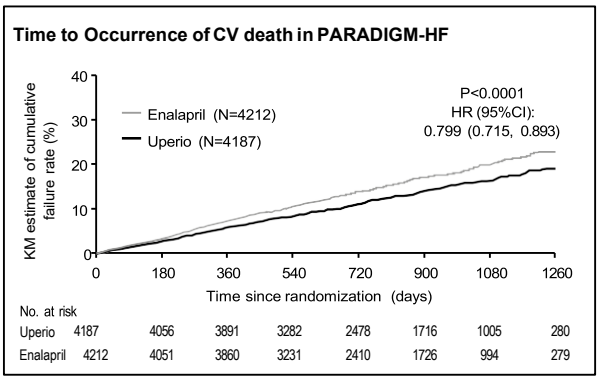
	Uperio N = 4187♯ n (%)	**Enalapril N = 4212♯ n (%)**	**Hazard Ratio (95% CI)**	**Relative Risk Reduction**	**p-value *****
Primary Composite Endpoint of CV Death and Heart Failure Hospitalizations*	914 (21.83)	1117 (26.52)	0.80 (0.73, 0.87)	20%	0.0000002
Individual Components of the primary composite 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%) naive 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.

PARAMOUNT

PARAMOUNT, a randomized, double-blind trial in patients with left ventricular ejection fraction ≥ 45% comparing 200 mg of Uperio (n=149) to 160 mg of valsartan (n=152) twice daily, demonstrated statistically greater reduction (p= 0.0050) in NT pro-BNP from baseline to Week 12. The reduction from baseline in NT-proBNP was similar at Weeks 12 and 36 in patients treated with Uperio, while NT-proBNP decreased from Week 12 to 36 in patients treated with valsartan. Significant reductions in left atrial size, both left atrial volume index (p=0.0069) and left atrial dimension (p=0.0337) were observed at Week 36. A statistically significant improvement in NYHA class was noted at Week 36 (p=0.0488).

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 1,200 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 750mg/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

The effects of Uperio on amyloid-beta concentrations in cerebrospinal fluid (CSF) and brain tissue were assessed in young (2 to 4 years old) cynomolgus monkeys treated with Uperio (50 mg/kg/day) for 2 weeks. In this study, Uperio had a pharmacodynamic effect on CSF A-beta clearance in cynomolgus monkeys, 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 2 week healthy volunteer study in humans (see section CLINICAL PHARMACOLOGY). Additionally, in a toxicology study in cynomolgus monkeys treated with Uperio at 300 mg/kg/day for 39-weeks, there was no amyloid-beta accumulation in the brain.

INCOMPATIBILITIES

Not applicable.

STORAGE

See folding box.

Uperio should not be used after the date marked “EXP” on the

pack. Uperio must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

Not applicable.

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MARKETING AUTHORIZATION NUMBER

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Uperio 100mg Tablet - NAFDAC Reg. No: B4-7237
Uperio 200mg Tablet - NAFDAC Reg. No: B4-7238

MARKETING AUTHORIZATION HOLDER

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