Uperio®/TM

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

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

Uperio®/TM 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.

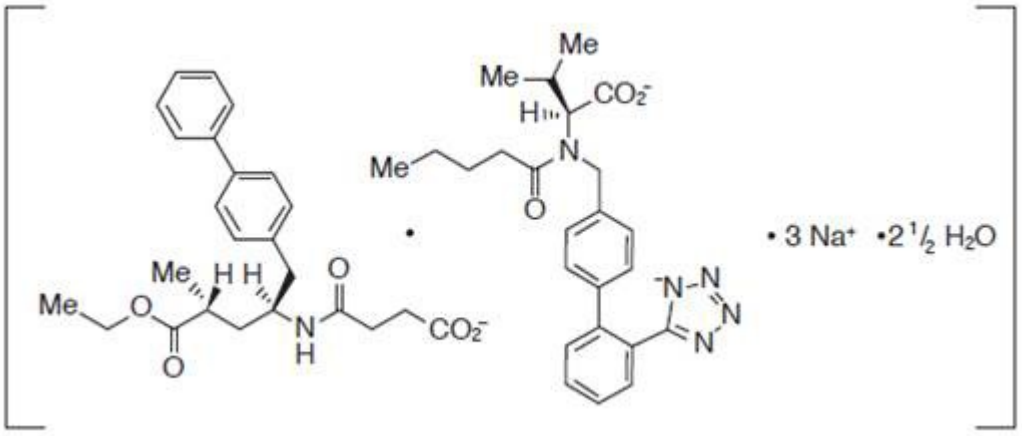
100 mg: Pale yellow, ovaloid, biconvex film-coated tablet with beveled edges, unscored, debossed with "NVR" on one side and "L1" on the other side.

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. The empirical formula of the complex (hemipentahydrate) is $C_{48}H_{55}N_{6O8}Na_3$ 2.5 H_2O. Its molecular mass is 957.99 and its schematic structural formula is:



Following oral administration, the complex 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.

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

Adult Heart Failure

UPERIO is indicated for the treatment of heart failure (NYHA class II-IV) in patients with reduced ejection fraction. Uperio has been shown to reduce the rate of cardiovascular death and heart failure hospitalization and to reduce the rate of all-cause mortality in these patients.

UPERIO is also indicated for the treatment of heart failure (NYHA class II-IV) in patients with preserved ejection fraction with left ventricular ejection fraction (LVEF) below normal. Uperio has been shown to reduce the rate of cardiovascular death and heart failure hospitalizations in these patients.

LVEF is a variable measure, so use clinical judgment in deciding whom to treat *[see Clinical Studies]*. Uperio is administered in place of an ACE inhibitor or ARB.

Pediatric Heart Failure

UPERIO is indicated for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients with body weight of at least 40 Kg. Uperio reduces NT-proBNP and is expected to improve cardiovascular outcomes.

DOSAGE AND ADMINISTRATION

General Considerations

UPERIO is contraindicated with concomitant use of an angiotensin-converting enzyme (ACE) inhibitor. If switching from an ACE inhibitor to UPERIO allow a washout period of 36 hours between administration of the two drugs *[see Contraindications and Drug Interactions]*.

Adult Heart Failure

The recommended starting dose of UPERIO is 100 mg orally twice-daily.

Double the dose of UPERIO after 2 to 4 weeks to the target maintenance dose of 200 mg twice daily, as tolerated by the patient.

Pediatric Heart Failure

Refer to Table 1 for the recommended dose for pediatric patients with body weight of at least 40 kg. Take the recommended dose orally twice daily. Adjust pediatric patient doses every 2 weeks, as tolerated by the patient.

Table 1: Recommended Dose Titration

	Titration Step Dose (twice daily)		
	Starting	**Second**	**Final**
Pediatric Patients At least 40 kg, less than 50 kg	50 mg	100 mg	150 mg‡
Pediatric Patients At least 50 kg	100 mg	150 mg‡	200 mg

‡Doses of 150 mg can be achieved using three 50 mg tablets.

Special populations

Dose Adjustment for Patients Not Taking an ACE inhibitor or ARB or Previously Taking Low Doses of These Agents

In patients not currently taking an ACE inhibitor or an angiotensin II receptor blocker (ARB) and for patients previously taking low doses of these agents, start UPERIO at half the usually recommended starting dose. After initiation, increase the dose every 2 to 4 weeks in adults and every 2 weeks in pediatric patients to follow the recommended dose escalation thereafter *[see Dosage and Administration (Adult Heart Failure and Pediatric Heart Failure)]*.

Note: only pediatric patients with body weight of at least 50 Kg with the above condition can start UPERIO at half the usually recommended starting dose *[see Dosage and Administration]*.

Dose Adjustment for Severe Renal Impairment

In adults and pediatric patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2), start UPERIO at half the usually recommended starting dose. After initiation, increase the dose to follow the recommended dose escalation thereafter *[see Dosage and Administration (Adult Heart Failure and Pediatric Heart Failure)]*.

Note: only pediatric patients with body weight of at least 50 Kg with the above condition can start UPERIO at half the usually recommended starting dose *[see Dosage and Administration]*.

No starting dose adjustment is needed in patients with mild or moderate renal impairment.

Dose Adjustment for Hepatic Impairment

In adults and pediatric patients with moderate hepatic impairment (Child-Pugh B classification), start UPERIO at half the usually recommended starting dose. After initiation, increase the dose to follow the recommended dose escalation thereafter *[see Dosage and Administration (Adult Heart Failure and Pediatric Heart Failure)]*.

Note: only pediatric patients with body weight of at least 50 Kg with the above condition can start UPERIO at half the usually recommended starting dose *[see Dosage and*

Administration]. No starting dose adjustment is needed in patients with mild hepatic impairment.

Use in patients with severe hepatic impairment is not recommended.

Method of administration

For oral use. Uperio may be administered with or without food (see section CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

UPERIO is contraindicated:

- in patients with hypersensitivity to any component
- in patients with a history of angioedema related to previous ACE inhibitor or ARB therapy *[see Warnings and Precautions]*
- with concomitant use of ACE inhibitors. Do not administer within 36 hours of switching from or to an ACE inhibitor *[see Drug Interactions]*
- with concomitant use of aliskiren in patients with diabetes *[see Drug Interactions]*

WARNINGS AND PRECAUTIONS

Fetal Toxicity

UPERIO can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system (RAS) during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. When pregnancy is detected, consider alternative drug treatment and discontinue UPERIO. However, if there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system, and if the drug is considered lifesaving for the mother, advise a pregnant woman of the potential risk to the fetus *[see Use in Specific Populations]*.

Angioedema

UPERIO may cause angioedema *[see Adverse Reactions]*. If angioedema occurs, discontinue UPERIO immediately, provide appropriate therapy, and monitor for airway compromise. 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 oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, administer appropriate therapy, e.g., subcutaneous epinephrine/adrenaline solution 1:1000 (0.3 mL to 0.5 mL) and take measures necessary to ensure maintenance of a patent airway.

UPERIO has been associated with a higher rate of angioedema in Black than in non-Black patients.

Patients with a prior history of angioedema may be at increased risk of angioedema with UPERIO *[see Adverse Reactions]*. UPERIO must not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy *[see Contraindications]*. UPERIO should not be used in patients with hereditary angioedema.

Hypotension

UPERIO lowers blood pressure and may cause symptomatic hypotension *[see Adverse Reactions]*. Patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), are at greater risk. Correct volume or salt depletion prior to administration of UPERIO or start at a lower dose. If hypotension occurs, consider dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g., hypovolemia). If hypotension persists despite such measures, reduce the dosage or temporarily discontinue UPERIO. Permanent discontinuation of therapy is usually not required.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), decreases in renal function may be anticipated in susceptible individuals treated with UPERIO *[see Adverse Reactions]*. In patients whose renal function depends upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria, progressive azotemia and, rarely, acute renal failure and death. Closely monitor serum creatinine, and down-titrate or interrupt UPERIO in patients who develop a clinically significant decrease in renal function *[see Use in Specific Populations and Clinical Pharmacology]*.

As with all drugs that affect the RAAS, UPERIO may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. In patients with renal artery stenosis, monitor renal function.

Hyperkalemia

Through its actions on the RAAS, hyperkalemia may occur with UPERIO *[see Adverse Reactions]*. Monitor serum potassium periodically and treat appropriately, especially in patients with risk factors for hyperkalemia such as severe renal impairment, diabetes, hypoaldosteronism, or a high potassium diet. Dosage reduction or interruption of UPERIO may be required *[see Dosage and Administration]*.

ADVERSE DRUG REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Angioedema *[see Warnings and Precautions]*
- Hypotension *[see Warnings and Precautions]*
- Impaired Renal Function *[see Warnings and Precautions]*
- Hyperkalemia *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 6,622 heart failure patients were treated with UPERIO in the PARADIGM-HF (vs. enalapril) and PARAGON-HF (vs. valsartan) clinical trials. Of these, 5,085 were exposed for at least 1 year.

Adult Heart Failure

In PARADIGM-HF, patients were required to complete sequential enalapril and UPERIO run-in periods of (median) 15 and 29 days, respectively, prior to entering the randomized double-blind period comparing UPERIO and enalapril. During the enalapril run-in period, 1,102 patients (10.5%) were permanently discontinued from the study, 5.6% because of an adverse event, most commonly renal dysfunction (1.7%), hyperkalemia (1.7%) and hypotension (1.4%). During the UPERIO run-in period, an additional 10.4% of patients permanently discontinued treatment, 5.9% because of an adverse event, most commonly renal dysfunction (1.8%), hypotension (1.7%) and hyperkalemia (1.3%). Because of this run-in design, the adverse reaction rates described below are lower than expected in practice.

In the double-blind period, safety was evaluated in 4,203 patients treated with UPERIO and 4,229 treated with enalapril. In PARADIGM-HF, patients randomized to UPERIO received treatment for up to 4.3 years, with a median duration of exposure of 24 months; 3,271 patients were treated for more than one year. Discontinuation of therapy because of an adverse event during the double-blind period occurred in 450 (10.7%) of UPERIO treated patients and 516 (12.2%) of patients receiving enalapril.

Adverse reactions occurring at an incidence of ≥ 5% in patients who were treated with UPERIO in the double-blind period of PARADIGM-HF are shown in Table 2.

In PARADIGM-HF, the incidence of angioedema was 0.1% in both the enalapril and UPERIO run-in periods. In the double-blind period, the incidence of angioedema was higher in patients treated with UPERIO than enalapril (0.5% and 0.2%, respectively). The incidence of angioedema in Black patients was 2.4% with UPERIO and 0.5% with enalapril *[see Warnings and Precautions]*.

Orthostasis was reported in 2.1% of patients treated with UPERIO compared to 1.1% of patients treated with enalapril during the double-blind period of PARADIGM-HF. Falls were reported in 1.9% of patients treated with UPERIO compared to 1.3% of patients treated with enalapril.

Table 2: Adverse Reactions Reported in ≥ 5% of Patients Treated with UPERIO in the Double-Blind Period of PARADIGM-HF

	UPERIO (n = 4,203) %	**Enalapril (n = 4,229) %**
Hypotension	18	12
Hyperkalemia	12	14
Cough	9	13
Dizziness	6	5
Renal failure/acute renal failure	5	5

In PARAGON-HF, no new adverse reactions were identified.

Pediatric Heart Failure

The adverse reactions observed in pediatric patients 1 to < 18 years old who received treatment with UPERIO were consistent with those observed in adult patients.

Laboratory Abnormalities

Hemoglobin and Hematocrit

Decreases in hemoglobin/hematocrit of > 20% were observed in approximately 5% of both UPERIO- and enalapril-treated patients in the double-blind period in PARADIGM-HF. Decreases in hemoglobin/hematocrit of >20% were observed in approximately 7% of UPERIO-treated patients and 9% of valsartan-treated patients in the double-blind period in PARAGON-HF.

Serum Creatinine

During the double-blind period in PARADIGM-HF, approximately 16% of both UPERIO- and enalapril-treated patients had increases in serum creatinine of > 50%. During the double-blind period in PARAGON-HF, approximately 17% of UPERIO-treated patients and 21% of valsartan-treated patients had increases in serum creatinine of > 50%.

Serum Potassium

During the double-blind period of PARADIGM-HF, approximately 16% of both UPERIO- and enalapril-treated patients had potassium concentrations > 5.5 mEq/L. During the double-blind period of PARAGON-HF, approximately 18% of UPERIO-treated patients and 20% of valsartan-treated patients had potassium concentrations > 5.5 mEq/L.

Post marketing Experience

The following additional adverse reactions have been reported in post marketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity including rash, pruritus, and anaphylactic reaction.

DRUG INTERACTIONS

Dual Blockade of the Renin-Angiotensin-Aldosterone System

Concomitant use of UPERIO with an ACE inhibitor is contraindicated because of the increased risk of angioedema *[see Contraindications]*.

Avoid use of UPERIO with an ARB, because UPERIO contains the angiotensin II receptor blocker valsartan.

The concomitant use of UPERIO with aliskiren is contraindicated in patients with diabetes *[see Contraindications]*. Avoid use with aliskiren in patients with renal impairment (eGFR < 60 mL/min/1.73 m^2).

Potassium-Sparing Diuretics

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium *[see Warnings and Precautions]*.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of NSAIDs, including COX-2 inhibitors, with UPERIO may result in worsening of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically.

Lithium

Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists. Monitor serum lithium levels during concomitant use with UPERIO.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

UPERIO can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. In animal reproduction studies, UPERIO treatment during organogenesis resulted in increased embryo-fetal lethality in rats and rabbits and teratogenicity in rabbits. When pregnancy is detected, consider alternative drug treatment and discontinue UPERIO. However, if there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system, and if the drug is considered lifesaving for the mother, advise a pregnant woman of the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Oligohydramnios in pregnant women who use drugs affecting the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension, and death.

Perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. If oligohydramnios is observed, consider alternative drug treatment. Closely observe neonates with histories of *in utero* exposure to UPERIO for hypotension, oliguria, and hyperkalemia. In neonates with a history of *in utero* exposure to UPERIO, if oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and replacing renal function.

Data

Animal Data

UPERIO treatment during organogenesis resulted in increased embryo-fetal lethality in rats at doses ≥ 49 mg sacubitril/51 mg valsartan/kg/day (≤ 0.06 [LBQ657, the active metabolite] and 0.72 [valsartan]-fold the maximum recommended human dose [MRHD] of 200 mg twice-daily on the basis of the area under the plasma drug concentration-time curve [AUC]) and rabbits at doses ≥ 5 mg sacubitril/5 mg valsartan/kg/day (2-fold and 0.03-fold the MRHD on the basis of valsartan and LBQ657 AUC, respectively). UPERIO is teratogenic based on a low incidence of fetal hydrocephaly, associated with maternally toxic doses, which was observed in rabbits at an UPERIO dose of ≥ 5 mg sacubitril/5 mg valsartan/kg/day. The adverse embryo -fetal effects of UPERIO are attributed to the angiotensin receptor antagonist activity.

Pre- and postnatal development studies in rats at sacubitril doses up to 750 mg/kg/day (2.2-fold the MRHD on the basis of LBQ657 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.

Lactation

Risk Summary

There is no information regarding the presence of sacubitril/valsartan in human milk, the effects on the breastfed infant, or the effects on milk production. Sacubitril/valsartan is present in rat milk. Because of the potential for serious adverse reactions in breastfed infants from exposure to sacubitril/valsartan, advise a nursing woman that breastfeeding is not recommended during treatment with UPERIO.

Data

Following an oral dose (15 mg sacubitril/15 mg valsartan/kg) of [^{14}C] UPERIO to lactating rats, transfer of LBQ657 into milk was observed. After a single oral administration of 3 mg/kg [^{14}C] valsartan to lactating rats, transfer of valsartan into milk was observed.

Pediatric Use

The safety and effectiveness of UPERIO in pediatric heart failure patients 1 to < 18 years old are supported by the reduction from baseline to 12 weeks in NT-proBNP in a randomized, double-blind clinical study *[see Clinical Studies]*. The analysis of NT-proBNP included 90 patients age 6 to 18 years and 20 patients age 1 to 6 years.

Safety and effectiveness have not been established in pediatric patients less than 1 year of age.

Animal Data

Sacubitril given orally to juvenile rats from postnatal day (PND) 7 to PND 35 or PND 70 (an age approximately equivalent to neonatal through pre-pubertal development or adulthood in humans) at doses ≥ 400 mg/kg/day (approximately 2-fold the AUC exposure to the active metabolite of sacubitril, LBQ657, at an UPERIO pediatric clinical dose of 3.1 mg/kg twice daily) resulted in decreases in body weight, bone length, and bone mass. The decrease in body weight was transient from PND 10 to PND 20 and the effects for most bone parameters were reversible after treatment stopped. Exposure at the No-Observed-Adverse-Effect-Level (NOAEL) of 100 mg/kg/day was approximately 0.5-fold the AUC exposure to LBQ657 at the 3.1 mg/kg twice daily dose of UPERIO. The mechanism underlying bone effects in rats and the translatability to pediatric patients are unknown.

Valsartan given orally to juvenile rats from PND 7 to PND 70 (an age approximately equivalent to neonatal through adulthood in humans) produced persistent, irreversible kidney damage at all dose levels. Exposure at the lowest tested dose of 1 mg/kg/day was approximately 0.2-fold the exposure at 3.1 mg/kg twice daily dose of UPERIO based on AUC. These kidney effects in neonatal rats represent expected exaggerated pharmacological effects that are observed if rats are treated during the first 13 days of life.

Geriatric Use

No relevant pharmacokinetic differences have been observed in elderly (≥ 65 years) or very elderly (≥ 75 years) patients compared to the overall population *[see Clinical Pharmacology]*.

Hepatic Impairment

No dose adjustment is required when administering UPERIO to patients with mild hepatic impairment (Child-Pugh A classification). The recommended starting dose in patients with moderate hepatic impairment (Child-Pugh B classification) is 50 mg twice daily. The use of UPERIO in patients with severe hepatic impairment (Child-Pugh C classification) is not recommended; as no studies have been conducted in these patients *[see Dosage and Administration, Clinical Pharmacology]*.

Renal Impairment

No dose adjustment is required in patients with mild (eGFR 60 to 90 mL/min/1.73 m^2) to moderate (eGFR 30 to 60 mL/min/1.73 m^2) renal impairment. The recommended starting dose in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) is 50 mg twice daily *[see Dosage and Administration, Warnings and Precautions, and Clinical Pharmacology]*.

OVERDOSAGE

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

Hypotension is the most likely result of over dosage due to the blood pressure lowering effects of UPERIO. Symptomatic treatment should be provided.

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

CLINICAL PHARMACOLOGY

Mechanism of Action

UPERIO contains a neprilysin inhibitor, sacubitril, and an angiotensin receptor blocker, valsartan. UPERIO inhibits neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and blocks the angiotensin II type-1 (AT_1) receptor via valsartan. The cardiovascular and renal effects of UPERIO in heart failure patients are attributed to the increased levels of peptides that are degraded by neprilysin, such as natriuretic peptides, by LBQ657, and the simultaneous inhibition of the effects of angiotensin II by valsartan. Valsartan inhibits the effects of angiotensin II by selectively blocking the AT_1 receptor, and also inhibits angiotensin II-dependent aldosterone release.

Pharmacodynamics

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 renin-angiotensin system 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. UPERIO also blocked the AT_1-receptor as evidenced by increased plasma renin activity and plasma renin concentrations. In PARADIGM-HF, UPERIO decreased plasma NT-proBNP (not a neprilysin substrate) and increased plasma BNP (a neprilysin substrate) and urine cGMP compared with enalapril.

In PARAMOUNT, a randomized, double-blind, 36-week study in patients with heart failure with LVEF ≥ 45% comparing 200 mg of UPERIO (n=149) to 160 mg of valsartan (n =152) twice-daily, UPERIO decreased NT-proBNP by 17% while valsartan increased NT-proBNP by 8% at Week 12 (p = 0.005).

In PARAGON-HF, UPERIO decreased NT-proBNP by 24% (Week 16) and 19% (Week 48) compared to 6% and 3% reductions on valsartan, respectively.

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

Amyloid-β: Neprilysin is one of multiple enzymes involved in the clearance of amyloid-β (Aβ) from the brain and cerebrospinal fluid (CSF). Administration of UPERIO 400mg 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 $A\beta_{1-40}$ or CSF $A\beta_{1-42}$. The clinical relevance of this finding is unknown *[see Nonclinical Toxicology]*.

Blood Pressure: Addition of a 50 mg single dose of sildenafil to UPERIO at steady state (400mg once daily for 5 days) in patients with hypertension was associated with additional blood pressure (BP) reduction (~ 5/4 mmHg, systolic/diastolic BP) compared to administration of UPERIO alone.

Co-administration of UPERIO did not significantly alter the BP effect of intravenous nitroglycerin.

Pharmacokinetics

Absorption

Following oral administration, UPERIO dissociates into sacubitril and valsartan. Sacubitril is further metabolized to LBQ657. The peak plasma concentrations of sacubitril, LBQ657, and valsartan are reached in 0.5 hours, 2 hours, and 1.5 hours, respectively. The oral absolute bioavailability of sacubitril is estimated to be ≥ 60%. The valsartan in UPERIO is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in UPERIO is equivalent to 40 mg, 80 mg, and 160 mg of valsartan in other marketed tablet formulations, respectively.

Following twice-daily dosing of UPERIO, steady state levels of sacubitril, LBQ657, and valsartan are reached in 3 days. At steady state, sacubitril and valsartan do not accumulate significantly, whereas LBQ657 accumulates by 1.6-fold. UPERIO administration with food has no clinically significant effect on the systemic exposures of sacubitril, LBQ657, or 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

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

Metabolism

Sacubitril is readily converted to LBQ657 by esterases; LBQ657 is not further metabolized to a significant extent. Valsartan is minimally metabolized; only about 20% of the dose is recovered as metabolites. A hydroxyl metabolite has been identified in plasma at low concentrations (< 10%).

Elimination

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

Linearity/Nonlinearity

The pharmacokinetics of sacubitril, LBQ657, and valsartan were linear over an UPERIO dose range of 24 mg sacubitril/26 mg valsartan to 194 mg sacubitril/206 mg valsartan.

Drug Interactions:

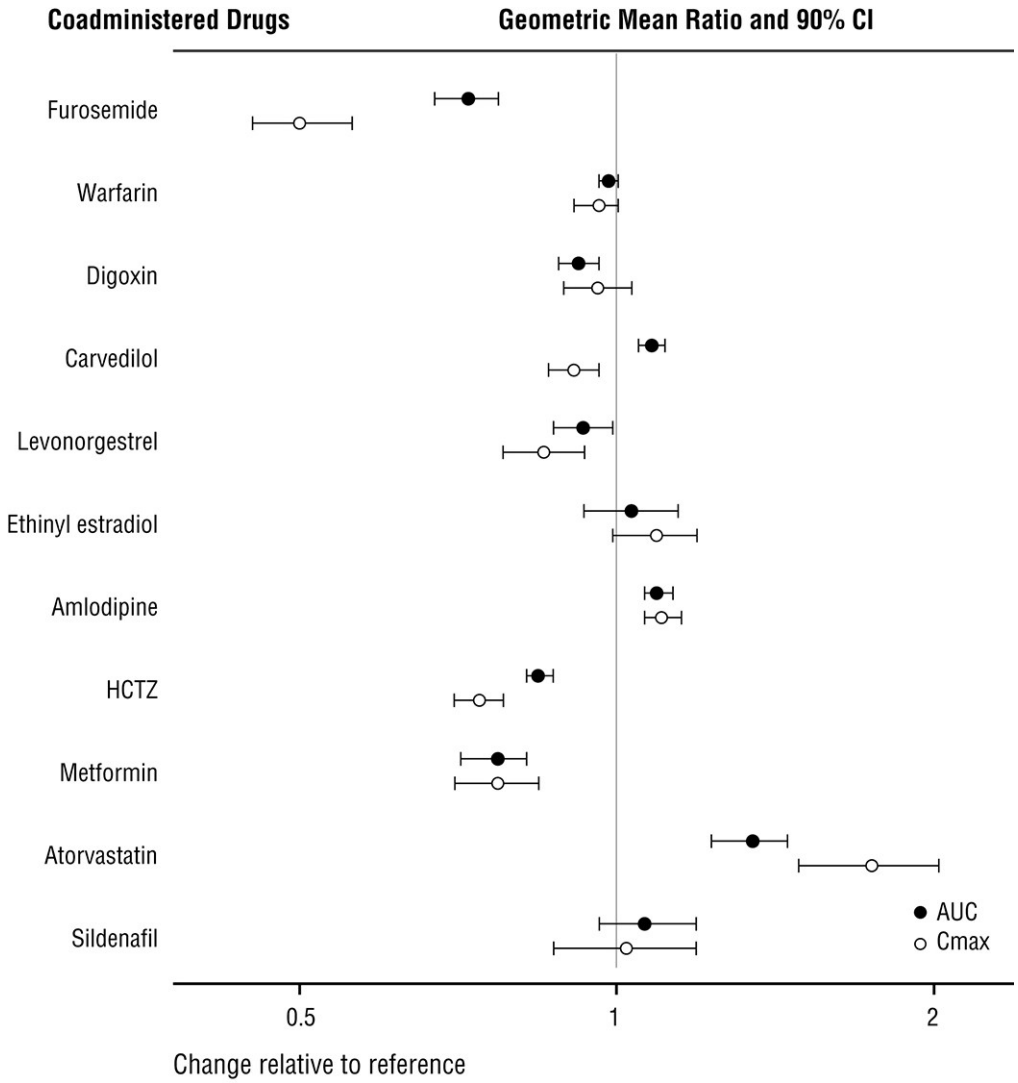
Effect of Co-administered Drugs on UPERIO:

Because CYP450 enzyme-mediated metabolism of sacubitril and valsartan is minimal, coadministration with drugs that impact CYP450 enzymes is not expected to affect the pharmacokinetics of UPERIO. Dedicated drug interaction studies demonstrated that coadministration of furosemide, warfarin, digoxin, carvedilol, a combination of levonorgestrel/ethinyl estradiol, amlodipine, omeprazole, hydrochlorothiazide (HCTZ), metformin, atorvastatin, and sildenafil, did not alter the systemic exposure to sacubitril, LBQ657 or valsartan.

Effect of UPERIO on Co-administered Drugs:

In vitro data indicate that sacubitril inhibits OATP1B1 and OATP1B3 transporters. The effects of UPERIO on the pharmacokinetics of coadministered drugs are summarized in Figure 1.

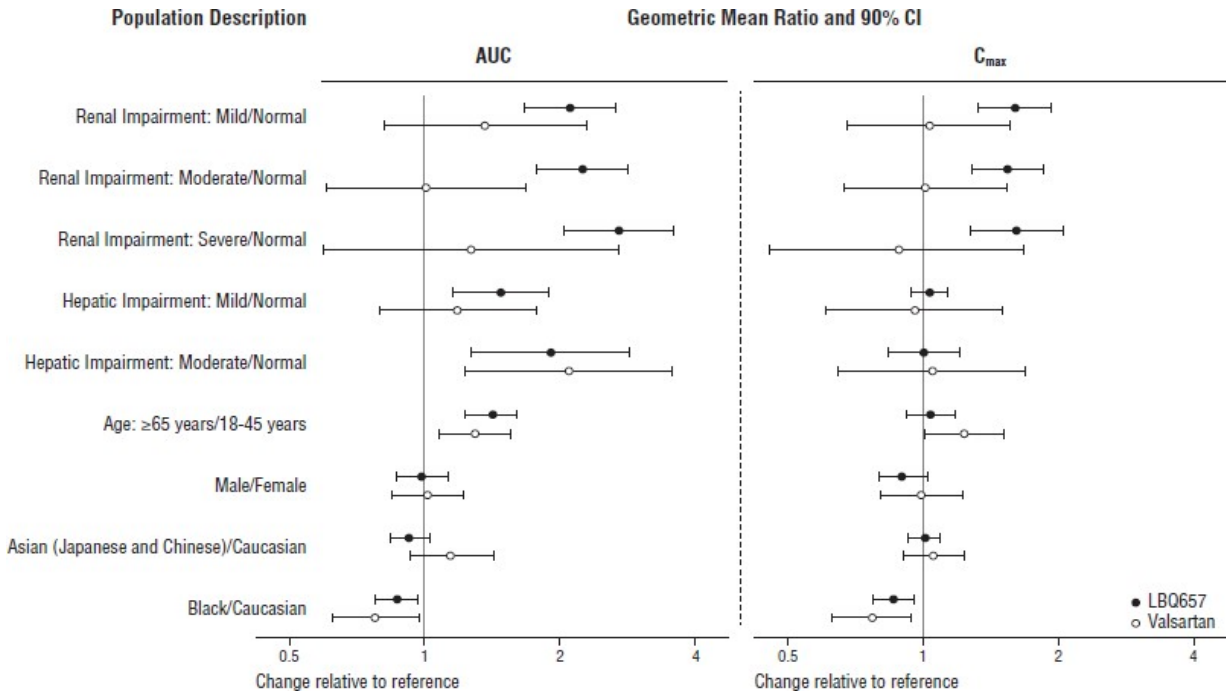
Figure 1: Effect of UPERIO on Pharmacokinetics of Coadministered Drugs



Specific Populations

Effect of specific populations on the pharmacokinetics of LBQ657 and valsartan are shown in Figure 2.

Figure 2: Pharmacokinetics of UPERIO in Specific Populations



Note: Child-Pugh Classification was used for hepatic impairment.

Pediatric Patients:

The pharmacokinetics of UPERIO were evaluated in pediatric heart failure patients 1 to < 18 years old administered oral doses of 0.8 mg/kg and 3.1 mg/kg of UPERIO. Pharmacokinetic data indicated that exposure to UPERIO in pediatric and adult patients is similar.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Carcinogenicity studies conducted in mice and rats with sacubitril and valsartan did not identify any carcinogenic potential for UPERIO. The LBQ657 C_{max} at the high dose (HD) of 1200 mg/kg/day in male and female mice was, respectively, 14 and 16 times that in humans at the MRHD. The LBQ657 C_{max} in male and female rats at the HD of 400 mg/kg/day was, respectively, 1.7 and 3.5 times that at the MRHD. 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 MRHD 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.

Impairment of Fertility

UPERIO did not show any effects on fertility in rats up to a dose of 73 mg sacubitril/77 mg valsartan/kg/day (≤ 1.0-fold and ≤ 0.18-fold the MRHD on the basis of the AUCs of valsartan and LBQ657, respectively).

Animal Toxicology and/or Pharmacology

The effects of UPERIO on amyloid-β concentrations in CSF and brain tissue were assessed in young (2 to 4 years old) cynomolgus monkeys treated with UPERIO (24 mg sacubitril/26 mg valsartan/kg/day) for 2 weeks. In this study, UPERIO affected CSF Aβ clearance, increasing CSF Aβ 1-40, 1-42, and 1-38 levels in CSF; there was no corresponding increase in Aβ levels in the brain. In addition, in a toxicology study in cynomolgus monkeys treated with UPERIO at 146 mg sacubitril/154 mg valsartan/kg/day for 39-weeks, there was no amyloid-β accumulation in the brain.

CLINICAL STUDIES

Adult Heart Failure

PARADIGM-HF

PARADIGM-HF was a multinational, randomized, double-blind trial comparing UPERIO and enalapril in 8,442 adult patients with symptomatic chronic heart failure (NYHA class II–IV) and systolic dysfunction (left ventricular ejection fraction ≤ 40%). Patients had to have been on an ACE inhibitor or ARB for at least four weeks and on maximally tolerated doses of beta-blockers. Patients with a systolic blood pressure of < 100 mmHg at screening were excluded.

The primary objective of PARADIGM-HF was to determine whether UPERIO, a combination of sacubitril and a RAS inhibitor (valsartan), was superior to a RAS inhibitor (enalapril) alone in reducing the risk of the combined endpoint of cardiovascular (CV) death or hospitalization for heart failure (HF).

After discontinuing their existing ACE inhibitor or ARB therapy, patients entered sequential single-blind run-in periods during which they received enalapril 10 mg twice-daily, followed by UPERIO 100 mg twice-daily, increasing to 200 mg twice-daily. Patients who successfully completed the sequential run-in periods were randomized to receive either UPERIO 200 mg (N = 4,209) twice-daily or enalapril 10 mg (N = 4,233) twice-daily. The primary endpoint was the first event in the composite of CV death or hospitalization for HF. The median follow-up duration was 27 months and patients were treated for up to 4.3 years.

The population was 66% Caucasian, 18% Asian, and 5% Black; the mean age was 64 years and 78% were male. At randomization, 70% of patients were NYHA Class II, 24% were NYHA Class III, and 0.7% were NYHA Class IV. The mean left ventricular ejection fraction was 29%. The underlying cause of heart failure was coronary artery disease in 60% of patients; 71% had a history of hypertension, 43% had a history of myocardial infarction, 37% had an eGFR < 60 mL/min/1.73m^2, and 35% had diabetes mellitus. Most patients were taking beta-blockers (94%), mineralocorticoid antagonists (58%), and diuretics (82%). Few patients had an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy-defibrillator (CRT-D) (15%).

PARADIGM-HF demonstrated that UPERIO, a combination of sacubitril and a RAS inhibitor (valsartan), was superior to a RAS inhibitor (enalapril), in reducing the risk of the combined endpoint of cardiovascular death or hospitalization for heart failure, based on a time-to-event analysis (hazard ratio [HR] 0.80; 95% confidence interval [CI], 0.73, 0.87, $p < 0.0001$). The treatment effect reflected a reduction in both cardiovascular death and heart failure hospitalization; see Table 3 and Figure 3. Sudden death accounted for 45% of cardiovascular deaths, followed by pump failure, which accounted for 26%.

UPERIO also improved overall survival (HR 0.84; 95% CI [0.76, 0.93], p = 0.0009) (Table 3). This finding was driven entirely by a lower incidence of cardiovascular mortality on UPERIO.

Table 3: Treatment Effect for the Primary Composite Endpoint, its Components, and All-cause Mortality in PARADIGM-HF

	UPERIO N = 4,187 n (%)	**Enalapril N = 4,212 n (%)**	**Hazard Ratio (95% CI)**	***p*-value**
Primary composite endpoint of cardiovascular death or heart failure hospitalization	914 (21.8)	1,117 (26.5)	0.80 (0.73, 0.87)	< 0.0001
Cardiovascular death as first event	377 (9.0)	459 (10.9)		
Heart failure hospitalization as first event	537 (12.8)	658 (15.6)		
Number of patients with events: *				
Cardiovascular death**	558 (13.3)	693 (16.5)	0.80 (0.71, 0.89)	
Heart failure hospitalizations	537 (12.8)	658 (15.6)	0.79 (0.71, 0.89)	
All-cause mortality	711 (17.0)	835 (19.8)	0.84 (0.76, 0.93)	0.0009

*Analyses of the components of the primary composite endpoint were not prospectively planned to be adjusted for multiplicity.
**Includes patients who had heart failure hospitalization prior to death.

The Kaplan-Meier curves presented below (Figure 3) show time to first occurrence of the primary composite endpoint (3A), and time to occurrence of cardiovascular death at any time (3B) and first heart failure hospitalization (3C).

Figure 3: Kaplan-Meier Curves for the Primary Composite Endpoint (A), Cardiovascular Death (B), and Heart Failure Hospitalization (C)

Figure A

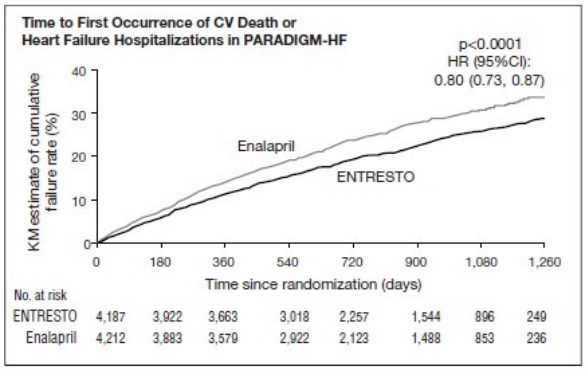


Figure B

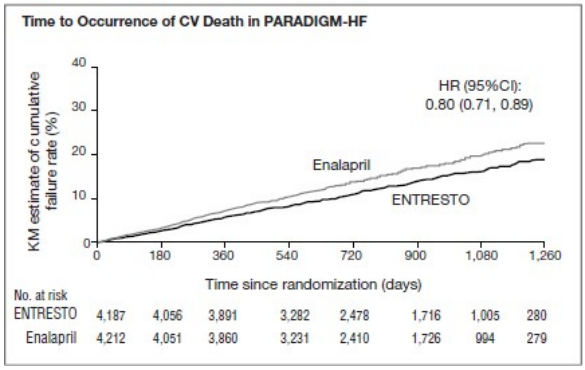
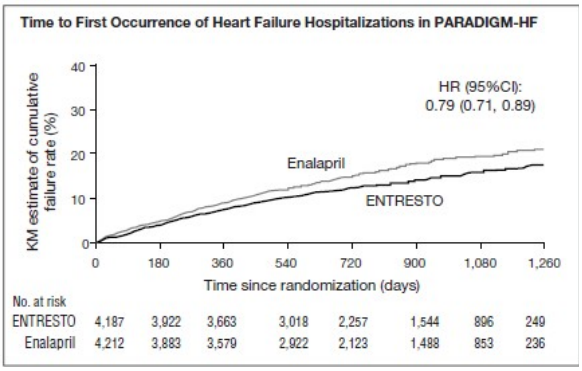


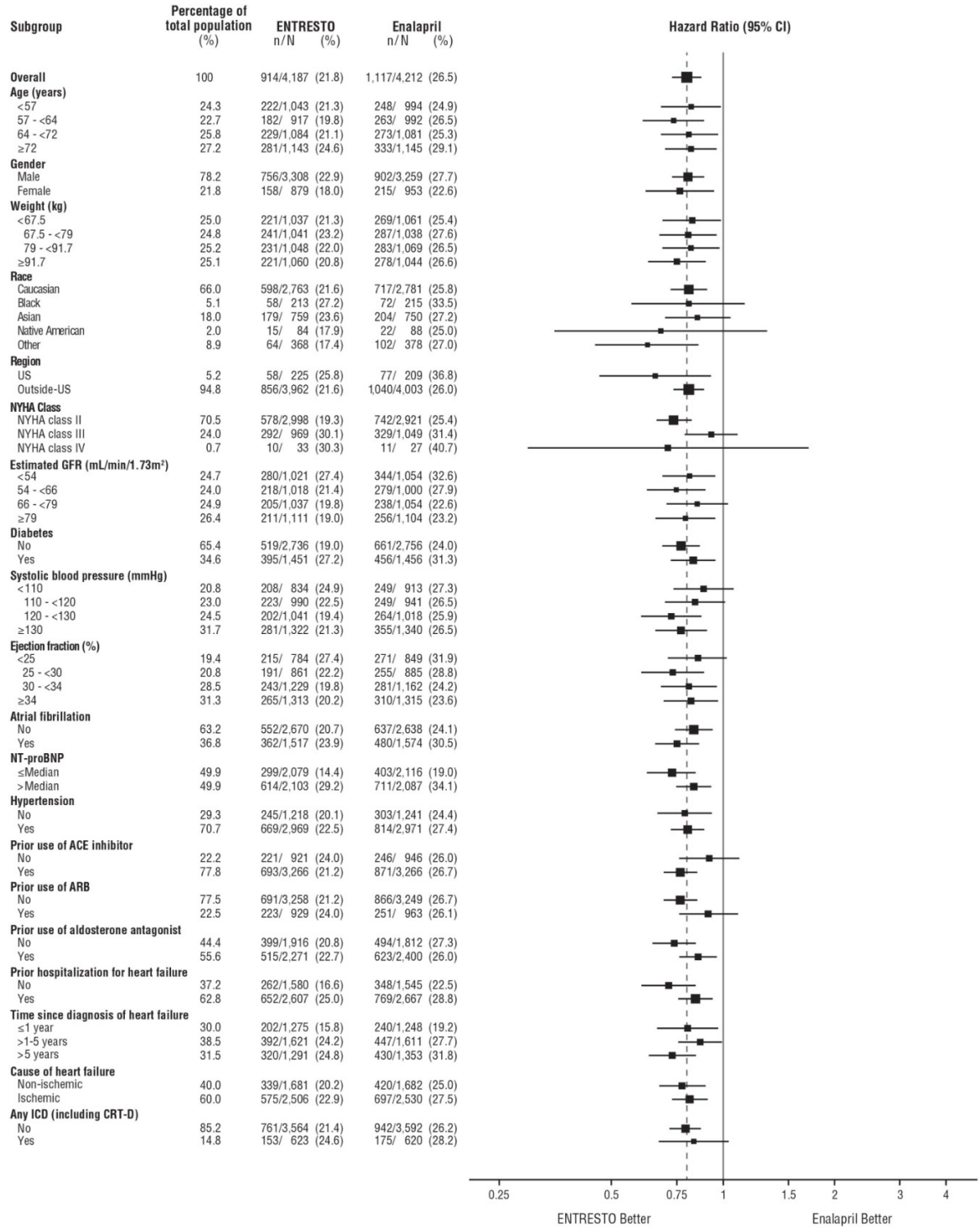
Figure C



Note: Brand name for Uperio in the U.S and E.U. is Entresto

A wide range of demographic characteristics, baseline disease characteristics, and baseline concomitant medications were examined for their influence on outcomes. The results of the primary composite endpoint were consistent across the subgroups examined (Figure 4).

Figure 4: Primary Composite Endpoint (CV Death or HF Hospitalization) - Subgroup Analysis (PARADIGM-HF)



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics. The 95% confidence limits that are shown do not take into account the number of comparisons made, and may not reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Note: Brand name for Uperio in the U.S and E.U. is Entresto

PARAGON-HF

PARAGON-HF, was a multicentre, randomized, double-blind trial comparing UPERIO and valsartan in 4,796 adult patients with symptomatic heart failure with left ventricular ejection fraction ≥ 45%, and structural heart disease [either left atrial enlargement (LAE) or left ventricular hypertrophy (LVH)]. Patients with a systolic blood pressure of < 110 mmHg and patients with any prior echocardiographic LVEF < 40% at screening were excluded.

The primary objective of PARAGON-HF was to determine whether UPERIO reduced the rate of the composite endpoint of total (first and recurrent) heart failure (HF) hospitalizations and cardiovascular (CV) death.

After discontinuing their existing ACE inhibitor or ARB therapy, patients entered sequential single-blind run-in periods during which they received valsartan 80 mg twice-daily, followed by UPERIO 100 mg twice-daily. Patients on prior low doses of an ACEi or ARB began the run-in period receiving valsartan 40 mg twice-daily for 1-2 weeks. Patients who successfully completed the sequential run-in periods were randomized to receive either UPERIO 200 mg (N = 2,419) twice-daily or valsartan 160 mg (N = 2,403) twice-daily. The median follow-up duration was 35 months and patients were treated for up to 4.7 years.

The population was 81% Caucasian, 13% Asian, and 2% Black; the mean age was 73 years and 52% were female. At randomization, 77% of patients were NYHA Class II, 19% were NYHA Class III, and 0.4% were NYHA Class IV. The median left ventricular ejection fraction was 57%. The underlying cause of heart failure was of ischemic etiology in 36% of patients. Furthermore, 96% had a history of hypertension, 23% had a history of myocardial infarction, 46% had an eGFR < 60 mL/min/1.73 m^2, and 43% had diabetes mellitus. Most patients were taking beta-blockers (80%) and diuretics (95%).

PARAGON-HF demonstrated that UPERIO had a numerical reduction in the rate of the composite endpoint of total (first and recurrent) HF hospitalizations and CV death, based on an analysis using a proportional rates model (rate ratio [RR] 0.87; 95% CI [0.75, 1.01], p = 0.06); see Table 4. The treatment effect was primarily driven by the reduction in total HF hospitalizations in patients randomized to UPERIO (RR 0.85; 95% CI [0.72, 1.00]).

Table 4: Treatment Effect for the Primary Composite Endpoint and its Components in PARAGON-HF

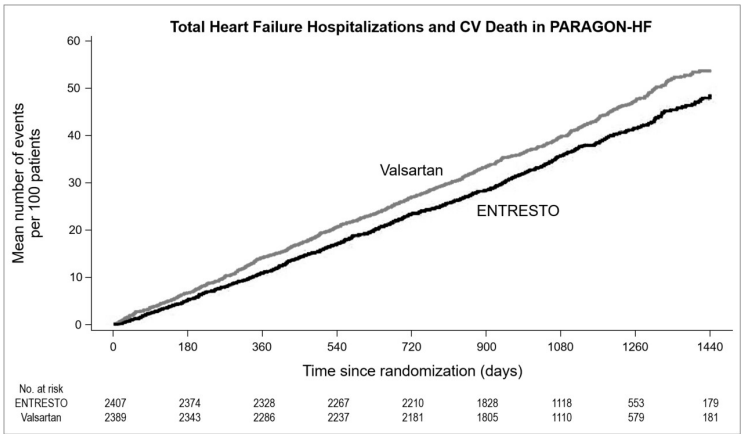
	UPERIO N = 2,407		**Valsartan N = 2,389**		**Effect Size (95% CI)**
Efficacy Endpoints	**n**	**Event Rate[a]**	**n**	**Event Rate[a]**	
Composite of total (first and recurrent) HF hospitalizations and CV death	894	12.8	1,009	14.6	RR = 0.87 (0.75, 1.01) *p*-value 0.06
Total HF Hospitalizations	690	9.9	797	11.6	RR = 0.85 (0.72,

					1.00)
CV Death[b]	204	2.9	212	3.1	HR = 0.95 (0.79, 1.16)

Abbreviations: RR = rate ratio, HR = hazard ratio.
[a] Event rate per 100 patient-years.
[b] Includes patients who had CV death following HF hospitalization event.

Figure 5 shows the mean number of composite endpoint events of total HF hospitalizations and CV death over time.

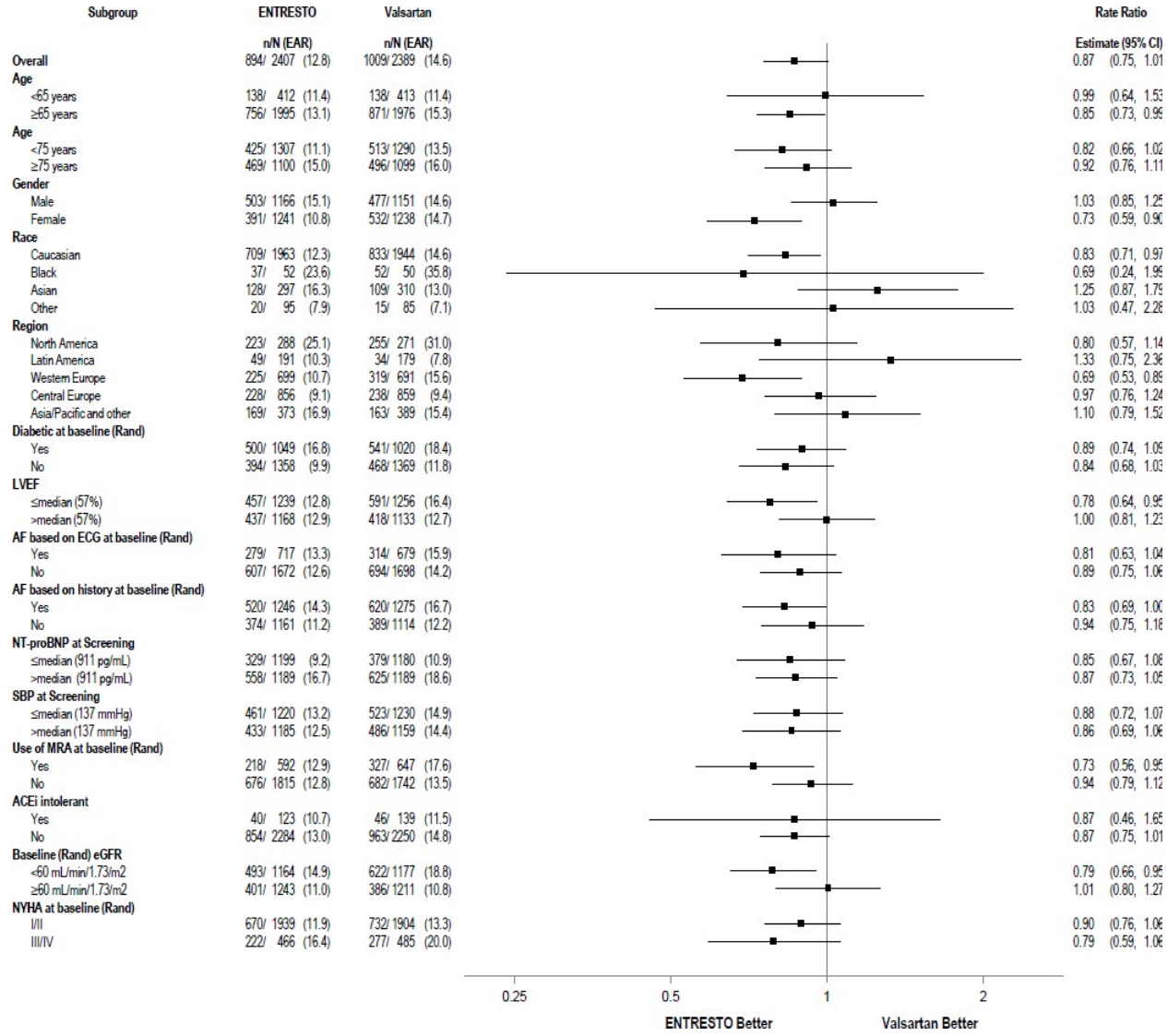
Figure 5: Mean Number of Events Over Time for the Primary Composite Endpoint of Total HF Hospitalizations and CV Death



Note: Brand name for Uperio in the U.S and E.U. is Entresto

A wide range of demographic characteristics, baseline disease characteristics, and baseline concomitant medications were examined for their influence on outcomes (Figure 6).

Figure 6: Primary Composite Endpoint of Total HF Hospitalizations and CV Death – Subgroup Analysis (PARAGON-HF)

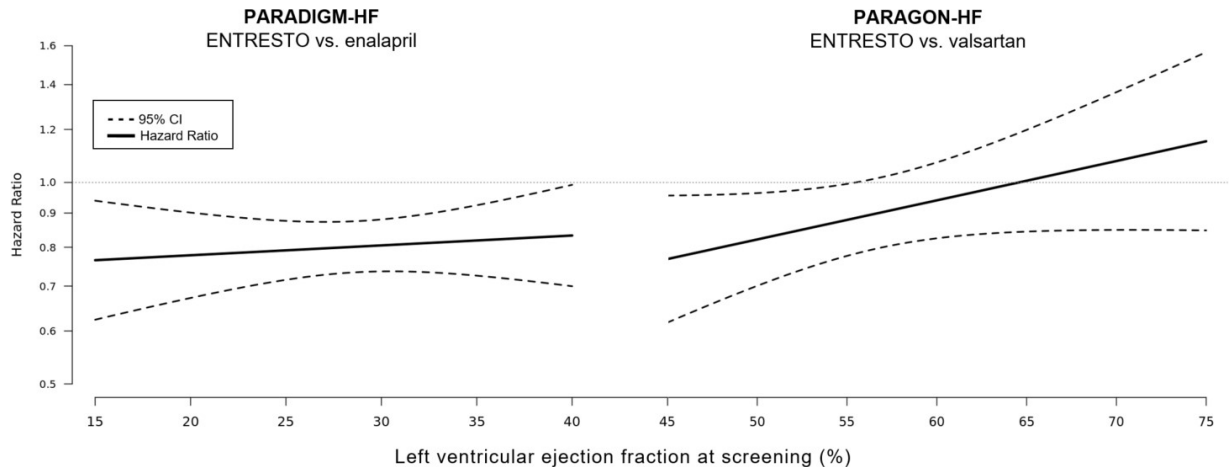


Note: The figure above presents effects in various subgroups, all of which are baseline characteristics. The 95% confidence limits that are shown do not take into account the number of comparisons made, and may not reflect the effect of a particular factor after adjustment for all other factors.

Brand name for Uperio in the U.S and E.U. is Entresto

In an analysis of the relationship between LVEF and outcome in PARADIGM-HF and PARAGON-HF, patients with LVEF below normal treated with UPERIO experienced greater risk reduction (Figure 7).

Figure 7: Treatment Effect for the Composite Endpoint of Time to First HF Hospitalization or CV Death by LVEF in PARADIGM-HF and PARAGON-HF



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Pediatric Heart Failure

PANORAMA-HF

The efficacy of UPERIO was evaluated in a multinational, randomized, double-blind trial comparing UPERIO and enalapril based on an analysis in 110 pediatric patients 1 to < 18 years old with heart failure (NYHA/Ross class II-IV) due to systemic left ventricular systolic dysfunction (LVEF ≤ 40%). Patients with systemic right ventricles and single ventricles were excluded from the trial. The target maintenance dose of UPERIO in pediatric patients 1 to < 18 years old was 3.1 mg/kg twice daily.

The endpoint was the between-group difference in the change in plasma NT-proBNP from baseline to 12 weeks. The reduction from baseline in NT-proBNP was 44% and 33% in the UPERIO and enalapril groups, respectively. While the between-group difference was not statistically significant, the reductions for UPERIO and enalapril were similar to or larger than what was seen in adults; these reductions did not appear to be attributable to post-baseline changes in background therapy.

Because UPERIO improved outcomes and reduced NT-proBNP in PARADIGM-HF, the effect on NT-proBNP was considered a reasonable basis to infer improved cardiovascular outcomes in pediatric patients.

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.

Manufacturer:

See folding box.

Package Leaflet

Information issued: Feb 2021

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Novartis Pharma AG, Basel, Switzerland