NDA #218772

Product: Losartan Potassium Oral Suspension, 10 mg/mL

Applicant: Scienture Inc.

Proposed Indications:

• Treatment of hypertension, to lower blood pressure in adults and children greater than 6 years old.

• Reduction of the risk of stroke in patients with hypertension and left ventricular hypertrophy.

• Treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria in patients with type 2 diabetes and a history of hypertension.

Regulatory Pathway: 505(b)(2)

Conclusion

According to the selected published literature, there is no indication of the safety profile of losartan products substantially being changed over the years and not reflected in the product label. Also, there is no indication that this product will be dissimilar to the safety profile of other currently marketed losartan products.

Introduction

The sponsor submitted 16 articles as the literature review for their product. The articles indicate that

-Higher doses of losartan appear not to increase the risk and frequency of AEs.

-There were no dose-related trends for losartan potassium with respect to the percentage of patients with any AE, serious AEs, drug-related AEs, laboratory AEs, or who withdrew because of an adverse event. (Alan H. Gradman, Karen E. Arcuri, Allan I. Goldberg, Leila S. Ikeda, Edward B. Nelson, Duane B. Snavely and Charles S. Sweet, A Randomized, Placebo-Controlled, Double-Blind, Parallel Study of Various Doses of Losartan Potassium Compared With Enalapril Maleate in Patients With Essential Hypertension. **Hypertension**. 1995; 25:1345–1350.

- There were no differences in the incidence of ADEs in the losartan twice-daily group compared to the losartan once-daily group. Catherine G. Derington, Jordan B. King, Thomas Delate, Sheila R. Botts, Miranda Kroehl, David P. Kao, Katy E. Trinkley; Twice-daily versus once-daily lisinopril and losartan for hypertension: Real-world effectiveness and safety; **https://doi.org/10.1371/journal.pone.0243371**

- The overall incidence of clinical and laboratory AEs in the losartan- and placebo-treated groups was similar among patients with hypertension and comorbidities (diabetes mellitus, renal impairment, heart failure). Losartan can be safely administered in hypertensive patients with concomitant illnesses. It can

be considered for first-line therapy and is suitable as an alternative therapy in patients already experiencing side effects with other agents. Michael Weber, MD; Clinical Safety and Tolerability of Losartan; **CLINICAL THERAPEUTICS**®Vol. 19, NO. 4, 1997

-In patients with congestive heart failure, high dose losartan (150 mg/day) has improved benefit over 50 mg/day dose. Renal impairment, hypotension, and hyperkalemia occurred more often in the high-dose group compared with the low-dose group, however, the frequency of discontinuation from study drug for any of these reasons was extremely low, supporting the conclusion that the benefit of the higher dose outweighed the risk. Konstam MA, et al. "Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure". **The Lancet**. 2009. 374(9704):1840-1848.

-high dose losartan reduced the incidence of hyperuricemia and the level of serum uric acid; João Pedro Ferreira, MD, PhD, Faiez Zannad, MD, PhD, Michael S. Kiernan, MD, Marvin A. Konstam, MD; High-versus low-dose losartan and uric acid: An analysis from HEAAL; **Journal of Cardiology** 82 (2023) 57–61, as well as the incidence of hypokalemia; João Pedro Ferreira, Marvin Konstam, Patrick Rossignol, Michael Kiernan, Faiez Zannad; High versus low dose losartan and serum potassium: an analysis from HEAAL; **Journal of Cardiac Failure**, 2023, 29 (1),pp.45-52.

Submitted clinical literature

Title/Authors/Source	Study design	Conclusions
Twice-daily versus once-daily lisinopril and losartan for hypertension: Real-world effectiveness and safety/ Catherine G. Derington, Jordan B. King, Thomas Delate, Sheila R. Botts, Miranda Kroehl, David P. Kao, Katy E. Trinkley/ https://doi.org/10.1371/journal.pone.0243371	Retrospective cohort study of patients taking Q Day lisinopril and losartan who experienced a dose-doubling (index date).	The findings support data generated from randomized trials and prospective cohort studies that have demonstrated no statistically significant differences in BP reduction or tolerability between once-daily and twice-daily dosing strategies of other ACEIs (ramipril, enalapril, trandolapril) and ARBs (losartan, eprosartan, irbesartan, olmesartan, valsartan, candesartan)
High versus low dose losartan and serum potassium: an analysis from HEAAL/João Pedro Ferreira, Marvin Konstam, Patrick Rossignol, Michael Kiernan, Faiez Zannad/ Journal of Cardiac Failure, 2023, 29 (1),pp.45-52	HEAAL was an international, multicentre, double-blind, event-driven trial, comparing the effect of two doses of losartan 150 (high-dose) vs. 50 (low-dose) mg/day	Compared with low-dose (50 mg/day), high-dose (150 mg/day) losartan slightly increased serum potassium by 0.1 mmol/L throughout the follow-up (4.7 years, on average), and decreased the

	among 3834 patients with symptomatic heart failure, a LVEF of 40% or less, stable cardiovascular medical therapy for at least 2 weeks, and known intolerance to ACEi defined as discontinuation of ACE-inhibitor treatment because of one or more of the following adverse effects: cough, symptomatic hypotension, azotaemia, hyperkalemia, taste disturbance, gastrointestinal upset, or rash.	incidence of hypokalemia (≤3.5 mmol/L) while increasing the incidence of hyperkalemia (≥5.5 and ≥6.0 mmol/L), with an absolute difference of 2-3% compared to the low-dose group. Drug discontinuation due to hyperkalemia was low (<1%). High-dose losartan was superior to low-dose for reducing the composite of cardiovascular death or HF hospitalizations across the full spectrum of baseline potassium.
High- versus low-dose losartan and uric acid: An analysis from HEAAL/João Pedro Ferreira, MD, PhD, Faiez Zannad, MD, PhD, Michael S. Kiernan, MD, Marvin A. Konstam, MD/ Journal of Cardiology 82 (2023) 57–61	HEAAL was a double-blind trial, comparing the effect of two doses of losartan 150 (high dose) vs. 50 (low dose) mg/day among 3834 patients with symptomatic HF, a left ventricular ejection fraction≤40 %, and known intolerance to angiotensin-converting enzyme inhibitors. In the present study, the authors studied the associations of serum acid levels with outcomes and the effect of high- vs. low-dose losartan on serum acid levels levels, incident hyperuricemia, and gout.	High-dose losartan reduced serum uric acid levels and hyperuricemia more than low-dose but did not reduce incident gout episodes. The benefit of high-dose losartan to reduce the composite of HF hospitalization or cardiovascular death was not modified by baseline serum acid levels levels.

A Randomized, Placebo-Controlled, Double-Blind, Parallel Study of Various Doses of Losartan Potassium Compared With Enalapril Maleate in Patients With Essential Hypertension/ Alan H. Gradman, Karen E. Arcuri, Allan I. Goldberg, Leila S. Ikeda, Edward B. Nelson, Duane B. Snavely and Charles S. Sweet/ Hypertension. 1995; 25:1345–1350	Double blind, randomized, placebo controlled	There were important clinically and statistically significant reductions (P≤.01) in trough and peak supine SBPs and DBPs with losartan potassium 50 mg compared with placebo. Doses of losartan potassium above 50 mg provided no additional mean reduction in blood pressure. Losartan potassium appeared to be well tolerated in this study. There were no dose-related trends for losartan potassium with respect to the percentage of patients with any adverse experiences, serious adverse experiences, or drug-related adverse experiences or who withdrew because of an adverse experience.
An intact renin±angiotensin system is a prerequisite for normal renal development/ Gregor Gurona and Peter Friberg/ Hypertens 2000, 18:123±137 & Lippincott Williams & Wilkins.	review	Blockade of the RAS with ACE inhibitors or losartan from d3 to d24 in rats induces highly reproducible renal abnormalities that persist after treatment.
Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure/ Konstam MA, et.al./ The Lancet. 2009. 374(9704):1840-1848.	double-blind, randomized, dose controlled trial	In patients with heart failure, high-dose losartan reduces all-cause mortality and hospitalization for heart failure more effectively, as compared to low-dose losartan. There were more cases of renalimpairment, hypotension, and hyperkalemia in the high-dose group. However,

		these did notlead to significantly more withdrawal from treatment.
Losartan metabolite EXP3179 is a unique blood pressure-lowering AT1R antagonist with direct, rapid endothelium-dependent vasoactive properties/ Elodie Sauge, Dmitri Pechkovsky, N.D. Prasad Atmuri, Arash Y. Tehrani, Zoe White, Ying Dong, Jessica Cait, Michael Hughes, Anthony Tam, Graham Donen, Christopher Yuen, Michael J.A. Walker, Kelly M. McNagny, Don D. Sin, Marco A. Ciufolini, Pascal Bernatchez/ Vascular Pharmacology 147 (2022) 107112	preclinical	The authors provided direct structure-activity evidence that EXP3179 is a BP-lowering AT1R blocker with unique endothelial function-enhancing properties not shared with losartan or EXP3174. The major pharmacological effects of losartan in patients are therefore likely more complex than simple blockade of AT1R by EXP3174, which helps rationalize its therapeutic and prophylactic properties, especially at very high doses. Reports relying on EXP3179 as an AT1R-independent losartan analogue may require careful re-evaluation
EXP3 l 7 4: The Major Active Metabolite of Losartan/ Toshiaki Tamaki, Akira Nishiyama, Shoji Kimura, Yasuharu Aki, Masanori Yoshizumi, Hitoshi Houchi, Kyoji Morita, and Youichi Abe/ Cardiovascular Drug Review Vol. 15, No. 2, pp. 122-136	preclinical	EXP3 l 74 is a selective, long-acting, noncompetitive angiotensin II AT 1 receptor antagonist. EXP3 l 7 4 is a major metabolite of losartan, found in plasma, it contributes to the antihypertensive effects of oral losartan in humans, although losartan itself is a selective AT csubtype, non peptide angiotensin II receptor antagonist and not a

		prodrug. The biotransformation of losartan to EXP3 l 7 4 is catalyzed by two cytocrome P450 subfamilies (CYP3A4 and CYP2C9). In normal healthy volunteers intravenously administered EXP3174 has a half-life of 6.3 h and is eliminated by both renal and nonrenal routes. The low bioavailability of EXP3174 after oral administration may limit its clinical efficacy.
Hypotensive Effect of Losartan, a Nonpeptide Angiotensin II Receptor Antagonist, in Essential Hypertension/ Kazuo Tsunoda, Keishi Abe, Takeshi Hagino, Ken Omata, Seiichi Misawa, Yutaka Imai, and Kaoru Yoshinaga/ American Journal of Hypertension-JANUARY 1993-VOL. 6, NO. 1	Open label, uncontrolled single center study	The oral, once-daily administration of losartan, a nonpeptide angiotensin II receptor antagonist, significantly lowered the blood pressure of patients (n=8) with essential hypertension for 24 h, but did not affect either the circadian rhythm or variability of blood pressure or pulse rate. Losartan did not affect creatinine clearance, urinary volume, or urinary sodium or potassium excretion. Also, losartan has a hypouricemic action, suggesting that it would be an important adjunct to treatment with diuretics.
Clinical Safety and Tolerability of Losartan/	review	Losartan, the well-tolerated prototype of a

Michael Weber, MD/ CLINICAL THERAPEUTICS®Vol. 19, NO. 4, 1997		new class of antihypertensive drugs, provides clinicians with another therapeutic option for patients with hypertension. This selective ATl-receptor blocker has demonstrated efficacy and an excellent tolerability profile in hypertensive patients in many placebo-controlled trials. Because of its efficacy, specificity, duration of action, and favorable safety profile, losartan can be considered for first-line therapy in many patients. It also appears to be suitable as an alternative therapy in patients already experiencing side effects with other agents. The data suggest that losartan can safely be administered in hypertensive patients with concomitant illnesses.

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/s/

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