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Livdelzi® (seladelpar) Mechanism of Action

This document is in response to your request for information regarding the mechanism of action of Livdelzi® (seladelpar [SEL]) for the treatment of primary biliary cholangitis (PBC).

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Product Labeling[1]

Clinical Pharmacology

Mechanism of action

SEL is a peroxisome proliferator-activated receptor (PPAR)-δ agonist. However, the mechanism by which SEL exerts its therapeutic effects in patients with PBC is not well understood. Pharmacological activity that is potentially relevant to therapeutic effects includes inhibition of bile acid (BA) synthesis through activation of PPARδ, which is a nuclear receptor expressed in most tissues, including the liver. Published studies show that PPARδ activation by SEL reduces bile acid synthesis through fibroblast growth factor 21-dependent downregulation of CYP7A1, the key enzyme for the synthesis of BAs from cholesterol.

Mechanism of Action of SEL

SEL is a potent and selective peroxisome proliferator-activated receptor δ (PPARδ) agonist, or delpar.[2] There are three proteins within the family of PPARs: PPARα, PPARγ, and PPARδ. PPARδ is a ligand-activated nuclear receptor that regulates glucose, lipid, and sterol metabolism.[3-5] PPARδ activation reduces BA synthesis in the liver through fibroblast growth factor 21–dependent downregulation of CYP7A1, the key enzyme for the synthesis of BAs from cholesterol, and by decreasing cholesterol synthesis and absorption.[3,6-8]

These actions result in lower BA exposure in the liver and reduced circulating BA levels. SEL also has positive effects on serum lipids, inflammation, and fibrosis.[9]

Additionally, one of the most common symptoms in patients with PBC is pruritus; however, the pathophysiology of pruritus in PBC is not completely understood. Treatment with SEL has been shown to reduce pruritis in patients with PBC, which is also associated with reduced BAs and interleukin-31 levels.[10]

Patients with moderate-to-severe pruritus who were treated with SEL experienced significant improvements in biochemical markers of cholestasis and significant reductions in patient-reported pruritus measurements.[6,9]

References

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9. Hirschfield GM, Bowlus CL, Mayo MJ, et al. A Phase 3 Trial of Seladelpar in Primary Biliary Cholangitis. *N Engl J Med.* 2024;390(9):783-794.
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Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Livdelzi US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/pbc/livdelzi/livdelzi_pi.

Follow-Up

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