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Thank you for contacting Neurocrine Biosciences to request information regarding the mechanism of action (MOA) of valbenazine (VBZ), also known as NBI-98854, for the treatment of Tardive Dyskinesia (TD).

INGREZZA is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of adults with tardive dyskinesia.

The etiology and pathophysiology of TD have not been fully elucidated. One leading hypothesis implicates the post-synaptic dopamine D2 receptor upregulation that may result from exposure to dopamine receptor blocking agents (DRBAs), such as first- and second-generation antipsychotics and the gastric motility agent metoclopramide. This upregulation of D2 receptors is thought to result in post-synaptic dopamine hypersensitivity with the subsequent, aberrant neurotransmission manifesting as the abnormal, involuntary movements of TD.<sup>1</sup>

The MOA of VBZ in the treatment of TD is unknown, though its pharmacology has been well characterized. VBZ is a selective vesicular monoamine transporter 2 (VMAT2) inhibitor.<sup>2,3</sup> VMAT2 is an integral presynaptic protein that regulates the packaging and subsequent release of dopamine and other monoamines from neuronal vesicles into the synaptic cleft.<sup>2,3</sup> It is believed that by inhibiting VMAT2 from packaging dopamine into synaptic vesicles for subsequent release, thereby reducing the dopamine available for binding to upregulated D2 receptors.<sup>2,3,4</sup>

**This letter and the enclosed material are provided in response to your unsolicited medical information inquiry. Please feel free to contact Neurocrine Medical Information at (877) 641-3461 or [medinfo@neurocrine.com](mailto:medinfo@neurocrine.com) if you would like to request additional information.**

#### References

1. Sayers AC, Burki HR, Ruch W, et al. Neuroleptic-induced hypersensitivity of striatal dopamine receptors in the rat as a model of tardive dyskinesias: effects of clozapine, haloperidol, loxapine and chlorpromazine. *Psychopharmacologia*. 1975;41(2):97-104.
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