# (R)-Isometheptene\* (IMH) Binds to the Imidazoline-1 Receptor and (S)-IMH increases Blood Pressure: Potentially Superior Benefit-to-Risk Ratio for (R)-IMH as an Analgesic for Headache

# Bruce Daugherty, Leland Gershell, Seth Lederman

Tonix Pharmaceuticals, New York, NY.

## Introduction

- Isometheptene (IMH) is a racemic drug that has been used clinically in the US for more than 70 years primarily as a treatment for headache. Yet its mechanism of action remains unknown.
- Racemic IMH has sympathomimetic effects that have been linked to cardiovascular effects reported in the product labeling.
- To elucidate the mechanism of action of IMH, we separated IMH into the individual isomers, (R)-IMH and (S)-IMH and studied their molecular and cardiovascular effects.

# **Racemic isometheptene (IMH) has a long track record of use**



Previously marketed isometheptene drugs were a mixture containing equal amounts of two chemically distinct, mirror-image isomers





Growth regulation

### **Model of I<sub>1</sub>-imidazoline receptor signalling pathways**



(PKC $\beta_{II}$  and PKC $\zeta$ ) and mitogen-activated protein kinase (MAPK); extracellular-regulated kinase (ERK); and c-jun kinase (JNK).

#### Methods

- Racemic IMH was screened on a broad panel of protein targets, which included enzymes, receptors (both GPCR and non-GPCR), ion channels and transporters.
- The effects on arterial blood pressure (BP) and heart rate (HR) of intravenous (IV) racemic IMH mucate, (R)-IMH mucate, and (S)-IMH mucate in anesthetized male Wistar rats were studied (using consecutive doses of 0.03, 0.1, 0.3, 1, 3, and 10 mg/kg IV with 10-minute interdose intervals).
- The pharmacokinetics (PK) of racemic and (R)-IMH were studied in rats using stereospecific liquid chromatography-mass spectrometry.

#### Results

#### **Comparative Binding Affinities of (R)-Isometheptene versus** (S)-Isometheptene to Receptors Expressed in the CNS

	K <sub>i</sub> (nM)										
Compound	I <sub>1</sub> R	I <sub>2</sub> R	a <sub>2B</sub>	Sigma-1 Receptor	Sigma-2 Receptor						
(R)-Isometheptene	18	62	50000	1900	5600						
(S)-Isometheptene	1100	180	55000	2100	5200						

#### Equilibrium Binding of (R)-Isometheptene, (S)-Isometheptene and Racemic **Isometheptene to I<sub>1</sub>-Imidazoline Receptor**



(R)-Isometheptene Has Reduced Effects on Blood Pressure Compared to (S)-Isometheptene and Racemic Isometheptene





#### (R)-Isometheptene Has Similar Effects on Heart Rate Compared to (S)-Isometheptene and Racemic Isometheptene



Each test substance versus vehicle: no indication = not significant; \* = P < .05; \*\* = P < .01; \*\*\* = P < .001

#### Pharmacokinetics of Racemic Isometheptene Mucate and (R)-Isometheptene Mucate in Rats

Test Article	Dose, mg/kg	C <sub>max</sub> , ng/mL		AUC, ng.h/mL		T <sub>max</sub> , h		T <sub>1/2</sub> , h	
		R-IMH	S-IMH	R-IMH	S-IMH	R-IMH	S-IMH	R-IMH	S-IMH
Racemic IMH	1	165	175	62	66	0.16	0.16	0.37	0.38
(R)-IMH	0.5	198	NC	76	NC	0.16	NC	0.47	NC

#### Conclusions



- Analgesic
- Binds to I<sub>1</sub>-imidazoline receptor



- Our finding that R-IMH binds to  $I_1R$  with high affinity suggests that this receptor is the primary site of action for R-IMH's analgesic effects. This is confirmed by recent results in the  $I_1R$  knock out mouse in which there is a decreased pain threshold.
- Our finding that S-IMH produces significantly higher increased BP suggest that this isomer is responsible for the cardiovascular liability observed with racemic IMH.
- These findings suggest that R-IMH is an agonist of  $I_1R$ , a receptor in the brain that regulates pain perception, and that it may have a superior benefit/risk ratio as an analgesic for headache compared to either the racemic or the (S)-isomer.

#### References

- 1. MigraTen Prescribing Information; Pharmelle; Gilbert AZ, 2004.
- 2. Diamond S, Medina JL. Isometheptene—a non-ergot drug in the treatment of migraine. *Headache*. 1975;15(3):211-213.
- 3. Zhang L, Zhao TY, Hou N, et al. Generation and primary phenotypes of imidazoline receptor antisera-selected (IRAS) knockout mice. Cns Neurosci Ther. 2013;19(12):978-981.
- 4. Daugherty, BL, Gershell, L and Lederman S. (R)-isometheptene (IMH) binds to the imidazoline-1 receptor and (S)-isometheptene increases blood pressure: Potentially superior benefit to risk ratio for (R)-IMH as an analgesic for headache. Headache. 2015: June Abstract PS29.55(53) 172.

\*(R)-IMH mucate is being investigated in the US for tension-type headache as TNX-201 under US Investigational New Drug and it is not approved for any indication.