RiVive™ Naloxone Nasal Spray

The scientific, regulatory, and public health rationale for 3 mg

HARM REDUCTION THERAPEUTICS

About RiVive

RiVive™ (naloxone HCl nasal spray 3 mg) is a novel over-the-counter intranasal formulation of naloxone delivered as an atomized spray that can save lives. It uses an easy-to-use standard nasal sprayer for single administration of naloxone for the emergency treatment of opioid overdose and is available without a prescription. RiVive produces a **3-fold higher systemic exposure** with comparable early absorption to the reference naloxone product (0.4 mg of naloxone delivered via intramuscular injection).

Why 3.0 mg of naloxone?

RiVive uses 3.0 mg of naloxone to reverse opioid overdoses, including fentanyl overdoses. The 3.0 mg dose is based on the scientific literature supporting the efficacy of naloxone in opioid overdose reversals broadly[1], and the efficacy of both 2.0 mg[2] and 4.0 mg intranasal (IN) naloxone formulations[3]. Extensive input from harm reduction experts, the long history of reversing opioid overdoses using 0.4 mg of intramuscular naloxone, and the desire to administer enough naloxone to restore spontaneous breathing[4] without inducing full blown acute opioid withdrawal, all supported our decision to formulate RiVive with 3.0 mg of naloxone. Moreover, recent studies have shown that both 8.0 mg and 4.0 mg intranasal naloxone products were equally effective (99%) in reversing overdoses, but the 8.0 mg dose was far more likely to induce serious opioid withdrawal[5].

Even 2.0 mg of intranasal naloxone given in various concentrations reverses opioid overdose in 74-82% of patients[6,7]. Opioid-related overdose deaths are increasingly being driven by exposure to highly potent fentanyl and fentanyl analogs[8,9]. A subset of opioid overdoses requires multiple administrations of 2.0 mg IN naloxone to successfully reverse. However, in a study of over 2166 people who received naloxone in the field followed by paramedic support, 91% experienced complete resolution and reversal of symptoms after a single (mostly 2.0 mg; 51%) dose of IN naloxone and required no further advanced life support intervention. Only 9% required two or more doses of naloxone, and only 2.4% required a third dose. Moreover, even in the context of illicitly manufactured fentanyl, studies have found no increases in the average number of naloxone doses used to reverse an overdose[10,11].

> *"State health agency staff, public health professionals, policymakers, and clinicians should be aware that more potent, longer- acting opioid antagonists are not necessary and may have unintended consequences."* – Hill et al. (2022) *Increasingly powerful opioid antagonists are not necessary*. Int. J. Drug Policy.

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