Announcement from the Medical Director Regarding neffy® Epinephrine Nasal Spray

Summary:
Based on its delivery method and resiliency to cold and heat exposure, neffy® (intranasal epinephrine) continues to be an intriguing non-injectable alternative to intramuscular epinephrine injections. However, current evidence does not yet support its use as a replacement for intramuscular epinephrine in austere or remote environments where back-up injectable epinephrine may not be available. **Therefore, WMA International does not recommend substituting neffy® in place of injectable epinephrine for the treatment of anaphylaxis in these environments at this time.**

Rationale:

- We have found no published human studies which have evaluated neffy® in human cases of grade 3 or 4, or severe*, anaphylaxis.
  - The largest study to date was performed by ARS Pharma, the manufacturer of neffy®, and has not been peer reviewed. This study includes 595 patients participating in an oral food challenge in healthcare settings, none of whom were experiencing severe anaphylaxis. The results of that study are qualified with the following statement: "*this observational analysis differs from a randomized clinical trial in several ways. The studies have different endpoints and there are inherent limitations in real-world observational studies, including lack of randomization, lack of uniform timing or type of clinical assessments and challenges with missing data.*"
  - One single small study (15 pediatric subjects in an oral food challenge) involved grade 2 anaphylaxis, and none involved severe cases.
- Absorption of intranasal epinephrine may be compromised:
  - in patients presenting with severe hypotension caused by a severe case of anaphylaxis with reduced blood flow to the mucosa.
    - We do not feel that existing studies in animal models (e.g., dogs) that indicate efficacy of neffy® for these conditions are sufficient to justify the use of neffy® in humans.
  - If the nasal mucosa is 'blocked' by *severe* congestion, sinusitis, rhinorrhea due to allergic and infectious rhinitis.

Cost of neffy® and Intramuscular Autoinjectors:
As of publication, the cash cost of one neffy® nasal spray was ~$700 and the cash price for the least expensive autoinjector available was ~$172. Costs can be significantly reduced, and even comparable, with some insurance co-pays. For reference, a notice to Colorado prescribers re: the wholesale cost can be found here.

Conclusion:
At this time, WMA International does not recommend neffy® as an alternative to intramuscular epinephrine in austere or remote settings. These recommendations may be reconsidered should robust, peer-reviewed data emerge demonstrating efficacy in acute, severe anaphylaxis and with practical absorption concerns addressed.

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Grade	Summary	Specific signs and symptoms
Grade 1	Generalised mucocutaneous signs	Erythema Urticaria Angioedema
Grade 2	Multi-organ manifestations	Mucocutaneous signs Bronchospasm Hypotension
Grade 3	Severe life threatening multi-organ manifestations	Arrhythmia Cardiovascular collapse Bronchospasm Can have cutaneous signs
Grade 4	Cardiopulmonary arrest	Cardiac arrest

Grading of anaphylaxis, adapted from the Ring and Messmer grading scale. Yim, 2016

Additional References:

Casale, T. B., Ellis, A. K., Nowak-Wegrzyn, A., Kaliner, M., Lowenthal, R., & Tanimoto, S. (2023). Pharmacokinetics/pharmacodynamics of epinephrine after single and repeat administration of neffy, EpiPen, and manual intramuscular injection. *Journal of Allergy and Clinical Immunology*, *152*(6), 1587–1596. https://doi.org/10.1016/j.jaci.2023.08.007

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Sparapani, S., Authier, S., Lowenthal, R., & Tanimoto, S. (2023). The impact of anaphylaxis on the absorption of intranasal epinephrine in anaesthetized non-naive beagle dogs. *Journal of Allergy and Clinical Immunology: Global*, *2*(4), 100165.

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