

Low Risk of Ocular Toxicity after Unintentional Exposure of Epinephrine Nasal Spray

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RATIONALE

- Unintentional ocular exposure to epinephrine nasal spray is a potential safety concern.
- Although epinephrine is used in multiple ocular formulations, unintentional ocular administration was assessed to determine tolerability and support the overall safety profile of a recently FDA-approved epinephrine nasal spray.

METHODS

STUDY DESIGN AND POPULATION

- A non-GLP ocular tolerability study was conducted using six naïve New Zealand white rabbits (3 males, 3 females).
- Placebo control or epinephrine nasal spray (1 mg) was applied via topical ocular drops to the right or left eye, respectively, once on Day 1.
- Animals were monitored over seven days for mortality, clinical signs, body weight changes, ophthalmic findings, ocular irritation (using the Modified Hackett-McDonald Scoring System), and gross necropsy findings.
- The study design and general assessments are presented in **Table 1** and **Table 2**.

Table 1: Study Design

Group No.	Treatment Right Eye	Treatment Left Eye	Dose Level (mg/eye)	Dose Volume (mL/eye)	Dose Concentration (mg/mL)	Main Study	
						No. of Males	No. of Females
1	Placebo control	Epinephrine nasal spray	1	100	10	3	3

Table 2: General In-life Assessments of Study Animals

Parameter	Population(s)	Frequency (minimum required)	Comments
Mortality/Cageside Observations	All Main Study Animals	At least twice daily ^{a,b} (morning and afternoon) beginning upon arrival through termination/release.	Animals were observed within their cage unless necessary for identification or confirmation of possible findings.
Detailed Clinical Observations	All Main Study Animals	Prior to randomization, Day -1, and prior to necropsy. ^c	Animals were removed from the cage. Observations included, but were not limited to, evaluation of the skin, fur, eyes, ears, nose, oral cavity, thorax, abdomen, external genitalia, limbs and feet, respiratory and circulatory effects, autonomic effects such as salivation, nervous system effects including tremors, convulsions, reactivity to handling, and unusual behavior.
Individual Body Weights	All Main Study Animals	At receipt, prior to randomization, Day -1, and prior to necropsy.	The body weights recorded prior to Day-1 are not reported but maintained in the study file.
Ophthalmic Examinations	All Main Study Animals	Pretreatment (all animals including source), Days 2 and 8, and prior to necropsy.	The ophthalmoscopic examinations were conducted by an ophthalmologist or a staff veterinarian via indirect ophthalmoscopy and slit-lamp biomicroscopy.
Ocular Scoring	All Main Study Animals	Pretreatment (all animals including source), Day 1, (0.5, 1, and 6 hours postdose), Day 2 (24 hours postdose), days 3 to 7, and once prior to necropsy.	Modified Draize scoring was performed by trained technicians in accordance with Testing Facility SOP. The scoring endpoints included Cornea Opacity Degree of Density, Area of Cornea Involved, Iris Values, Conjunctivae Redness, Conjunctivae Chemosis, and Conjunctivae Discharge.

^a Included alternate animals until released from study.

^b Except on days of receipt and necropsy where frequency was at least once daily.

^c For observations that could not be attributed to an individual animal due to social housing (e.g., watery feces), the observation was noted to each animal in the socialized group.

RESULTS

- Epinephrine nasal spray was well tolerated with no mortality, clinical abnormalities, or changes in body weight.
- Ophthalmic examinations via indirect ophthalmoscopy and slit-lamp biomicroscopy revealed no signs of irritation or ocular toxicity.
- Modified Hackett-McDonald ocular irritation scoring was graded as "0" for all parameters at all timepoints.
- No gross pathological changes were noted at necropsy.

CONCLUSIONS

- A single topical administration of epinephrine nasal spray 1 mg in rabbit eyes was not associated with any adverse effects, indicating a low risk of ocular toxicity.
- These results support the safety of epinephrine nasal spray in the event of unintentional ocular exposure and taken together with epinephrine's use in other ocular formulations, suggest that no further nonclinical ocular studies are necessary.

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