Apomorphine Film (APL-130277) Produces No Buccal Mucosal Irritation: Results from a 28-Day Toxicology Study in Hamsters

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BACKGROUND

- Apomorphine HCl is a highly acidic compound
- Non-parenteral formulations have been associated with mucosal irritation, prohibiting their use
- APL-130277 is a unique, sublingually-administered film containing apomorphine
- APL-130277 is designed with a buffer layer that rapidly neutralizes acid generation

OBJECTIVE

Determine the tolerance of and potential for mucosal irritation following the administration of apomorphine film (APL-130277)

METHODS

Buccal mucosal testing using Syrian hamsters is an internationally accepted model to determine potential irritation by drugs
(Gardner AF. J Dent Res. 1964;43:1211-1221).

Test Articles

- **APL-130277** film, each containing 2.08 mg of apomorphine HCl.
  Note: Dose is approximately 15 times higher than a 30 mg dose in a 60 kg human
- **Placebo** film, each containing 0 mg apomorphine HCl.
- *APL-130277 and placebo were manually sectioned into 12 strips (5.5 mm by 7.3 mm)*

Dosing

- Hamsters were administered APL-130277 or placebo three times daily for 28 days

APL-130277 or Placebo Administration

Right cheek pouch.

- Test strip placed onto buccal mucosa followed by 0.1 mL of water to enhance dissolution
- Successive strips were applied to same area of the cheek pouch for each dose.

Left cheek pouch

- Manipulated in the same manner without the placement of a strip but with the addition of water

Species

- Mesocricetus auratus and the strain was the Golden Syrian Hamster.
- Source: Charles River, Montreal, Canada.

METHODS (continued)

Animal Housing and Maintenance/Environment

- Hamsters were individually housed in Nalgene® cages
- The animal room environment was controlled (targeted ranges: temperature 18-26°C, relative humidity 30-70%, greater than 10 air changes/hour) and monitored.
- The photo-cycle was 12 hours light and 12 hours dark.

Study Assessments

Clinical Observations

- Clinical signs, body weight, and food consumption
- Cheek pouches everted, cleared of food, and examined for signs of irritation
  - Prior to the first dose on Days 1, 2, 3, 4, 8, 14, and 21
  - Prior to necropsy on Day 29 using
- Draize scoring system was utilized:
  - 0=no erythema; no edema;
  - 1=very slight erythema (barely perceptible); very slight edema (barely perceptible);
  - 2=well defined erythema; slight edema (edges well defined by definite raising);
  - 3=moderate to severe erythema; moderate edema (raised approximately 1 mm) and
  - 4=severe erythema (beet-redness) to slight, eschar formation (injuries in depth); severe edema (raised more than 1 mm and extending beyond the area of exposure).

Necropsy

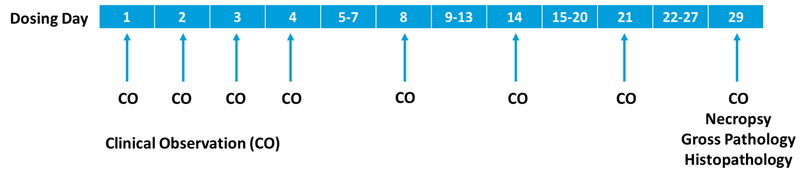
- Day 29, all animals on study were euthanized by CO2/02 exposure and necropsied.

Gross Pathology

- Left and right cheek pouches from each animal were macroscopically examined

Histopathology

- Changes observed in 3 separate samples of each cheek pouch / hamster were graded on a scale of:
  - None (0) [tissues were considered to be normal]
  - Minimal (1) [lesions were detectable within reasonable viewing]
  - Mild (2) [lesions easily seen, but enveloped a small amount of tissue area]
  - Moderate (3) [lesions were prominently present, involving 10% to 50% of area]
  - Marked (4) [lesions were extensive and may involve 50% to 75% of area]
  - Severe (5) [lesions were interpreted as within the worst possible scenario]



RESULTS

Treatment Group	Animals (N = 8/sex/group) Mean Body Wt Change ± SD		Apomorphine Dose (mg)	Dosing Frequency
	Male	Female		
Control	+9.5 ± 4.4 g	+15.2 ± 6.5 g	0	*t.i.d.* x 28d
APL-130277	-3.0 ± 4.1 g	-4.0 ± 8.9 g	2.08	*t.i.d.* x 28 d

Clinical Observations

Post-dose hyperactivity severity in APL-130277 group decreased during study. Initial body weight loss (starting body wt was 134 g in males and 143 g in females) and reduced food consumption showed recovery as study progressed.

No signs of irritation over the 28 days of dosing in males and females dosed either with the placebo or APL-130277

Gross Pathology

No gross lesions were found on either the left or right cheek in any of the buccal mucosa of any males or females treated with no strips, placebo or with APL-130277.

Histopathology

No histopathologic findings in the buccal mucosa of any males or females treated with no strips, placebo, or with APL-130277.

CONCLUSIONS

- APL-130277 produced no irritation of the cheek pouch buccal mucosa of male and female hamsters when administered at a dose of 2.08 mg (15 X higher than a 30 mg dose in a 60 kg human) three times daily for 28 consecutive days.

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