

3.4.6 Local tolerance

Table 2.6.7.16a. Local Tolerance (In Vitro)
Test Article: Cinacalcet Hydrochloride (AMG 073)

Species/ Strain	Method of Administration	Doses	Gender and No. Per Group	Noteworthy Findings	Study Number
Anticoagulated rat, non-human primate, and human blood	In vitro direct contact	5 mg/mL AMG 073 Mesylate (50mM lactate, 190mM dextrose, pH 4.20); 1.33 mg/mL AMG 073 HCl (50mM acetate, 222mM dextrose, pH 4.25); 5 mg/mL AMG 073 Mesylate (50mM acetate, 197mM dextrose, pH 4.20); 5 mg/mL AMG 073 Mesylate (50mM acetate, 4% w/v ethanol, pH 4.27)	n/a	All test articles and vehicle controls induced hemolysis in rat, non-human primate, and human blood.	100359
Human blood	In vitro direct contact	AMG 073 Mesylate and AMG 073 HCl at 0.005, 0.05, 0.5, 5.0, 50, 500, and 1000 µg/mL	n/a	Hemolysis observed in all test groups with a general dose-response trend	100399
Human blood	In vitro direct contact	AMG 073 in the following vehicles: Intralipid-low shear; Intralipid-high shear; 10mM Acetate/278mM Dextrose; 10mM Acetate/275mM Mannitol; 5% Captisol/50mM Phosphate; 11.6% Captisol/NaOH to adjust (pH~7.85); HCl to adjust pH(~4.10); 0.5% Tween 80/50mM Phosphate; DMSO, 15% Captisol/10mM Phosphate, pH7.0 All at 1 mg/mL concentration and at 5, 50, or 500µL volume	n/a	Inconclusive results for Intralipid samples due to opaque white appearance interfering with optical density. The following formulations were negative for producing hemolysis: 11.6% Captisol/NaOH to adjust and 15% Captisol/10mM Phosphate,pH7.0. All remaining test article formulations were positive for producing hemolysis in human blood at 1 mg/mL. Increasing hemolytic index values occurred with higher volumes of formulations used in the assays	100482

Table 2.6.7.16b. Local Tolerance (In Vivo)
Test Article: Cinacalcet Hydrochloride (AMG 073)

Species/ Strain	Method of Administration	Doses	Gender and No. Per Group	Noteworthy Findings	Study Number
New Zealand White Rabbit	Topical	0.5g/ 1mL distilled H ₂ O	3 males	AMG 073 caused only a very slight erythema reaction in 1/3 animals at the 4-hr observation point. No other dermal irritation was observed	100325
New Zealand White Rabbit	Instilled into the eye	32 mg	3 females	AMG 073 caused corneal opacity, iridal irritation, and severe conjunctival irritation in all 3 animals. Corneal opacity (3/3 animals) and conjunctival irritation (1/3 animals) were still present at day 21 after treatment	100324
Guinea Pig	Topical, Intradermal	Intradermal 0.1 mL/site (0.5% w/v) Topical 0.3 mL/site (25% w/v) Challenge 0.2 mL/site (25% w/v)	10 M & F (test article) 5 M & F (vehicle control) 3 M & F (positive control)	Mild Sensitizer (Grade I)	102943

Local tolerance studies showed that cinacalcet is a severe eye irritant and a mild dermal contact irritant. In the guinea pig sensitization study, cinacalcet was a mild dermal sensitizer.

4 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

3.5 REFERENCES

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3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Pending agreement on the label, this NDA can be approved (AP)

Recommendations: Based on *in vitro* and *in vivo* nonclinical data, thorough evaluation of clinical trial data for any events related to cardiac conduction abnormalities under resting or stress conditions (EKG), myocardial and coronary artery disease, and CNS excitation (seizures) is recommended.

Suggested labeling: Labeling changes for the "PRECAUTIONS" section relating to carcinogenicity and reproductive study results are appended (Team Leader Memo, K. Davis-Bruno, February 10, 2004)

Signatures (optional):

/S/

Reviewer Signature _____

Supervisor Signature /S/ Concurrence Yes ___ No ___

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