

**APPENDIX A**

**Summary of Published Evidence Relating to the Issue of  
Intranasally-Applied Decongestants and Possible Cardiovascular Changes**

[RE: Docket No. 76N-052N; Cold, Cough, Allergy, Bronchodilator, and Anti-asthmatic Drug Products for Over-the-Counter Human Use: Tentative Final Monograph for OTC Nasal Decongestant Drug Products]

## SUMMARY

The bulk of published evidence argues against the need for a warning contraindicating the use of nasally applied decongestants in hypertensive disorders. Oral threshold doses reported to be associated with changes in pulse-rate and/or blood pressure are 6-10 times higher than the maximal dose of phenylephrine or ephedrine administered intranasally. Furthermore, published clinical in-use studies with intranasally administered sympathomimetics provide more direct evidence that the nasal use of these agents is not associated with clinically significant cardiovascular changes. This has been demonstrated in normals as well as in patients with various cardiovascular disorders.

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While it is well documented that oral administration of sympathomimetic drugs, is associated with changes in mean arterial pressure and heart rate, the effect is dose-related and threshold doses have been established for those drugs that are used both orally and intranasally (i.e., phenylephrine and ephedrine). Stockton et.al.(1) found no increase in blood pressure in 5 subjects given single oral doses of phenylephrine (PE) ranging from 0.5 to 1.5 g. In the two subjects given the highest dose level however, there was a 12% increase in heart rate. In another study in which PE was administered by various routes of administration(2), the threshold dose required to increase blood pressure in 7 subjects was demonstrated to be about 50 mg orally. In addition, McLaurin et.al.(3) found that oral administration of 10 mg PE had no significant effect on blood pressure or heart rate as compared with placebo in a double-blind cross-over study in 88 patients. Orally administered ephedrine has been associated with increased systolic pressures at doses of 50 mg and above (4,5,6). However, blood pressure has been shown to be essentially unchanged at oral doses of 25 or 30 mg in a number of published studies (3,5,7,8). Drew et.al.(5) demonstrated that the threshold oral dose producing blood pressure elevation was 60 mg of ephedrine; 30 mg doses had no effect.

The results of the above studies indicate that neither PE nor ephedrine produce clinically significant increases in blood pressure or heart rate at doses of 50 mg PE or 30 mg ephedrine and below. Assuming a highly exaggerated intranasal dose of 500 mg of a 1% Active Spray, the total dose of either ephedrine or PE would amount to only 5 mg. Thus, even if the entire dose were swallowed, this level would be unlikely to produce any cardiovascular changes.

This is confirmed by the results of several published in-use clinical studies on intranasally administered decongestants in which blood pressure and heart rate were monitored. As shown in the attached chart, nasally administered phenylephrine, oxymetazoline, xylometazoline, ephedrine or desoxyephedrine were not found to be associated with increased blood pressure, even in patients with hypertensive disorders. Only a single study on oxymetazoline (0.05%) showed an appreciable effect on blood pressure in 2/52 subjects. In this study, the authors failed to indicate the dose or duration of treatment and the intervals in which the blood pressure was monitored and/or elevated.

In summary, the bulk of published evidence argues against the need for a warning statement for hypertensive disorders with the use of topically administered decongestants. Oral threshold doses associated with any cardiovascular effects are 6-10 times higher than the maximally administered doses of phenylephrine or ephedrine. Furthermore, published clinical in-use studies with intranasal decongestants provide more direct evidence that this route of administration is not associated with clinically significant cardiovascular changes.

Cardiovascular Effects of  
Intranasal Decongestants

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SUMMARY OF PUBLISHED INFORMATION ON THE CARDIOVASCULAR EFFECTS OF INTRANASALLY ADMINISTERED DECONGESTANTS

<u>DECONGESTANT</u>	<u>NO. OF PATIENTS</u>	<u>DRUG CONC.</u>	<u>DOSE</u>	<u>REGIMEN</u>	<u>RESULTS</u>	<u>REFERENCE</u>
Phenylephrine (PE)	12 Normals <sup>a</sup> 14 (HT's)	0.25% and 1.0%	0.5-4 mg	increasing doses at hourly intervals	No significant ↑ in BP after tmt and no signific. differences between PE and placebo in BP or HR	9
	22	0.25%	5 drops/ nostril	single dose	BP and pulse rates, determined at 0.5, 1,2,4 and 6 hours post-tmt, did not change significantly in any patients	10
	46 <sup>b</sup>	0.25% or 1.0%	5 drops/ nostril	single dose	BP and pulse rates (evaluated from 3-45 min. post- tmt) did not change with tmt in any group of subjects.	11
Oxymetazoline (OXY)	52	0.05%	?	bid or tid	2/52 had ↑ in systolic press. of 15-25 mm/Hg; 35/52 had ↑ systolic pressure (ave.7mmHg) and 14 patients had ↑ systolic press. (ave. 4 mm Hg). No indication of time BP was ↑'d	12
	33	0.05% spray	1 spray/ nostril	qid for 1 day	No change in BP in groups receiving either tmt after 1st dose or ~ 24 hours later; 1 patient ↑'d & 1 ↑'d systolic pressure by 20 mm Hg	13
	33	.05% drops	3 drops/nos.			
	30 (Children)	.025%	3 drops/ nostril	tid q 8 hrs. for 14 days	No change in BP or pulse rate following 3,7 or 14 days of tmt.	14
	22 (Children)	.025%	5 drops/ nostril	single dose	No change in BP or pulse rate at 30 min. or 1,2,4 or 6 hrs. following tmt	10
Xylometazoline (Xylo)	100 (Children)	.025% (13) .05% (83)	2-4 drops/ nostril	tid, 3 days to 6 mo.	No changes in BP	15
	108	.05%-0.1%	4-6 drops/ nostril or 2-3 sprays/ nostril	qid	No effect on BP	16
	69 (infants)	.01%+ 0.1%	2 drops/ nostril	?	No changes in cardiac activity in 69 infants and no effects on BP in the 11 infants evaluated including 4 with congenital cardiac defects	17
	100 Normals <sup>a</sup> 6 HT	.025%, .05%	?	bid or tid for 1-2 wks	No changes in BP	18
	35	.025%, .05%	2-3 drops/ nostril	tid or qid PRN	No changes in BP in either normo-, hypo- or hyper- tensive patients	19
Ephedrine	33	1.0%	1 spray/ nostril	qid for 1 day	No change in BP after 1st dose or 24 hours later	13
Desoxyephedrine Saccharinate	52 <sup>d</sup>		5 drops/ nostril	single dose	No change in BP or pulse rates (evaluated from 3-45 min. post-tmt)	11

a) normals with nasal congestion but no CV disorders; HT = Hypertensives

b) patients had cardiac disorders (13), HT (12), thyroid disorders (9) or diabetes (12)

c) patients then used 2-3 drops/nostril q 2-4 hrs. for 7 days and were reevaluated

d) patients had cardiac disorders (15), HT (19), thyroid disorders (11) or diabetes (7)