- Hospitalizations and other serious nonfatal AEs

CCNV Trials

8/943 (0.8%) of CCNV patients experienced a total of 14 serious nonfatal AEs requiring re-hospitalization (7 patients) or prolonging hospitalization (1 patient). These AEs were assessed by the investigator as unlikely or not related to test med. and included dehydration (n=2), pleural effusion (n=2), vomiting (n=2), acidosis, bronchospasm, fever, headache, and intestinal obstruction. Also rated as unlikely or not related to test med. were two events of potential concern (unexplained seizures, n=1) and atrial flutter/fibrillation with tachycardia (n=1). These 2 cases are briefly summarized below.

- A 73y old F with no prior Hx of seizures was re-hospitalized for Tx of seizures (coded to convulsions), which continued in the hospital and occurred 7 days after receiving DOLA•Mesyl 50 mg. A CAT scan, MRI of the brain and a spinal tap done during the second hospitalization were all negative. The events (seizures + headache) lasted for ca. 3h, placed the patient at immediate risk of death, but resolved without sequelae and were assessed by the investigator as unlikely related to test med. but rather to possible early sepsis.

- A 56y old M had sinus bradycardia on Predose EKG. The patient's EKG performed 2h after DOLA•Mesyl 100 mg showed sinus bradycardia plus nonspecific ST-T wave changes. The pt. was re-hospitalized when his 96h Postdose EKG showed atrial fibrillation + tachycardia (the ventricular rate varied between 92 to 140 bpm). The patient also reported unusual shortness of breath after mild exertion and stated he felt like his heart was racing. The duration of the AF was unknown but the event resolved without sequelae following Tx with quinidine and digoxin.

  The events were assessed by the investigator as severe and not related to test med. but rather to doxorubicin chemotherapy. This is certainly possible but it seems also possible that the AF + TACH were due to DOLA•Mesyl alone or in combination with doxorubicin. Blood levels of the latter were not determined.

PONV Trials

6/948 (936 adult and 12 pediatric) (0.6%) patients who received oral DOLA•Mesyl in PONV trials experienced a total of 7 nonfatal AEs requiring prolonged hospitalization (4 patients) or were at immediate risk (4 patients); 2 pts. required prolonged hospitalization and were at immediate risk of death. In the comparator (PL), 3/231 (1.3%) experienced a total of 5 SAEs requiring hospitalization (1 pt.) or were diagnosed with cancer (2 pts.).

Except for the two briefly summarized below assessed as possible and definitely related to test med., respectively, all other events were assessed by the investigators as unlikely or not related to test med.

- Pt. AE-PO-0292, 0010-0800 (200 mg)

- A 61y old F patient had a med. Hx that included first degree AV block (PR interval of 286 msec), hypertension (treated with Verapamil 80 mg [illegible] dose taken the morning of the surgery) and hypothyroidism. The pt. had abdominal hysterectomy. 1h postdose EKG interval was 0.32, [illegible] reported to have complete heart block (coded as AV dissociation) [illegible] and 19 min. after receiving oral DOLA•Mesyl 200 mg. [illegible]

block began 9 min. after initiation of anesthesia and 3 min. prior to the first incision. This lasted 13 min. before progressing to the reported complete heart block which lasted ca. 15 sec. The event occurred during intraperitoneal manipulations. It resolved after treatment with glycopyrrolate (0.4 mg).

The physician investigator assessed this event as definitely related to DOLA•Mesyl and felt that the event placed the patient at immediate risk of death. The reviewer assessed this case at the IND level and after a very detailed evaluation concurred with the investigator's assessment of drug causality.

- a 29y old F with no known Hx related to this AE, had a HR of 60 bpm immediately prior to test med. She was undergoing abdominal hysterectomy when she developed nodal bradycardia at 20 beats per min. This event occurred 2h and 55 min. following a single oral dose of DOLA•Mesyl 100 mg. The patient was treated with atropine 0.6 mg and recovered immediately. The duration of the event was less than 1 min. Immediately prior to this event the patient had sinus bradycardia of ca. 50 beats per min., had just received fentanyl 100 μg and was undergoing surgical traction of the uterus as part of the surgical procedure. The patient had also received d-tubocurarine, fentanyl, thiopental, succinylcholine and vecuronium. The event was assessed by the investigator to be serious and severe and possibly related to test med.

- Severe AEs

Overall 31/943 (3.3%) and 23/936 (2.5%) of the DOLA•Mesyl patients participating in CCNV and PONV trials, respectively, reported severe AEs compared with 2/83 (2.4%) and 8/231 (3.5%) of patients receiving ondansetron and PL, respectively. These severe events were not dose dependent.

In CCNV trials, headache was the most frequently reported severe AE (8/943=0.8%) in DOLA•Mesyl patients. Those reported with OND were abdominal pain (1/83=1.2%) and dermatitis (1/83=1.2%). The most frequently reported severe Tx-related AE in DOLA•Mesyl patients was headache (5/943=0.5%); in OND patients it was abdominal pain (1/83=1.2%).

ii) All AEs

CCNV Trials

It is important to point out that, as summarized below, the overall AE occurrence rates differed between the US and non-US studies. Higher occurrence rates were reported in the two US studies. Among the reasons for this discrepancy, was the higher occurrence rates in HR and rhythm AEs in US studies[31]. It is therefore important to realize that the inclusion of the European data in the overall computation lowers the rates in the 100 mg and 200 mg dose groups by 11% each. In addition, it does not make sense to compare rates to compare overall incidence from the three trials to that of OND in the European

[31] Pain was likely although not exclusively the [illegible] used in the US studies. The following [illegible] lead [illegible] which were a requirement in phase III US [illegible] T wave changes, extrasystoles, arrhythmia atrial and [illegible]

trial. Therefore, the Medical Officer concludes that the relevant comparison for AE occurrence rates between DOLA•Mesyl and OND is in Study -087 (only).

CCNV Trials:
Overall AE Occurrence Rates (%)

			DOLA•Mesyl Dose (mg)				
		OND	25	50	100	200	All
US Studies [-043, -048]	n	N/A	155	163	151	158	627
	%	N/A	(56.8)	(51.5)	(60.9)	(65.8)	(58.7)
Non-US Study [-087]	n	83	80	80	76	80	316
	%	(36.1)	(25.0)	(37.5)	(39.5)	(33.8)	(33.9)
All Studies	n	83	235	243	227	238	943
	%	(36.1)	(46.0)	(46.9)	(53.7)	(55.0)	(50.4)
Overall AE Occurrence Rates (%) in the HR and Rhythm SOC							
US Studies [-043, -048]	n	N/A	155	163	151	158	627
	%	N/A	(23.2)	(20.9)	(20.5)	(31.6)	(24.1)
Non-US Study [-087]	n	83	80	80	76	80	316
	%	(2.4)	(3.8)	(5.0)	(5.3)	(7.5)	(5.4)
All Studies	n	83	235	243	227	238	943
	%	(2.4)	(16.6)	(15.6)	(15.4)	(23.5)	(17.8)

- **As shown above the overall occurrence for AEs increased with increasing DOLA•Mesyl dose. The System Organ Classes most commonly affected across all DOLA•Mesyl doses were the Central and Peripheral Nervous System, HR and Rhythm, the G.I. System and Body as a Whole (Table 95). The incidence of headache, dizziness, drowsiness, T wave change, atrial arrhythmia, EKG Abnormal Specific and diarrhea appeared to increase with increasing DOLA•Mesyl dose. Especially noticeable is the difference between 25 and 200 mg of the drug.**

TABLE 95

Frequency (Percent) of Frequently Occurring (≥2%) AEs Regardless of Causality in CCNV Patients from Controlled Studies - Oral DOLA®Mesyl Single Dose

System Organ Class and Preferred Term	DOLA®Mesyl Dose (mg)				
	25 [n=235]	50 [n=243]	100 [n=227]	200 [n=238]	All Doses [n=943]
Central & Peripheral Nervous System	47 (20.0)	45 (18.5)	61 (26.9)	61 (25.6)	214 (22.7)
Headache	42 (17.9)	39 (16.0)	52 (22.9)	55 (23.1)	188 (19.9)
Dizziness	3 (1.3)	6 (2.5)	7 (3.1)	11 (4.6)	27 (2.9)
Drowsiness	0	2 (0.8)	3 (1.3)	5 (2.1)	10 (1.1)
Heart Rate & Rhythm	39 (16.6)	38 (15.6)	35 (15.4)	56 (23.5)	168 (17.8)
Bradycardia	12 (5.1)	11 (4.5)	9 (4.0)	10 (4.2)	42 (4.5)
T Wave Change	4 (1.7)	6 (2.5)	6 (2.6)	13 (5.5)	29 (3.1)
Tachycardia	7 (3.0)	6 (2.5)	6 (2.6)	7 (2.9)	26 (2.8)
ST-T Wave Change	6 (2.6)	4 (1.6)	6 (2.6)	8 (3.4)	24 (2.5)
Extrasystoles	5 (2.1)	6 (2.5)	3 (1.3)	5 (2.1)	19 (2.0)
Arrhythmia Atrial	1 (0.4)	4 (1.6)	4 (1.8)	7 (2.9)	16 (1.7)
EKG Abnormal Specific[a]	1 (0.4)	2 (0.8)	1 (0.4)	6 (2.5)	10 (1.1)
Gastro-Intestinal System	23 (9.8)	31 (12.8)	34 (15.0)	30 (12.6)	118 (12.5)
Diarrhea	5 (2.1)	12 (4.9)	12 (5.3)	[illegible]	[illegible]
Constipation	0	6 (2.5)	[illegible]	[illegible]	[illegible]
Body As A Whole	11 (4.7)	[illegible]	[illegible]	[illegible]	[illegible]
Fatigue	6 (2.6)	10 (4.1)	[illegible]	[illegible]	[illegible]
Pain	0	6 (2.5)	[illegible]	[illegible]	[illegible]

a/ Includes 7 cases of poor R wave progression alone, long P-R interval and short P-R interval.

- In Study -087 (Non-US), spontaneously reported AEs with DOLA•Mesyl were comparable to those reported with OND. As listed below, the most frequently occurring AEs were headache, fatigue, drowsiness and diarrhea. It is to be noted, however, that occurrence rates for AEs in the HR and Rhythm SOC were higher in pts. receiving DOLA•Mesyl although these differences could not be attributed to a single HR and Rhythm AE.

Frequency (Percent) of Frequently Occurring (≥2%) AEs in CCNV Patients from Study 73147-2-S-087 - Oral DOLA•Mesyl Single Dose

	Oral OND [n=83]	Oral DOLA•Mesyl [n=316]
Any Adverse Experience	30 (36.1%)	107 (33.9%)
Headache	14.5%	14.9%
Fatigue	7.2%	3.8%
Drowsiness	2.4%	2.8%
Diarrhea	1.2%	2.8%
Constipation	0	2.5%
Abdominal Pain	3.6%	1.6%
Tachycardia	2.4%	1.3%
Fever	4.8%	0.6%
Dermatitis	2.4%	0
Dry Mouth	2.4%	0.9%
HR and Rhythm SOC	2.4%	25 mg 3.8% 50 mg 5.0% 100 mg 5.3% 200 mg 7.5%

PONV Trials

- The overall AE occurrence rates were lower in the European than in the Canadian trial. This was primarily the result of higher occurrences in HR and Rhythm SOC in the Canadian study. As summarized in Table 96, the AEs most frequently reported for all doses of DOLA•Mesyl were bradycardia, headache, hypotension and dizziness. But none of the frequently reported AEs were dose-related or different [illegible] reported with PL. There were quantitative differences between DOLA•Mesyl and PL for dizziness (3% vs 0%) and headache [illegible]

TABLE 96

Frequency (Percent) of Frequently Occurring (≥2%) AEs Regardless of Causality in PONV Prevention Patients from Controlled Studies - Oral DOLA●Mesyl Single Dose

System Organ Class and Preferred Term	PL [n=231]	DOLA●Mesyl Dose (mg)				
		25 [n=235]	50 [n=240]	100 [n=228]	200 [n=233]	All Doses [n=936]
Heart Rate & Rhythm	28 (12.1)	35 (14.9)	29 (12.1)	25 (11.0)	22 (9.4)	111 (11.9)
Bradycardia	23 (10.0)	26 (11.1)	19 (7.9)	16 (7.0)	14 (6.0)	75 (8.0)
Tachycardia	2 (0.9)	3 (1.3)	6 (2.5)	5 (2.2)	0	14 (1.5)
Central & Peripheral Nervous System	13 (5.6)	22 (9.4)	20 (8.3)	25 (11.0)	22 (9.4)	89 (9.5)
Headache	11 (4.8)	17 (7.2)	16 (6.7)	16 (7.0)	14 (6.0)	63 (6.7)
Dizziness	0	7 (3.0)	5 (2.1)	10 (4.4)	6 (2.6)	28 (3.0)
Cardiovascular, General	21 (9.1)	18 (7.7)	27 (11.3)	18 (7.9)	24 (10.3)	87 (9.3)
Hypotension	15 (6.5)	13 (5.5)	18 (7.5)	12 (5.3)	19 (8.2)	62 (6.6)
Hypertension	7 (3.0)	4 (1.7)	7 (2.9)	5 (2.2)	4 (1.7)	20 (2.1)
Body as a Whole	11 (4.8)	7 (3.0)	7 (2.9)	12 (5.3)	7 (3.0)	33 (3.5)
Gastro-Intestinal System	7 (3.0)	7 (3.0)	2 (0.8)	3 (1.3)	3 (1.3)	15 (1.6)

iii) AEs of Particular Interest

a) Cardiovascular AEs

CCNV

- 3 pts. had events which were coded to ventricular arrhythmia but these events were in fact ventricular premature [illegible] 087-001/3 and 087-121/8) and [illegible] repolarization (1 pt. - 091-276/8) [illegible] by 12-lead ECGs that were taken at hour 24.

- Pt. MCPR0048, 0384-0029, a 56y old M that had sinus bradycardia on predose EKG, experienced atrial flutter/fibrillation with tachycardia considered not related to the 100 mg DOLA•Mesyl. But as discussed above, the reviewer believes that it seems possible that the AF-TACH were due to DOLA•Mesyl alone or in combination with doxorubicin. Blood levels of the latter were not determined.

- LBBB, reported for Pt. 73147-2-S-087, 087-176/B is described below.

A 64-y old F with a Hx of CAD and hyperthyroidism, developed a complete LBBB on a 24-h poststudy EKG taken ca. 5h following PL and 28.5h after receiving oral DOLA•Mesyl 25 mg. The patient's BL and 24-h respectively, [an increase of 40 msec]. This event was initially reported as a serious AE. Symptoms of severe nausea and cold sweating caused the investigator to suspect a possible MI. These symptoms preceded the event by ca. 20h and prompted the investigator to unblind the patient's drug therapy. Cardiac enzymes were drawn at this time and were found WNLs. Additionally, the patient exhibited no cardiac complaints, nor were any cardiac symptoms noted during the conduct of the study. A follow-up EKG performed ca. 17h after the diagnosis of LBBB revealed a , with no BBB, but did reveal an old anteroseptal M.I. Following the investigation of cardiac enzymes, the differential diagnosis of M.I. was excluded.

This event was reclassified as a nonserious AE and was rated by the investigator as moderate in severity and not related to test med. but rather to the doxorubicin chemotherapy.

However, as the above described case, the reviewer believes that it is also possible that the LBBB observed in this patient was due to DOLA•Mesyl alone or in combination with doxorubicin. Blood levels of the latter were not determined.

- Pt. MCPR0048, 0326-0006 had a BL BP of This pt. experienced orthostatic hypotension) with dizziness upon standing 2.5h after receiving DOLA•Mesyl 25 mg. The event was reported immediately after the completion of a cyclophosphamide infusion. The pt. was treated with fluids and the event resolved.

This event was assessed as moderate and probably related to test med.

- Pt. MCPR0043, 0156-0003 had a BL BP of 120/90 mmHg. The pt. experienced orthostatic hypotension) with associated weakness 65 min. after receiving DOLA•Mesyl 200 mg. The event lasted <1 min. and resolved without documented treatment.

The event was assessed as mild in severity and probably related to test med. The sponsor's assessment of mild in severity seems questionable because there were 60 and 40 mmHg decreases in systolic and diastolic BP, respectively.

PONV

- Nodal arrhythmias, thought to be possibly related
occurred in both patients receiving
with no real distinction except as follows:

[redacted]

- A 29y old F (AN-PO-0292, 0001-0403) developed nodal bradycardia of and 55 min. following DOLA•Mesyl 100 mg. This serious + severe event was considered as possibly related to test med.

- Pt. AN-PO-0292, 0009-0323 developed questionable nodal rhythm + BBB + intraoperative hypotension, 195 min. after a single oral dose of DOLA•Mesyl 200 mg. The nodal rhythm resolved in 15 min. and was assessed as possibly related to test med.

- The two cases of severe bradycardia + brief cardiac pulse, one moderate the other severe, and considered by the European investigator to be possibly related to PL are to be contrasted with the above-described case occurring in the Canadian PONV trial (61y old F, pt. AN-PO-0292, 0010-0290) assessed by the investigator and the Clinical Reviewer as definitely related to DOLA•Mesyl.

  - Pt. 73147-2-S-095, 095-0675, a 36y old F had no cardiovascular medical Hx and the pre-study EKG (taken the day prior to the study) was WNLs. The patient's vital signs taken just prior to test med. and just prior to induction were also WNLs.

    While undergoing vaginal hysterectomy, this patient was reported to have intraoperative complete plus 2:1 heart block (coded as AV block) 109 min. after a single oral dose of PL. This diagnosis was made from an intraoperative EKG tracing and no confirmatory EKGs were available. The patient became bradycardic 30 min. after the induction of anesthesia Four minutes later, the patient was diagnosed with complete heart block. The event resolved within 3 min. after treatment with 0.6 mg atropine. Vital signs at resolution showed a normal heart rate of

    The investigator assessed this event as moderate and possibly related to test med. Dr. Pratt (the cardiologist consultant) judged this event to be "typical of a vagal response during abdominal or pelvic surgery".

  - Pt. 73147-2-S-95, 095-0454, a 46y old F had a pre-study EKG taken the day before the study reported as WNLs. Vital signs taken just prior to study med. administration and 1h after test med. adm. were also WNLs.

    While undergoing an abd. hysterectomy, this patient was reported to have intraoperative bradycardia and asystole (coded to bradycardia) 80 min. after receiving PL. This diagnosis was made from a video monitor and no confirmatory EKGs or vital signs were available. The patient was reported to be bradycardic with 20 seconds of asystole, 15 min. after the induction of anesthesia. The event reversed within 1 min. after treatment with atropine 1 mg and Epifrine® (epinephrine) 5 mg.

    The investigator assessed this event as severe and possibly related to test med. Dr. Pratt (the cardiologist consultant) judged this event to be "typical of a vagal response during abdominal or pelvic surgery".

- There were no cases of Bundle Branch Block [illegible] given PL. For 1 of the 936 patients [illegible] was reported as follows:

- Pt. 73147-2-S-095, 095-0335 (50 mg) PROB
  Developed mild incomplete BBB 24h Postdosing

- Pt. 73147-2-S-095, 095-0095 (100 mg) POSS
  Developed moderate 1° heart block + partial LBBB 245 min. Postdosing

- Pt. AN-PO-0292, 0009-0323 (200 mg) POSS
  (Described above)

- Moderate hypotension, usually possibly related to test med. was reported with PL or DOLA•Mesyl. The only 2 cases of severe hypotension are briefly described below.

  - Pt. 73147-2-S-095, 095-0211 (25 mg) POSS
    This pt's BP immediately prior to test med. was The pt. was reported to have intraoperative hypotension 10 min. after induction of anesthesia and 80 min. after receiving test med. The pt. was treated with increased i.v. fluids. The event lasted 5 min. and was assessed as SEV and possibly related to test med.

  - Pt. AN-PO-0292, 0011-0394 (25 mg) POSS
    Immediately prior to test medication, this patient's BP was 98/60 mmHg and HR was The patient was reported to have intraoperative diastolic hypotension and bradycardia 140 min. Postdose. The pt. was treated with atropine. The events lasted 5 min. and were assessed as SEV and possibly related to test med.

iv) AEs Within Subgroups

CCNV

AE occurrence rates in adult pts. receiving oral DOLA•Mesyl were not influenced by age, race or body weight by gender. A somewhat higher incidence of headache and diarrhea was seen in F than in M patients.

PONV

AE occurrence rates in adult female patients receiving oral DOLA•Mesyl were not influenced by age, race or body weight.

v) AEs in the Pediatric Population

CCNV (only)

- 32 pediatric patients (aged 3 to 17y) received oral DOLA•Mesyl. No deaths, serious nonfatal AEs or clinically significant [illegible] or conduction disorders were reported in this patient [illegible] patients (ages 3 and 4y) developed seizures during [illegible] dose of 0.6 mg/kg. Two seizures in [illegible] as possibly related to DOLA•Mesyl. But the [illegible] opinion that concomitant chemotherapy may have [illegible] events.

vi) EKG Changes from BL

In pharmacology studies the sponsor showed that DOLA•Mesyl and its active metabolite, MDL 74,156, have electrophysiological properties associated with a reduction in the upstroke velocity (V_{max}) of the cardiac action potential due to blockade of the fast sodium channel. In Clinical Pharmacology studies in HVs, a dose dependent prolongation of the PR, QRS and QT_c intervals with minimal effect on the JT interval was shown. Acute effects on PR and QRS (and presumably for QT_c) were linearly associated with large increases in plasma MDL 174,156 levels. Except for the highest dose (200 mg), these EKG effects were primarily demonstrable during the acute period (ca. 15 min. to up to 4.5h post-dose). The EKG effects were less noticeable 24h after administration of DOLA•Mesyl.

In this section, summary statistics for mean change from BL for HR, PR, QRS and QT_c are presented. For the reasons mentioned above, the emphasis is on acutely induced changes; 24h data are only briefly mentioned. Shift changes are also given. Also included are presentations of data originating from those patients who would theoretically be considered at an increased risk. These groups of patients include situations where DOLA•Mesyl is administered to patients with concomitant cardiovascular medications,[32] those with a Hx of cardiovascular disease (i.e. arrhythmia/conduction disorders[33]), those with atherosclerotic heart disease[34], myocardial disease[35], endocardial/valvular disease and pericardial disease and to those with a BL serum potassium below the normal range.

a) Mean Data (Table 97)

CCNV

- The mean acute postdose HR decreased slightly from BL as a function of dose.
- For PR and QRS interval measurements, changes from BL appeared to be dose dependent. For QT and QT_c, changes from BL with the 200 mg dose level were clearly the greatest. [Note differences between the 200 vs the 25 mg dose.]

[32](i.e. ACE inhibitors, diuretics, digoxin, β-blockers, antiarrhythmic agents, calcium channel blockers).

[33]atrial, ventricular and unspecified

[34]coronary heart disease, MI, angina, coronary artery [illegible] peripheral vascular disease, cerebral vascular disease [illegible]

[35]congestive heart failure, cardiomyopathy and [illegible]

PONV

- Small no dose-dependent increases from BL were seen for acute postdose HR values.

- Again, for PR, QT and QT_c interval measurements, acute changes from BL appeared to be dose-dependent. The mean acute changes from BL for PR, QRS, QT and QT_c were greater with the 200 mg as well as the 100 mg than with PL or the lowest dose of DOLA•Mesyl tested (25 mg). Once again, for all EKG parameters evaluated, changes from BL with the 200 mg dose level were clearly the greatest (Table 97).

TABLE 97

Acute (15 min. to 4.5h Postdose) EKG Summary
Mean Changes from BL from Controlled Trials

		DOLA•Mesyl Dose (mg)			
		25	50	100	200
I. CCNV Patients					
HR (bpm)		-3.2	-2.8	-1.5	-1.2
PR (msec)		5.7	6.0	9.0	14.1
QRS (msec)		2.2	2.7	3.1	5.9
QT (msec)		13.6	11.3	11.3	20.3
QT_c (msec)		8.1	6.0	8.3	19.4
JT (msec)		11.5	8.6	8.2	14.5
II. PONV Patients					
HR (bpm)	3.6	9.4	3.4	7.7	7.5
PR (msec)	4.8	4.5	4.6	8.4	8.6
QRS (msec)	-1.4	-0.4	-0.4	0.3	1.6
QT (msec)	1.5	0.1	0.9	4.6	5.4
QT_c (msec)	7.5	8.4	11.1	13.0	17.5
JT (msec)	2.9	0.7	1.3	4.5	3.9

b) Shift Data

For PR interval, QRS duration and QT_c interval, patients could [illegible] any of the following Pre-treatment levels (msec):

PR	QRS	QTc
<200	<100	<440
200 - 219[a]		
220 - 239[b]		
≥240		
	≥140	
		480[g,h]

a) The group <200 msec Pre-Tx to ≥220 msec acute Post-Tx had to have an increase in PR interval of at least 20 msec to reach the threshold for Tx-emergent first degree AV block.
b) First degree AV block=PR interval ≥220 msec.
c) QRS duration ≥100 msec = Intraventricular Conduction Delay (IVCD).
d) The group <100 msec Pre-Tx to ≥120 msec acute Post-Tx had to have at least an 20 msec increase in QRS duration to reach the threshold for one of the diagnostic criteria for BBB (not all pts. with a QRS duration ≥120 msec were diagnosed by the central reader as having BBB).
e) QRS duration <120 msec Pre-Tx to ≥120 msec Post-Tx = Tx-emergent QRS duration consistent with a diagnosis of BBB, irrespective of the msec change this represented.
f) The grouping <440 msec Pre-Tx to ≥440 msec acute Post-Tx identifies pts. who developed Tx-emergent QTc prolongation at the acute time point, irrespective of the msec change this represented.
   - QTc prolongation was defined as QTc interval ≥440 msec.
g) The patients in the subgroup <440 msec Pre-Tx to >480 msec acute Post-Tx had an increase in QTc to at least 40 msec above that defined as the ULN.
h) Pt. in the subgroup <440 msec Pre-Tx to ≥500 msec acute Post-Tx had developed Tx-emergent QTc prolongation and had increased at least 60 msec above that defined as the ULN. This group of patients is identified as having a high propensity to develop clinically significant disturbances in cardiac rhythm.

The sponsor presented the shift data in a number of Tables, for every DOLA•Mesyl dose level. Percentages (of shifts) were calculated even if the total or number of patients was small (example 10) or even if the cell consisted of one patient. Also, a summary shift data for all doses pooled was included. The reviewer elected not to present the pooled data because this approach masks the dose level of compound originating the shift. With regard to CCNV studies, shift data with the lowest dose tested, 25 and the recommended dose, 100 mg are presented by the reviewer. With regard to PONV totals, the data with 100 mg are compared to those reported for PL. For both types of clinical trials, the shifts of interest are, of course, those occurring to the right of the shadowed box in summary Table 98.

a. Shifts from BL in PR Interval

CCNV (Table 98, upper panel)

- 6/142 (4.2%) of the patients in the 25 mg DOLA•Mesyl [illegible] Tx PR interval of <200 shifted to 200-219 level [illegible] number of patients in the 100 mg dose group [illegible]

all dose levels (data not shown), the frequency of the acute increases appeared to be dose dependent.

25 mg	50 mg	100 mg	200 mg
1/147 (0.7%)	2/155 (1.3%)	4/143 (2.8%)	7/152 (4.6%)

- The majority of those acute increases did not exceed 240 msec.
- One patient had a BL PR interval <200 msec that increased to an acute postdose PR interval of ≥240 msec after receiving 200 mg DOLA•Mesyl **[40 msec increase]**.
- No patient with a prolongation in PR interval, including those with a BL PR interval ≥220 msec, developed second degree or higher AV block or other clinically significant arrhythmia or conduction abnormalities.

PONV (Table 98a, upper panel)

- Only 1/107 (0.9%) of the patients in the PL group that had Pre-Tx PR interval of <200 msec shifted to the 200-219 level. The corresponding number of patients in the 100 mg dose group was 6/104 (5.8%)
- 3 DOLA•Mesyl patients had a BL PR interval of ≥220 msec.
  - One of these (AN-PO-0292-0010-0290) was a 61y old F undergoing abd. hysterectomy under general anesthesia who developed complete heart block (coded to AV dissociation) that the investigator assessed to be definitely related to the 200 mg DOLA•Mesyl.
  - The two other pts. had a BL PR interval of ≥220 msec (none were ≥240 msec) but they did not have acute EKGs. The EKG information in these two patients is incomplete although, from 24h EKG data, none of the two had clinically significant arrhythmias or conduction abnormalities.

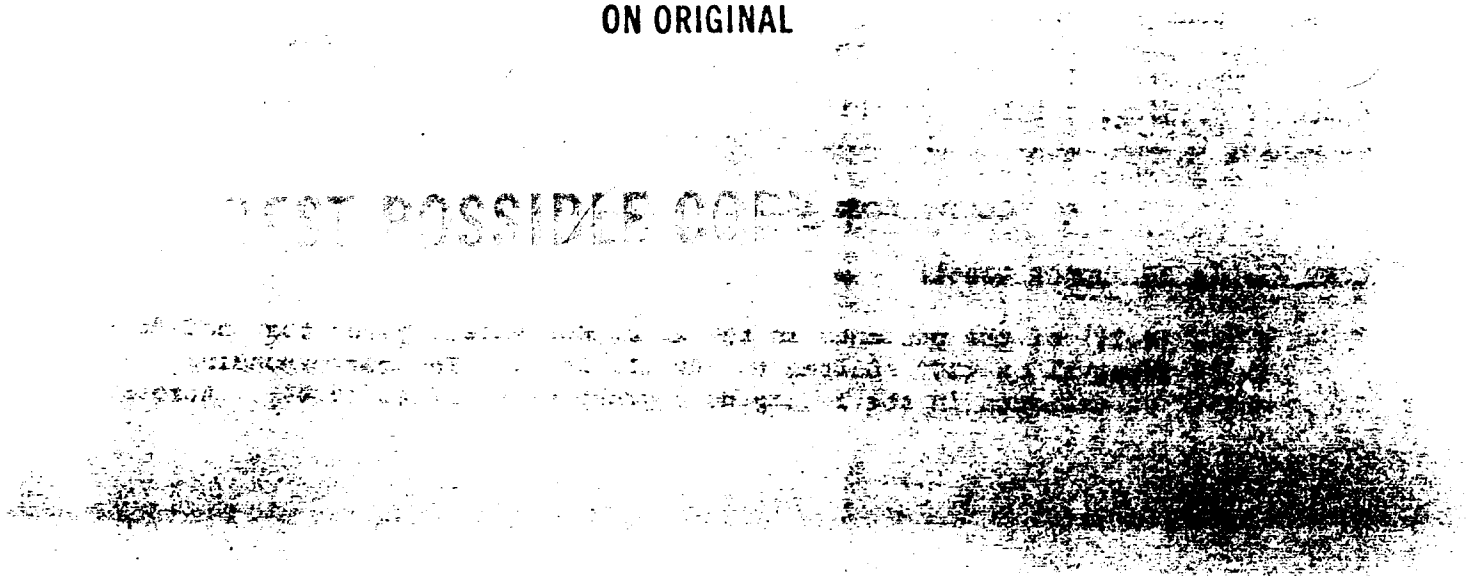

TABLE 98

Shift Tables for Acute EKG Measures in CCNV Patients from Controlled Studies - Oral DOLA•Mesyl/Single Dose

I. PR Interval						
Number of Patients with Shift from Pretreatment to Posttreatment						
Dose (mg)	Pretreatment PR Interval	n	Acute Posttreatment PR Interval			
			<200	200-219	220-239	≥240
25	<200	142	[illegible]	6 (4.2%)	0	0
	200-219	5	2	[illegible]	0	1
	220-239	1	0	0	[illegible]	0
	≥240	1	0	0	0	[illegible]
100	<200	141	[illegible]	8 (5.7%)	3 (2.1%)	0
	200-219	2	0	[illegible]	0	1
	220-239	1	0	0	[illegible]	1
	≥240	1	0	0	0	[illegible]

II. QRS Interval							
Dose (mg)	Pretreatment QRS Interval	n	Acute Posttreatment QRS Interval				
			<100	100-109	110-119	120-139	≥140
25	<100	134	[illegible]	10 (7.5%)	1 (0.7%)	0	0
	100-109	10	3	[illegible]	0	0	0
	110-119	2	0	1	[illegible]	1	0
	120-139	2	0	0	0	[illegible]	1
	≥140	1	0	0	0	[illegible]	[illegible]
100	<100	110	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	100-109	12	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	120-139	2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	≥140	1	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

III. QTc Interval								
Dose (mg)	Pretreatment QTc Interval	n	Acute Posttreatment QTc Interval					
			<440	440-449	450-459	460-469	470-479	≥480
25	<440	108	88 (81.5%)	8 (7.4%)	7 (6.5%)	2 (1.9%)	0	3 (2.8%)
	440-449	18	5	1	6	3	3	0
	450-459	12	4	2	1	0	3	2
	460-469	6	0	0	2	1	1	2
	470-479	2	1	0	0	0	1	0
	≥480	3	0	0	1	1	0	1
100	<440	124	97 (78.2%)	15 (12.1%)	7 (5.6%)	3 (2.4%)	2 (1.6%)	0
	440-449	7	3	1	0	2	0	1
	450-459	6	1	1	1	2	0	0
	460-469	5	3	0	2	0	0	0
	≥480	3	0	0	1	0	1	1

b. Shifts from BL in QRS duration

CCNV (Table 98, middle panel)

- 11/134 (8.2%) and 6/130 (4.6%) of the patients in the 25 mg and 100 mg DOLA•Mesyl groups, respectively, that had Pre-Tx normal QRS (<100 msec) shifted to the 100-109 or 110-119 level. Across all dose levels (data not shown) the frequency of the acute increases was mostly to the 100-109 msec level and not dose dependent:

25 mg	50 mg	100 mg	200 mg
11/134 (8.2%)	17/141 (12.1%)	6/130 (4.6%)	20/135 (14.8%)

- Except as described below, no pt. developed clinically significant arrhythmia or conduction abnormality.

- Patient 73147-2-B-087, 087-176/B had a 120ms on a Post-Tx ECG performed 5h following PL (28.5h following 25 mg oral DOLA•Mesyl).
  - The BL and Post-Tx QRS durations were 80 and 140 msec, respectively.
  - The patient also had an increased HR; predrug and Post-Tx ECG (BL HR=61 bpm, Post-Tx HR=113 bpm, BL QTc=398 msec, Post-Tx QTc=470 msec, Post-Tx QTc=487 msec). The investigator assessed moderate and not related to test medication.

- No other patients with a prolonged QRS duration, including those with a baseline QRS duration ≥100 msec, developed a clinically significant arrhythmia or conduction abnormality.

PONV (Table 98a, middle panel)

- 1/105 (1%) and 3/101 (3%) of patients in the PL and 100 mg groups, respectively, that had Pre-Tx normal QRS (< msec) shifted to the 100-109 level. Across all dose levels, the frequency of the acute increases from <100 to ≥100 msec appeared to be dose dependent.

PL	25 mg	50 mg	100 mg	200 mg
1/105 (1%)	2/106 (1.9%)	2/106 (1.9%)	3/101 (3%)	4/111 (3.6%)

- PT. 73147-2-S-095, 095-0095 developed partial LBBB 4h and 5 min. after a single oral dose of DOLA•Mesyl 100 mg. However, interpretation of the EKG by the central cardiologist showed the QRS duration to be unchanged at 100 msec throughout the study period.
- Pt. 73147-2-S-095, 095-335 was reported as having RBBB ca. 24h after a single oral dose of DOLA•Mesyl 50 mg. However, the sponsor states that the QRS interval at that time was 100 msec and that this should be more accurately described as incomplete BBB. The event was assessed as mild and resolved.
- None of the remaining patients with BL QRS durations ≥100 msec experienced a clinically significant arrhythmia or conduction abnormality.

c. Shifts from BL in QT_c Interval

CCNV (Table 98, lower panel)

- 20/108 (18.6%) and 27/124 (21.7%) of patients in the 25 mg and 100 mg, respectively, that had Pre-Tx normal QT_c (<440 msec) shifted to the 440-449 or higher levels. Actually, 3 of these patients (2.8%) in the 25 mg group, shifted from <440 to ≥480 msec (a shift of at least 40 msec). Other shifts were inconsistent and not dose dependent.
- Pt. M2PR0048, 0323-0018 had a BL QT_c interval <440 msec that increased to ≥500 msec at 24h [a shift of at least 60 msec]. This patient did not develop a clinically significant arrhythmia or conduction abnormality. The frequency of DOLA•Mesyl pts. with a BL QT_c interval <440 msec which increased to an acute postdose QT_c interval ≥500 msec was 3/477 (0.4%); one pt. in the 25 mg dose group and one in the 200 mg dose group.
- 126 DOLA•Mesyl patients with acute EKGs had a BL [illegible] msec; 51 additional DOLA•Mesyl patients, not presented in [illegible], did not have acute EKGs, but also had baseline QT, interval [illegible]. One of these patients (73147-2-S-087,087-176/[illegible]) was reported [illegible] BBB 23.5h after a single oral dose of [illegible] for this patient were 470 msec at baseline and [illegible] [a shift of 17 msec]. The event was assessed as [illegible] and not related to test medication but rather to [illegible]

chemotherapy. But as already mentioned by the reviewer, blood levels of this chemotherapeutic agent were not determined.

- None of the remaining patients with baseline QT_c interval ≥440 msec experienced a clinically significant arrhythmia or conduction abnormality.

- There were a total of 15 DOLA•Mesyl patients who had a BL QT_c ≥480 msec; 7 of these 15 were less than 480 msec following DOLA•Mesyl exposure, 2 of which were less than 440 msec. One of these patients (73147-2-S-087, 087-251/C) had a baseline QT_c interval . This patient had a baseline and 24-h QT_c interval of respectively, but did not have an acute EKG taken.

- No patient with a prolonged QT_c interval, including those with a BL QT_c interval ≥480 msec, developed a clinically significant arrhythmia or conduction abnormality.

PONV (Table 98a, lower panel)

- 13/103 (12.6%) and 16/100 (16%) of patients in the PL and 100 mg groups, respectively, that had Pre-Tx normal QT_c (<440 msec) shifted to the 440-449 or higher levels. The frequency of the increase across all dose levels (data not shown) to QT_c ≥480 msec appeared to be dose dependent.

PL	25 mg	50 mg	100 mg	200 mg
2/103 (1.9%)	0/105 (0%)	2/107 (1.9%)	4/100 (4%)	5/108 (4.6%)

- None of these pts. developed an arrhythmia or conduction abnormality.

- 1 of these patients had a BL QT_c interval that increased from <440 msec to ≥500 msec acutely following 200 mg DOLA•Mesyl. This patient (73147-2-S-095, 095-0052), had a BL, acute and 24-h QT_c interval of , respectively. All other EKG intervals remained WNLs and the patient reported no AEs.

TABLE 98a

Shift Tables for Acute EKG Measures in PONV Prevention Patients
from Controlled Studies - Oral DOLA®Mesyl Single Dose

I. PR Interval						
Number of Patients with Shift from Pretreatment to Posttreatment						
Dose (mg)	Pretreatment PR Interval	n	Acute Posttreatment PR Interval			
			<200	200-219	220-239	≥240
PL	<200	107	[illegible]	1 (0.9%)	0	0
	200-219	4	2	[illegible]	0	0
100	<200	104	[illegible]	5 (4.8%)	1 (1.0%)	0
	200-219	3	2	[illegible]	0	0

II. QRS Interval							
Dose (mg)	Pretreatment QRS Interval	n	Acute Posttreatment QRS Interval				
			<100	100-109	110-119	120-139	≥140
PL	<100	105	[illegible]	1 (1.0%)	0	0	0
	100-109	5	3	[illegible]	0	0	0
	120-139	1	0	0	0	[illegible]	0
100	<100	101	[illegible]	3 (3.0%)	0	0	0
	100-109	6	4	[illegible]	0	0	0

III. QTc Interval							
Dose (mg)	Pretreatment QTc Interval	n	Acute Post-treatment QTc Interval				
			<440	440-449	450-459	460-469	≥470
PL	<440	103	[illegible]	[illegible]	[illegible]	[illegible]	2 [illegible]
	440-449	4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	450-459	3	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
100	<440	100	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	440-449	2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	450-459	1	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

vii) 24-h Changes in QTc from BL

- At 24h, the frequency of increases from a BL QT_c interval <440 msec to ≥440 msec at 24h postdose was 44/597 (7.4%) in DOLA•Mesyl patients and 19/143 (13.3%) in PL patients.

- The frequency of increases from a BL QT_c interval <440 msec to ≥480 msec at 24h postdose was 2/597 (0.3%) in DOLA•Mesyl patients and 1/143 (0.7%) in PL patients. Neither of these DOLA•Mesyl patients experienced a clinically significant arrhythmia or conduction abnormality. One of these patients had a 24-h postdose QT_c interval ≥500 msec. This patient (73147-2-S-095, 095-299) had a baseline QT_c of 436 msec that increased to 503 msec 24h following a 25 mg oral DOLA•Mesyl dose. All other EKG intervals remained WNLs and the patient reported no AEs.

- 30 DOLA•Mesyl patients with acute EKGs had a BL QT_c interval ≥440 msec.

- 18 additional DOLA•Mesyl patients who did not have acute EKGs, also had BL QT_c intervals ≥440 msec. One of these patients (73147-2-S-095, 095-0335) was reported as having RBBB ca. 24h after a single oral dose of DOLA•Mesyl 50 mg; however, the QRS interval at that time was 100 msec. QT_c intervals for this patient were 461 msec at BL and 467 msec at 24h postdose.

  - None of the remaining patients with BL QT_c interval ≥440 msec experienced a clinically significant arrhythmia or conduction abnormality.

- There were 2 DOLA•Mesyl patients with a BL QT_c interval ≥480 msec, both were ≥500 msec.

  - The first patient (73147-2-S-095, 095-0176) had a BL and 24-h QT_c interval of and respectively. This patient did not have an acute EKG. All other EKG intervals remained within normal limits and the patient reported no AEs.

  - The second patient (73147-2-S-095, 095-968) had a BL and 24-h QT_c interval of and c, respectively. This patient did not have an acute EKG. All other EKG intervals remained WNLs. This patient experienced an episode of hypotension ca. 90 min. following test med. dosing. The investigator assessed the event as mild and unlikely related to test med.

- No patients with a significant postdose shift in QT_c interval, including those with a baseline QT_c interval [illegible] developed a clinically significant arrhythmia or conduction [illegible].

viii) Arrhythmias/Conduction [illegible]

Since these have been addressed in detail above, they are [illegible] complications below.

CCNV	PONV
• Pt. MCPR0048, 0384-0029 (100 mg) - Atrial fibrillation with a ventricular rate between 92 and 140 bpm on a post-study EKG performed 96h after test med. Related to doxorubicin? (No blood levels of DOX available) NOT REL	• Pt. AN-PO-0292, 0010-0290 (200 mg) - Complete heart block coded as AV dissociation. DEF • Pt. AN-PO-0292, 0001-0403 (100 mg) - Nodal arrhythmia at 20 bpm during surgery (serious + severe) POSS • Pt. AN-PO-0292, 0009-0323 (200 mg) - IVCD (Coded to BBB) POSS - See Nodal arrhythmias above.
	• Pt. 73147-2-S-095, 095-0675 (PL) - Complete plus 2:1 ca. 109 min. after receiving test med. POSS • Pt. 73147-2-S-095, 095-0454 (PL) - Intraoperative bradycardia and asystole (severe) POSS

ix) Tx-emergent EKG Interval Changes (Table 99)

CCNV (Studies -043 and -048)

As shown in the upper panel of this Table, the frequency of AV block first degree was dose dependent and there was no apparent trend with dose in the frequency of IVCD. There was an apparent trend with dose in the frequency of QT/QT_c interval prolongation. Once again, the proportion of patients with QT/QT_c interval prolongation was higher in those patients dosed with 200 mg DOLA•Mesyl (38%) than in those given 25 mg doses of the compound (23%).

PONV (Study -0292 only)

As shown in the lower panel of Table 99, there was no difference in the frequency of AV block first degree between DOLA•Mesyl or PL groups. There was an apparent trend with dose in the frequency QRS prolonged [illegible] 200 mg=11% vs PL=3% or 25 mg=3.3%). No difference [illegible] prolongation between the DOLA•Mesyl or PL groups [illegible]

TABLE 59

Frequency (%) of Tx-emergent EKG Changes From Controlled Studies
Oral DOLA•Mesyl/Single Dose

I. CCNV Prevention (Studies -043 and -048)

Treatment-Emergent EKG Interval Change	DOLA•Mesyl Dose (mg)				
	25 [n=155]	50 [n=163]	100 [n=151]	200 [n=158]	All Doses [n=627]
AV Block First Degree	3 (1.9)	3 (1.8)	4 (2.6)	7 (4.4)	17 (2.7)
IVCD[a]	14 (9.0)	20 (12.3)	8 (5.3)	20 (12.7)	62 (9.9)
QT/QTc Prolonged	35 (22.6)	40 (24.5)	39 (25.8)	60 (38.0)	174 (27.8)

II. PONV Prevention (Study -0292)

	PL [n=75]	25 [n=76]	50 [n=74]	100 [n=74]	200 [n=75]	All Doses [n=299]
AV Block First Degree	1 (1.3)	0	0	1 (1.4)	1 (1.3)	2 (0.7)
QRS Prolonged	2 (2.7)	1 (1.3)	2 (2.7)	5 (6.8)	8 (10.7)	16 (5.4)
QT/QTc Prolonged	35 (46.7)	25 (32.9)	30 (40.5)	29 (39.2)	34 (45.3)	118 (39.5)

a) Intraventricular Conduction Delay.

x) <u>Subgroup Analyses</u>

The sponsor presented EKG data on QT_c interval from oral DOLA•Mesyl studies analyzed by gender, age, race and weight by gender. For this purpose all doses of DOLA•Mesyl were combined. Again, when some cells end up with a small number of patients, the true effects of that subgroup cannot be assessed with confidence.

<u>Gender</u>

Comments refer to CCNV studies only. For PONV studies, no gender analysis was performed because all patients in these studies were females.

- The frequency of shifts from a BL QT_c interval of [illegible] to an acute postdose QT_c interval of ≥440 msec was [illegible] for males and 88/292 (30.1%) for females. This difference could [illegible] effect of gender. Besides, there were no other [illegible] seen at acute or at 24h observations between [illegible]

in females. Data were presented showing that any gender imbalance seen in QT_c interval may be due to differences in baseline QT_c interval between the genders and anthracycline therapy, rather than any differential effect of the test med. There seemed to be no need for dosage adjustment for the antiemetic or the basis of gender.

Age

- Data from CCNV and PONV studies are summarized as follows:

Frequency of QT_c Interval Shifts as a Function of Age

	16 to 39y	40 to 64y	≥65y
CCNV - Acute			
BL <440 to ≥440	13/58 (22.4%)	65/250 (26%)	53/169 (31.4%)
<440 to ≥480	0/58 (0%)	2/250 (0.8%)	6/169 (3.6%)
-24h			
BL <440 to ≥440	12/96 (12.5%)	72/404 (17.8%)	43/206 (20.9%)
PONV - Acute			
BL <440 to ≥440	11/128 (8.6%)	54/289 (18.7%)	1/3 (33.3%)
<440 to ≥480	2/128 (1.6%)	9/289 (3.1%)	0/3 (0%)
-24h			
BL <440 to ≥440	11/192 (5.7%)	33/401 (8.2%)	0/4 (0%)

The above depicted findings suggest that the frequency DOLA•Mesyl patients experiencing increases from BL QT_c <440 to either ≥440 or ≥480 increases with age. But at 24h, similar increases with age were observed in CCNV patients treated with ondansetron. Also, these differences among age groups were seen both acutely and at 24h postdose when the blood levels of both antiemetics are expected to be low. In addition, in PONV studies, PL-treated patients experienced similar shifts in QT_c interval with age as those seen with DOLA•Mesyl.

- From the above, the reviewer agrees with the sponsor that there seems to be no need for a dose adjustment in the elderly.

Race

In all trials, predominantly Caucasian patients were enrolled. The number of patients in Black or other categories is too small to [illegible] patient number must be considered when interpreting [illegible] differences did not appear to notably influence [illegible] DOLA•Mesyl.

Weight

For CCNV trials, analyses of QT_c interval shifts from Pre-Tx to acute and 24h Post-Tx by weight were provided for male and female patients separately. In the PONV trials only females were randomized. The weight groups were 40-59, 60-79 and ≥80 Kg. In summary, weight differences did not seem to notably influence EKG interval changes due to DOLA•Mesyl.

xi) Effect of Concomitant Cardiovascular Medications

Because of their interest, the Clinical Reviewer addresses these data in a separate subsection. To properly interpret these findings it is important to note that the number of patients being compared are vastly different. The conclusions reached can only be termed preliminary and any trend or finding of interest should be interpreted as a signal that additional evaluation/ experience is needed. Also only acute EKG changes from BL are addressed because, in the majority of patients, the 24h data showed a return to BL values.

Number of Patients Receiving Cardiovascular Medications in Addition to Orally Administered DOLA•Mesyl

	Clinical Studies		
	CCNV[a] [Studies -043 and -048]	PONV[b] [Studies -095 and -0292]	
	No. of Pts.		
No CV Medication	435	401	PL 97
ACE Inhibitors	37	1	3
Diuretics	33	3	1
Digitalis Glycosides	12	1	0
Class Ib Antiarrhythmics	1	0	1
βeta Blockers	40	[illegible]	[illegible]
Verapamil	17	2	0
Diltiazem	17	[illegible]	[illegible]
Nifedipine	31	[illegible]	[illegible]
All Calcium Channel Blockers	65	[illegible]	[illegible]

a,b) [illegible]

Because the number of patients taking concomitant cardiovascular medication was quite small (or in some instances none at all) in the PONV trials, the reviewer has elected not to comment on PONV data because those were too incipient findings. According to the sponsor's computations, in PONV trial -095 (n=637) and -0292 (n=299), a total of 401/936 or 43% did not take a concomitant cardiovascular medication. But the proportion of patients taking a particular CV medication of interest was quite small (1% or less).

CCNV

Table 100 lists the mean change from BL in HR, PR, QRS, QT, QT_c and JT intervals both acutely and 24h after test med. administration for those patients who had taken a concomitant CV medication during the trial period. It is of interest to note that in trials -043 (n=307) and -048 (n=320), a total of 435/627 or 69.4% of the patients did not take a concomitant cardiovascular medication during the study period. The proportion of patients taking individual CV medication was 10% or less (i.e. 2% for digitalis glycosides).

When compared to the acute mean change from BL in patients taking no cardiovascular medication,

- Slightly greater decreases in acute HR were seen with calcium channel blockers, diuretics, nifedipine dilitiazem and digitalis glycosides.
- The PR interval was 3.8, 3.8 and 3.2 msec greater for patients taking βeta blockers, verapamil and diltiazem, respectively.
- According to these evaluations, the QRS interval was little or not influenced by concomitant cardiovascular medications.
- The QT interval was 7.4, 9.0, 4.8, 14.3 and 4.0 msec greater for patients taking calcium channel blockers, nifedipine, verapamil, diltiazem and digitalis glycosides, respectively.
- The QT_c interval was 3.9, 4.3, 5.3 and 7.3 msec greater for patients taking calcium channel blockers, nifedipine, verapamil and dilidiazem, respectively.
- The JT interval was acutely increased by the concomitant use of calcium channel blockers (7.2 msec greater), beta blockers (4 msec), nifedipine (7.4 msec), digitalis glycosides (4.4 msec) and especially diltiazem (15.7 msec) in comparison to patients taking no cardiovascular medication.

When compared to the 24h mean change from BL in patients taking no cardiovascular medication, most concomitant cardiovascular medications increase or have decreases, with the following exceptions:

- Increases in HR of 1.8 and 3.2 [illegible] digitalis glycosides, respectively.

TABLE 100

Acute and 24h Mean Changes from BL in EKG Measures by Concomitant Cardiovascular Medication in Patients Receiving Single Oral Doses of DOLA®Mesyl in Controlled CCNV Trials[a]

	Acute Effects						Effects at 24h					
	HR	PR	QRS	QT	QTc	JT	HR[a]	PR	QRS	QT	QTc	JT
NO CV Medication	-1.9	8.3	3.4	13.3	10.1	9.9	0.0	1.3	-0.1	3.6	4.3	3.7
All Calcium Channel Blockers	-3.5	9.3	3.6	20.7	14.0	17.1	0.3	-0.3	-1.1	-0.7	2.4	0.4
Beta Blockers	-1.7	12.1	2.3	16.2	11.4	13.9	-0.2	1.7	0.1	9.2	9.0	9.1
ACE Inhibitors	-2.2	6.1	3.9	13.9	10.4	10.0	0.2	3.3	0.1	-1.0	1.0	-1.1
Diuretics	-4.0	10.4	4.1	15.6	9.9	11.5	-1.0	2.2	1.6	5.5	6.8	3.9
[redacted]	-3.7	6.4	5.0	22.3	14.4	17.3	-2.1	-2.0	-1.9	3.5	-1.7	5.4
[redacted]	-2.4	12.1	5.0	18.1	15.4	13.1	3.8	-0.9	-3.2	-7.5	4.2	-4.3
[redacted]	-4.7	11.5	1.9	27.6	17.4	25.6	-1.5	4.5	0.1	3.7	4.0	3.6
[redacted]	-3.3	7.1	3.0	17.3	12.3	14.3	4.2	1.8	0.0	-3.3	6.6	-3.3
[redacted]	6.0	-2.0	13.0	-40.0	-10.0	-53.0	14.0	-2.0	2.0	-60.0	0.0	-62.0

When compared to the 24h mean changes from BL in patients with no Hx of cardiovascular disease, the Hx of most concomitant cardiovascular conditions produced little effect, except as noted below.

- Hx of pericardial disease produced an increase of 18.1 msec in QT_c, 16.5 msec in QT and 15.2 msec in JT greater than the changes in those patients who did not have a Hx of pericardial disease.

- The QRT and JT intervals were 7 and 8.7 msec greater for those patients with a Hx of arrhythmia/conduction disorders than for those without a Hx of cardiovascular disease.

In conclusion, a Hx of cardiovascular disease had varying degrees of effect on the EKG interval changes produced by DOLA•Mesyl, especially during the acute Post-Tx period. Within the frame of the small number of observations assessed herein, these interactions have not resulted in clinical conditions of concern in CCNV prevention patients. But more experience, in larger numbers of patients, is needed. Also needed are data on the effects of Hx of cardiovascular disease on EKG interval changes produced by DOLA•Mesyl in PONV patients.

xiii) Effect of BL Serum Potassium

This important question cannot be answered with certainty because of the very small number of DOLA•Mesyl patients with below normal BL serum potassium in both trials:

Serum Potassium	CCNV [n=627]	PONV [n=936]
In Normal Range	543/627 (86.6%)	388/936 (41.5%)
Below Normal Range	10/627 (1.6%)	11/936 (1.2%)

What can be concluded from observations in the 1.6% or less of the patients that had hypokalemia in the DOLA•Mesyl trials?

It is concluded that it is not known if a decrease in serum potassium has a deleterious effect on the EKG interval changes produced by DOLA•Mesyl in CCNV or PONV patients.

It is of interest to mention that prolongation of the QT interval duration is seen during therapy with many different types of [illegible] antiarrhythmics, ketanserin (a selective [illegible] amiodarone, bepridil, sotalol, [illegible] erythromycin, antihistamines, quinidine [illegible] Morganroth et al, Amer J Cardiol [illegible] manufacturers of Hismanal (astemizole), a [illegible] H_1-receptor antagonist, have added warning [illegible] This warning indicates that concomitant or [illegible] ketoconazole tablets, itraconazole [illegible] available), erythromycin, or quinine if [illegible]

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has been included in the prescribing information for PROPULSID (cisapride, an oral g.i. prokinetic agent). This warning indicates that serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, tosades de pointes and QT prolongation have been reported in patients taking PROPULSID with other drugs that inhibit cytochrome P_{450} 3A4 such as ketoconazole, itraconazole, miconazole, troleandomycin, erythromycin, fluconazole and clarithromycin. There is virtually no information on the possible interaction (alteration of pharmacokinetics resulting in prolongation of the QT/QT_c intervals when the drugs are administered concomitantly or one soon after the other) between DOLA•Mesyl and any of these commonly used drugs.

It is also important to realize that the normal QT_c is highly variable [J. Morganroth et al. (locus cited) (1991). For example, the clinical course of patients with long QT syndrome is quite variable and could range from an asymptomatic course through a normal life span in some patients to the development of malignant ventricular arrhythmias with recurrent syncope and sudden death in others, despite similar degrees of QT_c prolongation [A.J. Moss and J.L. Robinson, Heart Dis. and Stroke, 1:309-314 (1992)]. According to B.N. Singh the practical message is however clear. Combination regimens very numerous in CCNV and PONV patients involving 2 or more QT-prolonging agents or the use of QT prolonging agents in the context of potassium-losing states should be considered with great caution or preferably avoided altogether [Amer. J. Cardiol., 63:867-869 (1989)].

XV. RECOMMENDATIONS FOR REGULATORY ACTION

In the present submission, results of two adequate and well controlled trials (-043 and -048) showed that orally administered dolasetron mesylate (AZEMET® tablets) is effective in the prevention of initial courses of moderately emetogenic cancer chemotherapy. Data from two adequate and well controlled trials (-095 and -0292) demonstrated that dolasetron mesylate tablets is effective in the prevention of postoperative nausea and vomiting. The orally administered drug produces acute usually but not always dose-dependent prolongations of PR, QRS and QT_c. Although (in comparison to baseline) EKG alterations are more readily seen with the 200 mg dose, the reviewer's assessment shows that the other doses of the drug, especially 100 mg, the recommended dose for both indications, also produce significant changes from BL in EKG parameters. But the EKG changes with the 100 mg and the lower doses occurred less frequently.

Although these EKG changes were usually reversible, some clinically significant arrhythmias, changes in vital signs and [illegible] where the possible role of this drug cannot be excluded [illegible] have been observed. Reported very rare cases of [illegible] related to DOLA•Mesyl and instances of prolonged [illegible] block and orthostatic hypotension. Some of these [illegible] complete heart block) have placed patients at [illegible]

Further assessment of the EKG changes from baseline [illegible] related to QT and QT_c prolongation (i.e., torsades de [illegible]

- The QT, QT_c and JT intervals were 5.6, 4.7 and 5.4 msec, respectively, for patients taking beta blockers.

- In the one patient taking concomitant class 1b antiarrhythmics, the changes in all EKG parameters both acutely and at 24h postdose were very, very marked (rather bizarre).

In conclusion, the concomitant use of various cardiovascular medications had varying degrees of effect on the EKG interval changes produced by DOLA•Mesyl, especially during the acute Post-Tx period. It is true that within the frame of the small number of observations assessed herein, these interactions have not resulted in clinical conditions of concern in CCNV prevention patients. But more experience in larger numbers of patients is needed. Also needed are data on the effects of concomitant use of cardiovascular medications on EKG interval changes produced by DOLA•Mesyl in PONV patients.

xii) Effect of History of Cardiovascular Disease

Since in PONV trials, the number of patients with concomitant cardiovascular Hx was too small, the reviewer's comments are on CCNV trials only. It is worth noting that in studies -043 (n=307) and -048 (n=320), a total of 311/627 or ca. half of the patients did not have a history of cardiovascular disease. The proportion of patients with a Hx of atherosclerotic heart disease was 15.5%, but the proportion of patients with other cardiovascular conditions was quite small (6% or less). The observations we are talking about are from a small proportion of patients.

The reader is referred to Table 101. When compared to the acute mean change from BL in patients who did not have a cardiovascular history,

- Greater decreases in the mean change from BL in acute heart rate were seen for patients with a Hx of myocardial (-4 bpm) or pericardial disease (-8.4 bpm).

- There was little influence of cardiovascular history on PR or QRS intervals.

- The QT interval was 4.1, 8.4, 11.9 and 19.2 msec greater for patients with a Hx of atherosclerotic heart disease, arrhythmia/conduction disorders, myocardial and pericardial disease, respectively.

- The QT_c interval was greater for patients with [illegible] (5.9 msec), myocardial (8.2 msec) and [illegible]

- The JT interval was acutely increased for [illegible] cardiovascular disease, with [illegible]

TABLE 101

Acute and 24h Mean Changes from BL in EKG Measures by Concomitant Cardiovascular History in Patients Receiving Single Oral Doses of DOLA®Mesyl In Controlled CCNV Trials*

	Acute Effects						Effects at 24h					
	HR	PR	QRS	QT	QTc	JT	HR	PR	QRS	QT	QTc	JT
NO CV History (n=211)	-1.4	7.8	3.3	12.0	9.8	8.6	0.6	0.6	-0.1	2.3	4.7	2.4
[illegible] Disease (n=97)	-2.8	9.3	3.8	16.1	11.1	12.3	0.6	1.6	-0.4	4.2	7.0	4.6
[illegible] Vascular Disease (n=56)	-1.9	8.5	2.9	15.1	12.3	12.2	0.8	0.4	-0.2	2.3	4.8	2.5
[illegible] Disorder	-2.3	10.9	1.9	20.4	15.7	18.5	-0.9	4.3	-1.8	9.3	7.4	11.1
[illegible]	-5.4	6.4	2.7	23.9	16.0	21.2	3.9	-3.9	-3.6	-5.3	4.1	-1.8
[illegible]	-9.8	2.4	6.0	31.2	18.0	25.2	-1.2	-2.0	1.2	18.8	22.8	17.6
[illegible]												

But it is important to note that the clinical experience with dolasetron mesylate is limited. Specifically, more experience is needed on the potential interaction between dolasetron mesylate and cardiovascular medications in general and those drugs and conditions that prolong the PR, QRS and especially the QT_c intervals in particular. Also lacking are data on possible interaction of this drug with clinical conditions involving patients with history of cardiovascular disease. This information is notoriously lacking in clinical settings involving the use of the drug for the prevention of the PONV indication.

The reviewer concludes that there is a potential safety hazard and this should be acknowledged in the labeling. The reviewer's appraisal of data in NDA 20-623 seems to justify the following recommendations for regulatory action.

1. Approval of ANZEMET® (dolasetron mesylate) for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy, including initial and repeat courses.

   Based on results of pivotal trials -043 and -048, the recommended dose regimen is one 100 mg tablet one hour prior to chemotherapy.

2. Approval of ANZEMET® (dolasetron mesylate) for the prevention of postoperative nausea and vomiting.

   Based on results of pivotal trials -095 and -0292, the recommended dose regimen is one 100 mg tablet within two hours prior to surgery.

3. The labeling, being considered separately, should include a warning, preferably in a box. Such warning should state that there is reasonable evidence for the potential for serious and severe safety hazards - primarily in the cardiovascular/cardiac electrophysiological areas - that may place patients at the risk of death.

May 31, 1996

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/S/

Hugo E. Gallo-Torres, M.D., Ph.D.

cc:
NDA 20-623
HFD-180
HFD-180/SFredd
HFD-180/HGallo-Torres
HFD-181/CSO
HFD-180/JChoudary
HFD-180/GDibbs
r/d 4/18/96 jgw
r/d 4/24/96 jgw
f/t 5/[illegible]/96 jgw
HFD\M\20623602.0HG