CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020623

MEDICAL REVIEW(S)

MAY 31 1996

NDA 20-623

ANZEMET® (Dolasetron Mesylate)

25, 50, 100 and 200 mg tablets

a) Prevention of nausea and vomiting associated with emetogenic cancer chemotherapy including initial and repeat courses

b) Prevention of postoperative nausea and vomiting

Reviewer:
Hugo E. Gallo-Torres, M.D., Ph.D.
HFD-180

MAY 31 1996

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	20-623
Sponsor:	Hoechst Marion Roussel, Inc. Kansas City, MO
Date Submitted to HFD-180:	October 2, 1995
Date Assigned to Reviewer:	October 12, 1995
First Draft to Supervisor:	April 30, 1996
Date Finalized:	May 9, 1996
Name of Drug:	ANZEMET® (Dolasetron Mesylate)
Pharmacological Category:	Selective Inhibitor of the 5-hydroxytryptamine subtype receptor
Formulation:	Tablets (25, 50, 100 and 200 mg)
Route of Administration:	Oral
Proposed Clinical Use: (Indications Sought)	1. Prevention of N&V associated with emetogenic cancer chemotherapy, including initial and repeat courses. 2. Prevention of PONV
Reviewer:	Hugo E. Gallo-Torres, M.D., Ph.D.

Material Submitted (Clinical Data Section)	Vol. No.
1) Clinical Reports for C-I N&V Indication	
S-95-0009-C	222 to 236
K-94-0927-CDS	237 to 252
S-95-0009-CDS	253 to 268
AN-PD-0192 (Pediatric Population)	539
2) Clinical Reports for PONV Indication	
L-95-0001-CS	269 to 277
S-95-0011-C	278 to 297
AN-PD-0593 (Pediatric Population)	588
3) Biopharm. Summaries	59, 175, 176, 221

MEDICAL OFFICER REVIEW OF

NDA 20-623

ANZEMET® (Dolasetron Mesylate) tablets

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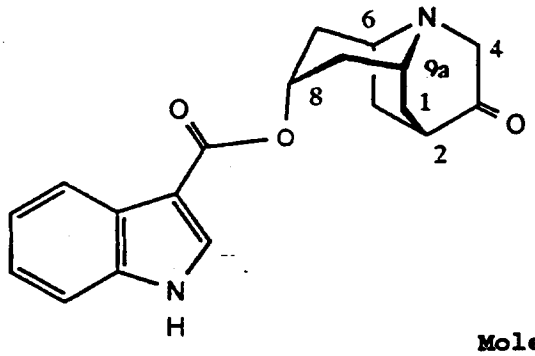
I. GENERAL INFORMATION

1. Drug Substance

Code Numbers

MDL 73,147EF (Mesylate)
MDL 73,147A (HCl salt)
MDL 73147 (free base)



$\cdot CH_3SO_3H \cdot H_2O$

Empirical Formula

$C_{19}H_{20}N_2O_3 \cdot CH_3SO_3H \cdot H_2O$

Molecular Weight

438.50

1H-Indole-3-carboxylic acid, octahydro-3-oxo-2,6-methano-2H-quinolizin-8-yl ester, (2α,6α,8α,9aß)-,monomethanesulfonate,monohydrate

Generic Name	**Trade Name**
Dolasetron mesylate	Anzemet®

Dolasetron Mesylate (DOLA•Mesyl) is a white to off-white powder. It is crystalline and it is monohydrate. It does not gain nor lose water under relative humidity conditions of 23 to 93% at temperature ca. 22°C. The solubility in water for the free base is 0.922 mg/dl; for the mesylate salt, 280 mg/ml. DOLA•Mesyl is not optically active. DOLA•Mesyl is chemically and physically stable when stored for up to 48 months at 30°C in

bags with It is also stable when stored at accelerated temperature and humidity conditions for up to 12 months.

2. Drug Product

Dolasetron mesylate film coated tablets include 4 different strengths - 25 mg, 50 mg, 100 mg and 200 mg.

An immediate release formulation was developed which contains: 1) dolasetron mesylate monohydrate, 2) lactose 3) pregelatinized starch 4) croscarmellose sodium 5) magnesium stearate 6) which contains hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, polysorbate 80 and synthetic red iron oxide 7) carnauba wax and white wax and 8) black ink lecithin, pharmaceutic glaze propylene glycol, synthetic black iron oxide

Manufacturer and Packager
Hoechst Marion Roussel, Inc.
(Marion Merrell Dow Inc.)
Building 28
2110 E. Galbraith Road
Cincinnati, OH 45215

The tablet investigational formulations (25, 50, 100, 200 mg) were all the same as their respective intended commercial formulations with the exception of lack

II. INTRODUCTION/RATIONALE

The sponsor of this NDA is seeking approval for the marketing of ANZEMET® (dolasetron mesylate) tablets for two indications: 1) the prevention of nausea and vomiting associated with cancer chemotherapy, including initial and repeat courses; and 2) the prevention of post-operative nausea and vomiting. Both indications are clinically important.

Nausea and Vomiting (N&V) induced by chemotherapeutic drugs is very important in the management of patients with cancer because, when severe, these AEs may lead to withdrawal of potentially curative treatments. Morbidity due to N&V may also defeat the aim of palliative treatment to improve the quality of life. Although, at present, there is no unifying theory for the mechanism of all cytotoxic drug- and radiation-evoked N&V, it appears that cytotoxic therapy stimulates the release and synthesis of neuroactive agents (e.g. 5-HT, prostanoids, free radicals) from the gut. 5-HT directly activates and/or sensitizes g.i. afferent axons (probably vagal) of the EC cells of the small intestinal mucosa. N&V is initiated by the vomiting center in the medulla following stimulation from a number of sites including the [illegible] trigger zone) in the fourth ventricle, the cerebral cortex, the [illegible] apparatus (in motion sickness) and the g.i. tract. [illegible] emesis is of multifactorial nature. The three recognized [illegible] are defined as follows:

- Acute-onset N&V occurs within 24 h of treatment.

- Delayed-onset N&V occurs 24 h or more after treatment. This is an increasingly recognized problem, particularly with cisplatin therapy. The delay mechanism may involve protein- or tissue-binding of the drug, followed by slow release.

- Anticipatory N&V occurs before chemotherapy. This syndrome is a conditioned response that arises from fear and anxiety about the treatment, possibly triggered by a combination of external and internal sensory stimuli. It is a significant problem, very difficult to manage which can often be avoided by effective antiemetic treatment of acute- and, perhaps, delayed-onset N&V.

A number of prognostic factors increase the risk of vomiting. These include: gender (F>M), younger age, absence of a history of heavy alcohol use and poor previous antiemetic control. Emesis depends upon the type of drug, dose, and duration of administration. In clinical trials, in addition to the standardization of the study population (naive vs previously treated) and chemotherapy regimens, it is critical to standardize the emetogenic stimulus. The following is a classification of chemotherapeutic agents on the basis of their emetic potential.

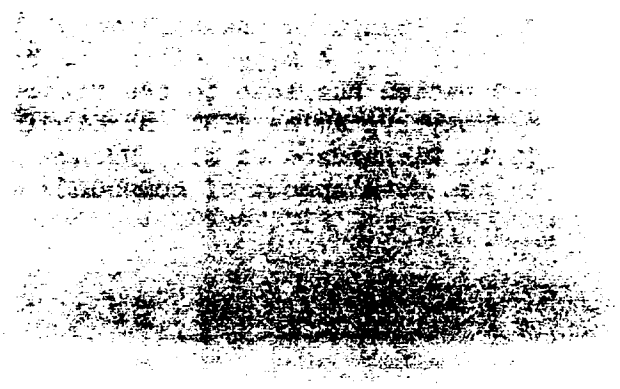
Classification of Chemotherapy Regimens
According to Their Emetic Potential[a]

Class I: Greatest emetic potential

- Cisplatin[b], mg/m²
- Combination of agents, including
  - nitrogen mustard, cyclophosphamide (>1,200 mg/m²)
  - dactinomycin, dacarbazine (>300 mg/m²)
  - camustine (>200 mg/m²) or
  - lomustine (>60 mg/m²)

Class II: Moderate emetic potential[c]

- Combination of agents, including
  - cyclophosphamide (mg/m²)
  - doxorubicin (>50 mg/m²)
  - carmustine (mg/m²)
  - Lomustine (<60 mg/m²)



Class III: Least emetic potential

- Combinations of agents, including
  - cyclophosphamide (<500 mg/m²)
  - MTX, 5-FU
  - doxorubicin (<50 mg/m²)
  - VINB, VINC or ETOP

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a) Adapted from S.B. Trum et al. Cancer 53:1432 (1984).
b) Lower doses of cisplatin are of moderate emetic potential, especially if injected slowly (>3h).
c) Low-dose carboplatin is of moderate emetic potential.

PONV is also an important complication of anesthesia and surgery. There are a number of factors that influence the incidence and severity of PONV. These include the patient's characteristics [gender (F>M), age (children <3y of age < adults), weight, hormonal balance, mental state], pre-medication (such as the use of opiates) and anesthetic techniques. A full stomach is best avoided although fasting is an unpredictable measure [M. Miller et al., Br. J. Anesth. 55:1185 (1983)]. Women have a greater incidence then men following abdominal operations. The highest incidence of N&V is associated with intra-abdominal and ear, nose and throat surgery. Gynecological operations frequently use emetic hormones, such as ergometrine, which in themselves could distort post-operative comparisons. Other factors include post-operative pain, vestibular disturbances, too early moving (→ ambulatory), first oral intake of fluid or food. It is also of interest to note that routine prophylaxis appears justified for certain susceptible groups. These include oral surgery where jaws are occluded by wires with a high risk of aspiration of vomitus, operations on the ear, eye or plastic operations to avoid the problems of disruption of delicate surgical work, women presenting for gynecological operations and children. There are patients with a high likelihood of vomiting who could also be protected. These include patients with a Hx of motion sickness or post-operative sickness. If the operating room is a distant rough ride away and a woman has not been given an opioid for an upper abdominal operation, then prophylaxis is not unreasonable. Vomiting at emergence should be treated because it could be more dangerous for the patient than prolonged vomiting. Finally, as pointed out in many literature publications, the available antiemetics have only limited efficacy by themselves. It may be that agents with different modes of action need to be combined to block more than one pathway to achieve 100% success. In addition, when the PL response is high, this makes it more difficult to convincingly show efficacy, even in studies where PL is used as a comparator.

The rationale to use DOLA•Mesyl for both indications can be briefly summarized as follows. A major effort to develop and assess the efficacy of anti-emetic medication has lead to the discovery of the important role of 5-hydroxytryptamine (5HT, serotonin) in the mediation of emetogenic stimuli [B.P. Richardson et al., Nature 316:126-131 (1985)]. This, in turn, has lead to the development of compounds which selectively bind the functional receptor

for 5-HT, the 5-HT_3 receptor. Two 5-HT_3 receptor blockers have been approved, ondansetron and granisetron. The indications and the dose regimens for which these compounds have been approved are given in Table 1. The corresponding wording in the proposed labeling for DOLA•Mesyl is included in this Table, to

TABLE 1
NDA 20-623

List of Available Dosage Forms, Indications and Recommended Regimens for Approved 5-HT_3 Receptor Antagonists in Comparison to ANZEMET® (Proposed)

Dosage Form	Indication	Regimen
ZOFRAN® (ondansetron hydrochloride)		
Injection	1. Prevention of N&V associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin.	Single 32 mg dose or three 0.15 mg/Kg doses
	2. Prevention of PONV in patients where nausea and/or vomiting must be avoided post-operatively.	4 mg immediately before induction of anesthesia or postoperatively if the patient experiences nausea and/or vomiting occurring shortly after surgery.
Tablets	1. Prevention of N&V associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.	One 8-mg tablet b.i.d. (every 12h) for 1 to 2 days after completion of chemotherapy.
	2. Prevention of N&V associated with radio-therapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen.	One 8-mg tablet t.i.d.
	3. Prevention of PONV, in patients where nausea and/or vomiting must be avoided post-operatively.	16 mg (2 8-mg tablets) 1h before induction of anesthesia.
KYTRIL® (granisetron hydrochloride)		
Injection	1. Prevention of N&V associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin.	10 µg/Kg, 30 min. before initiation of chemotherapy, and only on the day(s) chemotherapy is given.
Tablet	1. Prevention of N&V associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin.	1 mg b.i.d., continued treatment, while not on chemotherapy, has not been found to be useful.
ANZEMET® (dolasetron mesylate)		
Tablets	1. Prevention of N&V associated with emetogenic cancer chemotherapy, including initial and repeat courses.	One 100 mg tablet in proximity to chemotherapy
	2. Prevention of PONV	One 100 mg tablet within 2h prior to surgery

facilitate comparisons. For the prevention of N&V associated with emetogenic cancer chemotherapy if approved, DOLA•Mesyl tablets would represent an advantage over the other two (one-a-day vs b.i.d. dosage).

For the latter indication, Zofran® has been approved for use in those patients where nausea and/or vomiting must be avoided post-operatively.

III. NONCLINICAL PHARMACOLOGY, TOXICOLOGY AND METABOLISM

At this time, Pharmacologist's review of NDA 20-623 is not available. The material summarized below was taken from sponsor's vol. 1.2 (several sections).

A. Functional Antagonism at 5-HT$_4$ Receptors

DOLA•Mesyl

- In conscious and anesthetized rats, following oral and i.v. administration, at 1 mg/Kg, almost completely inhibited the Bezold-Jarisch Reflex over a period of 5h.
- In the isolated perfused rabbit heart, blocked the positive chronotropic effect of 5-HT.
- Exhibited affinity for the 5-HT$_4$ receptor with Kis of 0.33 μM. In the isolated guinea pig ascending distal colon preparation, neither DOLA•Mesyl nor its metabolites exhibited agonist activity and only weak antagonism was detected.

B. Antiemetic Activity

- In the ferret, DOLA•Mesyl administered po (single dose ≥0.5 mg/Kg) or i.v. (≥0.5 mg/Kg x 2) significantly abolished cisplatin-induced retching and vomiting and delayed the onset of the first vomiting episode.
- In the dog, DOLA•Mesyl i.v. doses of 0.1, 0.3 and 1 mg/Kg significantly prolonged time to the first emetic episode and significantly reduced the number of emetic episodes over the 5-h observation period. The effects of DOLA•Mesyl in this model were comparable to those of Zofran® at i.v. doses of 0.5 and 1.5 mg/Kg.

C. CNS Effects

- Chronic (but not acute) administration of high doses of DOLA•Mesyl reduced dopaminergic activity in the rat brain, as measured by levels of dopamine or DOPAC and HVA, an effect which may be predictive of antipsychotic activity.

  (ondansetron had similar effects)

- In behavioral experiments in rats, DOLA•Mesyl (0.01 to 1 mg/Kg sc) reversed a learning and memory deficit induced by scopolamine (a cholinergic receptor antagonist.

  [ondansetron (0.1 mg/Kg sc) and tropisetron (0.01 mg/Kg sc) had similar effects].

D. Hemodynamic and Electrophysiologic Effects

- In conscious, normotensive rats, DOLA•Mesyl (1 to 50 mg/Kg) administered i.v. produced a transient (<5 min.) elevation of BP and HR which were not dose related. No major ganglion blocking activity, adrenergic neuron blocking activity or interference with vagally-mediated bradycardia was observed.

- Following oral administration of DOLA•Mesyl (10 mg/Kg/day x 4 days) to conscious dogs, there was no significant change in mean arterial BP in the following 24-h period. HR was significantly increased (ca. 16 bpm) at only 2 timepoints (3 and 4h postdosing). DOLA•Mesyl (10 mg/Kg po) elicited some minor changes in EKG intervals, but all values remained WNRs; there were no significant changes in P, R, or T wave amplitudes, the QRS interval or the ST segment.

- In conscious dogs, DOLA•Mesyl (4 mg/Kg/day i.v. x 5 days) had no significant effect on BP and HR measured over a 24-h period. In anesthetized dogs, DOLA•Mesyl had no significant effects on cardiovascular reflexes. But a cumulative i.v. dose of 18.5 mg/Kg reduced LV dp/dt_{max} and administration of a further 12.5 mg/Kg dose significantly decreased LV pressure, systemic BP and HR. Cumulative total i.v. doses of 3 mg/Kg and 10 mg/Kg DOLA•Mesyl reversibly increased the PR interval by 9 and 17 msec, respectively. DOLA•Mesyl, at 10 mg/Kg did not significantly increase the QT_c interval, but 30 mg/Kg induced a 47-msec increase.

- DOLA•Mesyl at micromolar concentrations reduced action potential duration, contractile force and the action potential upstroke velocity (V_{max}) of dog Purkinje fibers.

- The reduction in V_{max} was also observed in guinea pig papillary muscle fibers during superfusion with DOLA•Mesyl, the metabolites MDL 73,405 ([+]-enantiomer of MDL 74,156) and MDL 73,349 ([-]-enantiomer of MDL 74,156).

  [Granisetron and tropisetron had similar effects but neither the hydroxylated metabolites of MDL 102,382 and MDL 73,492 nor ondansetron significantly affect the V_{max} of the action potential.]

- The actions of DOLA•Mesyl, MDL 74,156 and MDL 73,405 were also tested on the cloned α-subunit of the human cardiac muscle sodium channel expressed heterologously in *Xenopus* oocytes,

  - Significant channel blocking activity was only observed at concentrations exceeding 10 μM.

  - A summary of the values obtained for tonic and use-dependent block suggest that the test compounds produce only a low affinity tonic block (K_ds mM range).

  - Use-dependent block was only observed at concentrations exceeding 10 μM.

  - In this model, flecainide produced tonic and use-dependent block at 65 and 10 μM, respectively.

- In guinea pig papillary muscle the action potential duration was unaffected by DOLA•Mesyl and its metabolites (all ≤10 μM).

  [tropisetron and ondansetron (1 μM) both induced small increases].

  - In perfused guinea pig heart, DOLA•Mesyl, MDL 74,156 and tropisetron (all 1 μM) increased the absolute refractory period by 29%, 17% and 17%, respectively.

Antiarrhythmic Effects

- In anesthetized rats, DOLA•Mesyl, at 5, 12.5 and 25 mg/Kg given 1 p x 30 min. had a marked protective effect against ischemia-induced arrhythmias. The incidence, number and duration of ectopic beats, percent of time spent in VT and VF, and mortality, were all reduced.

- In another animal model of antiarrhythmic effects following occlusion of the L main coronary artery in anesthetized rats, doses of 5, 12.5 and 25 mg/Kg DOLA•Mesyl were given i.p. x 15 min. The incidence and number of PVCs together with the incidence and duration of VT were significantly reduced in a dose-dependent manner. The incidence of and duration of VF was reduced and mortality was decreased.

- In renal hypertensive dogs, DOLA•Mesyl, at i.v. doses of 1.5 or 12.5 mg/Kg x 105 min. reduced the occurrence of PVCs and increased the threshold for VF.

- The effects of [redacted] DOLA•Mesyl or [redacted] MDL 73,902, both given i.v., were tested for the occurrence of ventricular hyperautomaticity (VHA) in normotensive dogs. A cumulative dose of 31 mg/Kg DOLA•Mesyl significantly increased the amount of current needed to induce VHA in anesthetized dogs. MDL 73,902 (2 mg/Kg) also prolonged the time to onset of VHA.

E. Drug Interactions

- DOLA•Mesyl (5 mg/Kg po or i.v.) given simultaneously with cisplatin to mice implanted with one of three tumor models, did not affect the toxicity or antitumor properties of cisplatin, against all three models.

- DOLA•Mesyl did not potentiate or antagonize the actions of general anesthetics in mice.

  - No statistically significant effect on the sleep time induced by the anesthetics thiopental, halothane, isoflurane or enflurane, or the resleep time of thiopental were observed.

  - Similarly, DOLA•Mesyl (10 mg/Kg intragastrically) did not affect hexobarbital sleep or resleep time.

- DOLA•Mesyl did not reverse the sedative action of chlordiazepoxide in mice, but flumazenil did.

- Based upon studies on neuromuscular transmission, it is unlikely that DOLA•Mesyl prior to surgery will alter the neuromuscular blockade induced by d-tubocurarine or atracurium.

- DOLA•Mesyl and its metabolites had no effect on electric eel or human erythrocyte acetylcholinesterase and were only weak inhibitors of human butrylcholinesterase.

  - DOLA•Mesyl did not affect the inhibitory activity of the cholinergic antagonist atropine or affect the activity of acetylcholine.

  - DOLA•Mesyl is predicted to have little affect on the activity of the H_2 antagonist RAN.

F. Reviewer's Conclusions on Pre-Clinical Pharmacology

The pre-clinical data summarized here demonstrate that DOLA•Mesyl possesses functional antagonism at 5-HT_3 receptors and exhibits some affinity for the 5-HT_4 receptor. The latter may also play a part in emetic responses. It is

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important to note that a 5-HT_4-like receptor, with both chronotropic as well as inotropic effects, has been identified in human right atrial tissue. It is theoretically possible that some **5-HT_3 antagonists**, like DOLA•Mesyl may have activity at this receptor. Additional information for the 5-HT_4 is of interest here. From in vitro studies, cisapride (PROPULSID®), a 5-HT_4 agonist, was associated with at least seven cases of sinus tachycardia. Rechallenge precipitated relapse in some of these patients. With cisapride, rare cases of cardiac arrhythmias, including ventricular arrhythmias, torsades de pointes and QT prolongation, in some cases resulting in death, have been reported. It is important to point out that most of these patients had been receiving multiple other medications and had pre-existing cardiac disease or risk factors for arrhythmias. Although a causal relationship to PROPULSID® has not been established, it is worth noting that drugs that inhibit the hepatic cytochrome P_{450} 3A4 isoenzyme system, the enzymes that normally metabolizes PROPULSID®, such as keto-, itra- flu- and micronazole, clari- and erythromycin or troleandomycin can lead to elevated cisapride blood levels. A study in 14 M and F suggested that co-administration of PROPULSID® and ketoconazole can result in prolongation of the QT intervals. Normalization of the QT interval after cisapride was D/C has been observed.

The antiemetic effects of DOLA•Mesyl appears to be comparable to that of ondansetron. Hemodynamic and electrophysiologic effects of DOLA•Mesyl were shown at very high dose of compound (i.e. 10 mg/Kg) and were similar to those elicited by granisetron and tropisetron. In several animal models, DOLA•Mesyl was shown to have antiarrhythmic effects. The significance of these pre-clinical findings is not known, as, in the clinic, DOLA•Mesyl has been shown to possess arrhythmic effects.

On the basis of the pre-clinical drug interaction data, DOLA•Mesyl would not be expected to affect the antitumor efficacy of chemotherapeutic agents or influence the depth or duration of anesthesia produced in humans by agents such as thiopental, halothane, isoflurane, enflurane or hexobarbital. In addition, these preclinical data demonstrate that DOLA•Mesyl does not act in vivo as a benzodiazepine receptor antagonist. It also seems unlikely that DOLA•Mesyl prior to surgery will alter the neuromuscular blockade induced by d-tubocurarine or atracurium. Finally, DOLA•Mesyl did not affect the inhibitory activity of atropine, a cholinergic antagonist nor affected the activity of acetylcholine or the H_2-receptor antagonist ranitidine.

G. Pre-Clinical Toxicology

The sponsor noted:

- Acute toxicity of DOLA•Mesyl has been studied in mice, rats, dogs and monkey by both the oral and i.v. routes.
  - For mice and rats, the LD_{50} values following oral administration were 545 mg/Kg and 446 mg/Kg, respectively, and following i.v. administration, they were 165 mg/Kg and 150 mg/Kg, respectively. The dog appeared to be the most sensitive [illegible] appeared to be the species most resistant.

- Multiple dose toxicity of DOLA•Mesyl has been studied in the mouse, rat, dog and monkey by oral (dietary, gavage, or capsule) and i.v. administration.

- In a 3-month dietary study, doses of DOLA•Mesyl were administered to mice. The liver appeared to be the target organ, as hepatocellular centrilobular hypertrophy accompanied by increased liver weights and increased serum ALT and AST were observed. Decreased body weight and increased phosphorus was also observed.

- DOLA•Mesyl 2-y oral carcinogenicity studies were conducted in mice and rats.

  - DOLA•Mesyl was not carcinogenic in rats at doses 53 and 105 times (based on mg/Kg) the highest recommended human dose (200 mg), in M and F, respectively.

  - In mice, DOLA•Mesyl was not carcinogenic at doses 26 times the highest recommended human dose. Liver tumors in Ms and endometrial polyps in Fs were found at 53 times the highest recommended human dose.

  - Fertility and reproductive performance were not affected by oral administration of DOLA•Mesyl to M and F rats at doses 140 and 35 times the highest recommended human dose, respectively.

- In M and F fertility studies, DOLA•Mesyl had no effect on reproductive capacity at oral doses 140 and 35 times the highest recommended human dose (200 mg), respectively. The only finding was increased liver weights in the F_0 females treated through lactation. This was not present in females treated only through gestation.

- Developmental toxicity was studied by oral and i.v. administration of DOLA•Mesyl in rats and rabbits during the period of organogenesis at doses up to 35 times the highest recommended human dose (200 mg).

  - In both species, by both routes, DOLA•Mesyl was nonteratogenic.

  - In the oral studies, maternal toxicity (decreased body weight gain at 100 mg/K/day in rats and ≥20 mg/Kg/day in rabbits) was associated with decreased fetal body weight at 100 mg/Kg/day in rats (6%) and rabbits (13%) and increased postimplantation loss at ≥20 mg/Kg/day in the rabbit, while in intravenous studies, maternal toxicity [convulsions and death in rats and tremors (1 female, 1 day) in rabbits] were observed without evidence of effects on embryofetal development.

- No evidence of toxicity was observed when DOLA•Mesyl was administered orally to monkeys for 1 week to 3 months at doses of [illegible] mg/Kg/day and intravenously for 1 month at doses of 2 to 10 mg/Kg/day.

- The genetic toxicity of DOLA•Mesyl was studied in the Ames bacterial mutagenicity assay, rat lymphocyte chromosomal aberration assay, rat hepatocyte unscheduled DNA synthesis, Chinese hamster ovary cell/hypoxanthine-guanine-phosphoribosyl transferase forward mutation assay, and an oral and i.v. mouse bone marrow micronucleus test.

    - All tests demonstrated the absence of mutagenic and genotoxic activity for DOLA•Mesyl.

H. ADME in Animals

As pointed out by the sponsor:

- Oral doses of DOLA•Mesyl are well absorbed in rats, rabbits, dogs, monkeys and man.

    - The absorption of the free base is rapid with peak concentrations observed within 2 h.

    - Depending on the dose and species, the absorption of the free base ranged from a minimum of

    - The bioavailability of DOLA•Mesyl ranged from in rats, dogs, and monkeys.

    - Plasma concentrations of the free base are much lower than the major metabolite, MDL 74,156. As a result of the rapid metabolism of the free base, the apparent absolute bioavailability of the free base was calculated using the major metabolite, MDL 74,156, and ranged from depending on the species.

- Studies with orally administered ^{14}C-labeled DOLA•Mesyl in rats have shown that a single dose is rapidly and widely distributed to tissues (t_{max} plasma = 0.5 h, t_{max} tissues = <2 h).

    - The highest concentrations of radioactivity were found in the stomach and small intestine and the excretory organs, liver and kidney.

    - Over 84% of a [^{14}C] dose was excreted within 96 h with less than 1% of the administered radioactivity remaining in the tissues and carcass 96 h after dosing. In man, more than 80% of an i.v. or oral dose of DOLA•Mesyl was excreted within 4 days.

- Protein binding of MDL 73,147 was found to range in plasma of animals and 90% in human plasma.

    - The protein binding of MDL 74,156 ranged in the plasma of animals and in human plasma.

- Protein binding in healthy volunteers was 69% for MDL 74,156 and in cancer patients receiving chemotherapeutic agents.

- Virtually no unchanged free base has been detected in the urine or feces of laboratory animals or man following oral and i.v. administration.

  - The free base is rapidly and completely reduced to the alcohol MDL 74,156 by carbonyl reductases in all species tested.

  - MDL 74,156 is the major metabolite identified in all species.

  - The biotransformation pathways for the free base are the same for all species tested and follow the expected routes based upon its chemical structure: keotone reduction to the alcohol (by carbonyl reductases), then conjugation at the hydroxyl group, or hydroxylation in the indole ring (by cytochrome P4502D6) and subsequent conjugation of these hydroxyl groups and a minor route of N-oxidation of the nitrogen in the quinolizine ring (<2% of dose).

  - All [^{14}C]-metabolites have been identified and their structures confirmed in urine (animals and man) and feces (animals) following oral and i.v. administration of [^{14}C]-labeled DOLA•Mesyl.[1]

  - All metabolites found in man have also been identified in rats and dogs, the animal species used in toxicity testing.

  - The biotransformation pathways for DOLA•Mesyl are the same for all species tested.

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[1]As shown below, all of the identified metabolites are biotransformations of MDL 74,156.

Metabolites: Compound Numbers and Their Corresponding Definitions	
Compound Number	*Definition*
MDL 73,147EF	Dolasetron mesylate salt (DOLA•Mesyl)
MDL 73,147A	Dolasetron hydrochloride salt
MDL 74,156	Primary metabolite of MDL 73,147 (racemic mixture)
MDL 73,405	[+] - enantiomer of MDL 74,156
MDL 73,369	[-] - enantiomer of MDL 74,156
MDL 102,392	5'-hydroxy MDL 74,156
MDL 73,402	6'-hydroxy MDL 74,156
MDL 28,577	Early number for the primary metabolite of [illegible] replaced by MDL 74,156

- Stereoselective reduction of the free base was observed in all species studied, and the (+)-enantiomer of MDL 74,156 was the major enantiomer found in urine.

- The clearance of the free base in rats after oral and i.v. dosing was determined to be 5402 mL/min/Kg after oral dosing and 189 mL/min/Kg after i.v. dosing, suggesting extensive metabolism.

  - The plasma elimination half-life of the free base and MDL 74,156 in the rat after i.v. administration of DOLA•Mesyl was 0.52 h and 3.7 h, respectively.

  - In the dog, the systemic clearance of the free base was 187 mL/min/Kg or ca. seven times the hepatic plasma flow of the dog.

  - Clearance of the active metabolite MDL 74,156 was comparable to hepatic plasma flow at after oral and i.v. dosing, respectively.

  - In the dog, the plasma elimination half-life of the free base and MDL 74,156 after i.v. administration of DOLA•Mesyl was 0.10 h and 5.1 h, respectively.

- DOLA•Mesyl is eliminated almost entirely as metabolites, rapidly and completely, via the urine and feces of animals and man.

  - Over 84% of the [^{14}C] dose was excreted within 48 h in the rat and dog, 72 h in the rabbit and 96 h in man.

  - Biliary excretion would appear to be the slightly preferred route of excretion in animals following oral dosing. However, at higher doses in the rat and rabbit, urinary excretion of radiolabeled metabolites becomes more important.

  - Urinary excretion is the primary route in man as well.

I. <u>Reviewer's Conclusions on ADME in Animals</u>

Orally administered DOLA•Mesyl is rapid and well absorbed in animals (55 to 100% of the given dose), with low bioavailability 3.5 to 13.2% in rats, dogs and monkeys. Together, these findings suggest extensive pre-systemic metabolism of the free base. As a consequence, absolute oral bioavailability of DOLA•Mesyl cannot be determined by monitoring parent drug because its rapid reduction prevents its consistent detection. The absorbed radioactivity (from ^{14}C-labeled DOLA•Mesyl) distributes widely into tissues, especially to excretory organs (liver and kidney). High uptake by the [illegible] tissue was not shown in animals. Biotransformation occurs to a great extent. The major (+)-enantiomer of MDL 74,156 (Ketone reduction product, [illegible] of the free base) was the major enantiomer found in urine. Extensive [illegible] is

also suggested by clearance data. At high doses in the rat and rabbit, the main route of elimination in animals and man - primarily as metabolites - is the urine but biliary excretion would appear to be the slightly preferred route of excretion in animals following oral dosing. It is not known if the DOLA•Mesyl metabolites undergo enterohepatic circulation. Protein binding of the primary metabolite is not affected by either chemotherapy or concurrent cancer.

IV. HUMAN PKs AND BIOAVAILABILITY

At this point in time, a Biopharm. Review is not available. The material that follows was extracted from the sponsor's Summary on subject matter (vol. S2-1.2).

A. Oral Absorption/Basic PKs

The data presented by the sponsor demonstrate that orally administered DOLA•Mesyl is well absorbed, although parent drug is rarely detected in plasma due to rapid and complete metabolism (reduction of its Ketone group) to the most clinically relevant species, MDL 74,156. This active reduced metabolite is responsible for the majority of clinical antiemetic activity.

TABLE 2
Protocol 73147-1-C-029 (Report K-93-0341-D)

Mean (% CV) PK Parameters for [^{14}C]-Radioactivity and MDL 74,156
(n=6)

	[^{14}C]-radioactivity	*MDL 74,156*
AUC(0-∞) (ng-eqv•h/mL or ng•h/mL)	26027 (15)	6854 (46)
C_{max} (ng-eqv•h/mL or ng/mL)	2119 (13)	1197 (23)
t_{max} (h)	1.52 (76)	0.77 (34)
$t_{\frac{1}{2}}$ (h)	8.37 (15)	7.14 (19)
$CL_{app.po}$ (mL/min/Kg)	2.76 (12)	9.10 (42)
CL_R (mL/min/Kg)	1.60 (13)	2.31 (11)
K_r[a]	0.86 (3)	NA
AUC(0-∞) ratio (%)[b]	NA	34.8 (40)

NA: Not applicable
CV: Coefficient of variation
a) Blood to plasma concentration ratio of [^{14}C]-radioactivity
b) AUC(0-∞) ratio of MDL 74,156 to [^{14}C]-radioactivity calculated based on molar equivalent concentrations

This Table corresponds to sponsor's Table 2-22 (S2. V 1.2, p. 196) with minor modifications.

- Data from Protocol 73147-1-C-029 (Report K-93-0341-D) showed that MDL 74,156 appears rapidly in plasma, with a maximum concentration occurring ca. 1h after dosing. It is eliminated with a mean half-life of 7 to 9h. It represented 35% and 61% of [^{14}C]-radioactivity in plasma and urine, respectively. It was eliminated by multiple routes (i.e., excretion, hydroxylation, glucuronide conjugation, and N-oxidation). The N-oxidation of MDL 74,156 was a very minor elimination pathway compared to other routes. The biotransformation profile of DOLA•Mesyl after the oral dose was identical to that after i.v. dosage (i.v. data are not presented in this review). The mean plasma concentration time plots and PK parameters for [^{14}C]-radioactivity and MDL 74,156 are presented in Table 2.

B. Dose Proportionality

Protocol MCPR0081 (Report K-94-0864-CDS)

This was an open-label, randomized, three-way crossover design study in 18 HMV . Each subject received 200, 100 and 50 mg DOLA•Mesyl injectable solution given orally.

- The plasma AUC and C_{max} of MDL 74,156 increased proportionally with dose over the single and multiple oral dose range of 50 to 200 mg DOLA•Mesyl.
- There was no significant accumulation of MDL 74,156 following once daily oral doses of 50 to 200 mg DOLA•Mesyl.
- The mean plasma concentration vs time plots for MDL 74,156 observed after single (Day 1) and multiple (Day 7) oral administration of DOLA•Mesyl is depicted in Fig. 1.

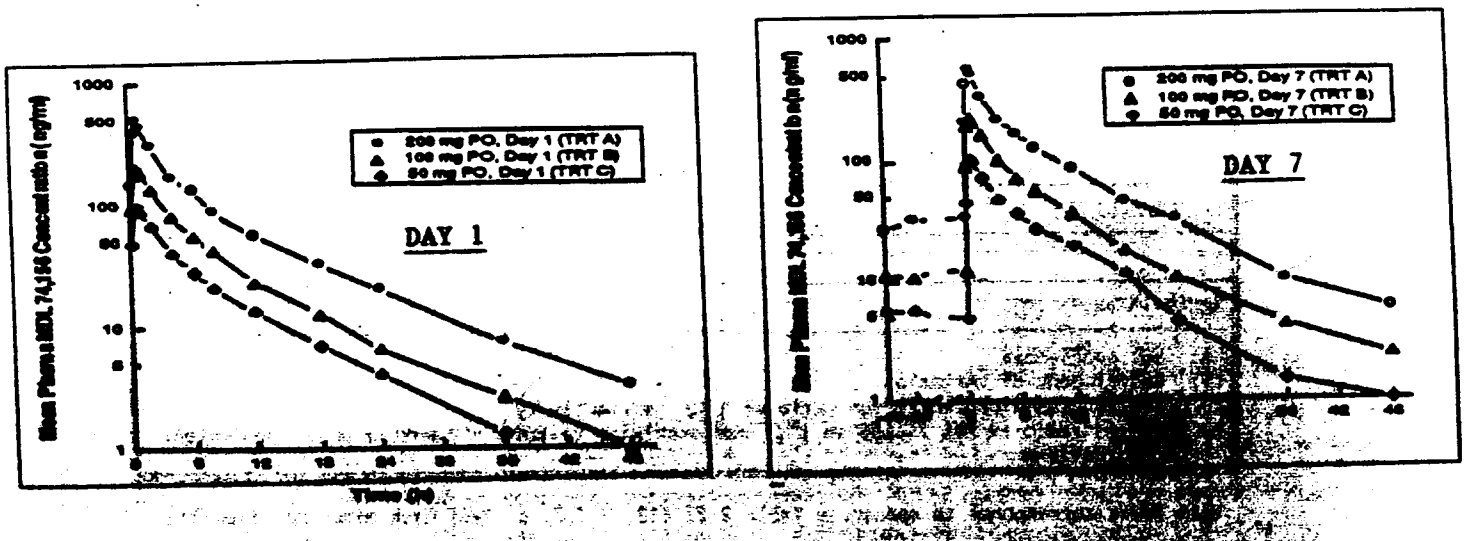

Fig. 1. - Study Protocol MCPR0081 (Report K-94-0864-CDS): Mean Plasma Concentration vs Time [illegible] on Day 1 and Day 7 in HMV (n=18) Orally [illegible] 200, 100 and 50 mg [illegible]

- In this study, PK parameters of MDL 74,156 obtained at steady-state were similar to those obtained after a single dose, indicating the linear disposition of the metabolite after multiple doses of DOLA•Mesyl.

- In this study, some PD data of interest were reported:

  - They consisted of acute, asymptomatic, reversible changes in PR interval and QRS duration.

  - These changes were observed after single and multiple oral doses of 50 to 200 mg DOLA•Mesyl and were linearly related to plasma concentrations of MDL 74,156.

  - The population slopes for PR and QRS were 0.0267 and 0.0088 msec/ng/ml, respectively.

  - The population predicted changes in PR interval and QRS duration over the plasma MDL 74,156 concentrations observed following oral administration of DOLA•Mesyl were <20 msec and 7 msec, respectively.

- In this study, there was no cumulative effect on PR and QRS changes after multiple oral doses of DOLA•Mesyl.

Study Protocol MCPR0080 (Report K-94-0734-CDS)

This study investigated dose proportionality and absolute bioavailability of DOLA•Mesyl after 3 i.v. infusion doses and one oral dose in normals.

- In this study, the mean apparent oral biovailability of DOLA•Mesyl solution, determined by comparing the AUC (0-∞) of the free base obtained after oral and i.v. administration of DOLA•Mesyl was 76%.

- As shown in Fig. 2, the mean plasma concentration with 200 mg given orally was very similar to that seen with the intravenously administered 200 mg.

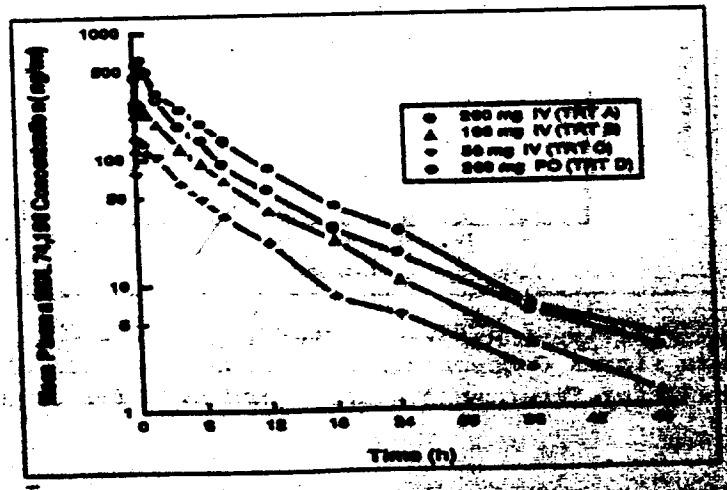

Fig. 2 - Study Protocol MCPR0080 (Report [illegible])
Mean Plasma Concentration vs [illegible]
MDL 74,156 (n=24)

- In this study, acute, asymptomatic, reversible changes in PR interval (population slope = 0.0316 msec/ng/ml) and QRS duration (population slope = 0.0141 msec/ng/ml) were observed after 50 to 200 mg i.v. and 200 mg oral doses of DOLA•Mesyl.

- As in the previous study, these EKG changes were linearly related to plasma concentrations of MDL 74,156.

- The magnitude of PR and QRS changes with plasma concentrations of MDL 74,156 was not influenced by the route of administration of the compound (i.v. = oral).

C. Bioavailability of Prototype Tablet

Study Protocol MCPR0035 (Report K-94-0243-CDS)

One important objective of this study in 24 HMV was to determine the relative bioavailability of the DOLA•Mesyl prototype tablet compared to an oral solution.

- This was assessed by comparing plasma AUC (0-∞) of the major, active metabolite, MDL 74,156, and determined to be 103.7%.

- The apparent absolute oral bioavailability of the prototype table, determined by comparing plasma AUC (0-∞) of the major, active metabolite was 73.6%.

- As shown in Fig. 3 the mean plasma concentration for the 200 mg tablet given orally, was very similar to the 200 mg orally administered solution and to the i.v. administered 200 mg i.v. infusion.

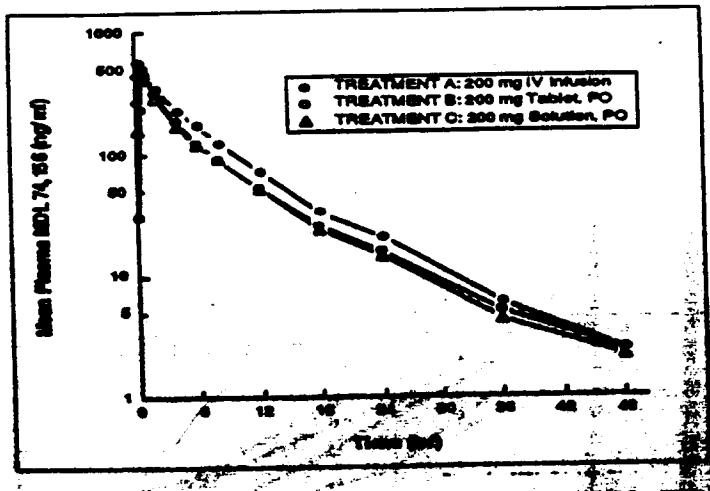

Fig. 3. - Study Protocol MCPR0035 (Report -94-0243-CDS) Mean Plasma Concentration vs Time Plots for MDL 74,156 (n=31 for Treatments A and C and n=30 for Treatment B)

D. Bioavailability of Tablet and Food Effect
Study Protocol MCPR0089 (Report K-94-0687-CDS)

This open-label, randomized, four-way crossover study with 24 HMV aged 18 to 45 years, had three objectives:

1) To determine the bioequivalence of the proposed final marketed

2) To characterize the effect of a high fat meal on the apparent oral bioavailability of the proposed marketed DOLA•Mesyl tablet.

3) To determine the apparent oral bioavailability of a prototype phase III DOLA•Mesyl tablet and proposed final marketed DOLA•Mesyl tablet as compared to a DOLA•Mesyl oral reference solution (Lot No. C-49127).

- Heart rate and EKG measurements were done pre-dose and 1-5h and 48h post-dose. These results can be summarized as follows:

  a) Both the prototype phase III DOLA•Mesyl tablet and proposed final marketed DOLA•Mesyl tablet showed complete bioavailability compared to the oral reference solution.

  b) The proposed final marketed DOLA•Mesyl tablet was found to be equivalent to the prototype phase III DOLA•Mesyl tablet utilized in the controlled clinical trials.

  c) As depicted in Fig. 4, there was a slight delay in absorption when the proposed final marketed DOLA•Mesyl tablet was given with a high fat meal. However, the apparent extent of absorption was not significantly affected by food.

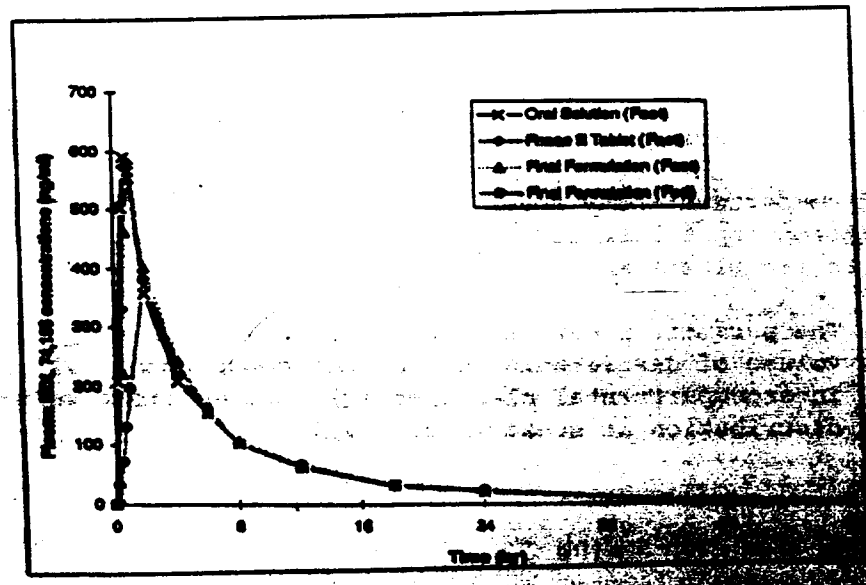

Fig. 4 - Study Protocol MCPR0089 (Report K-94-0687-CDS)
Mean Plasma Concentration vs. Time
(n=23 for all treatments).

E. PKs and PDs in Patients Receiving Moderately Emetogenic Chemotherapy

These were evaluations in patients participating in Phase III Clinical trials with oral DOLA•Mesyl.

i) Protocol MCPR0043 (Report K-95-0096-D)

- This was a four arm, D-B, randomized, parallel, multicenter, dose-response study in which patients with confirmed malignant disease were to receive orally either 25, 50, 100 or 200 mg dose of DOLA•Mesyl.
- 300 cancer patients of either sex and any race due to receive i.v. carboplatin or cisplatin containing chemotherapy were required.
- Blood samples for PK/PD analysis were obtained from 68 patients from 9 study sites.
- EKGs were obtained at Pre-Tx and at 1 to 2, and 24 to 36h after the start of chemotherapy infusion. But results of EKG evaluations are evaluated under Safety, Study MCPR0043.

  NOTE: The carboplatin regimen is considered to be of moderate emetogenic potential. The cisplatin regimen, especially if infused for >3h is of low to moderate emetic potential.

- Plasma concentration-time data for the reduced metabolite, MDL 74,156, were analyzed by NONMEM[2].
- The changes in EKG parameters from the pretreatment value (ΔPR interval and ΔQRS duration) and plasma MDL 74,156 concentrations were fitted to a linear pharmacodynamic model using NONMEM.
- The covariates included in the PK/PD analysis were: demographics (patient age, height, weight, body surface area, gender, and race), serum creatinine, albumin, disease, DOLA•Mesyl dose, and concomitant medications including chemotherapy agents.
- A two-compartment body model (2-CBM) with first-order formation/absorption input rate and elimination from the central compartment was used to fit plasma MDL 74,156 concentration-time data.
  - The parameters were apparent oral clearance (CL_{ss}/F) and apparent volume of distribution of central compartment (V_c/F), and apparent intercompartmental clearance (Q), and apparent volume of distribution at steady-state (V_{ss}/F).

[2]Non-linear mixed effect modeling

- The proportional error model in $CL_{app,po}$, V, and V_{ss} was used for interindividual variability.

Results

- From NONMEM analysis, the patient covariates such as height, serum creatinine, carboplatin infusion rate, and cisplatin infusion rate when included in $CL_{app,po}$ significantly influenced the objective value function. The dose of DOLA•Mesyl and race did not influence MDL 74,156 apparent clearance.

  [PKs of MDL 74,156 in these patients were linear and similar to those in healthy subjects (see above)].

- The intersubject variability in $CL_{app,po}$ (square root of ω^2_{CL}) was estimated to be 55.6% (95% CI: 44.0 to 65.1%).

- The residual or intrasubject variability (square root of σ^2) was 33.0% (95% CI: 25.9 to 38.9%).

- The %CV for coefficients (θs) ranged

- According to the sponsor, DOLA•Mesyl was well tolerated during all treatments administered in this study.

  - The changes in PR interval and QRS width were linearly related to plasma MDL 74,156 concentrations. The maximum mean increase of 9.8 and 5.5 msec in PR interval and QRS duration, respectively, is predicted based on the maximum mean plasma MDL 74,156 concentration observed in this study.

  - The magnitude of change (slope parameter) in PR interval and QRS width with plasma MDL 74,156 concentration in cancer patients was comparable to healthy subjects reported previously.

ii) Protocol AN-PD-0292 (Report K-95-0372-D)

- This open-label, dose-escalation study was conducted in cancer patients between the ages of 3 and 17-y-old receiving moderately emetogenic chemotherapy. The objective of the study was to determine the appropriate single oral doses of DOLA•Mesyl for children undergoing chemotherapy by conducting PK assessments of MDL 74,156 plasma concentrations and monitoring safety and efficacy assessments.

- DOLA•Mesyl was supplied to each of five participating clinics in ampules (Lot No. 92A014) containing 10 ml of a 20 mg/ml solution of the drug.

- Each dose level was administered to consecutive groups of [illegible] patients in a stepwise fashion based on tolerance to each preceding dose. New patients were recruited for each dose [illegible]

- A total of 32 pediatric cancer patients received oral doses of 0.6 (n=9), 1.2 (n=13), or 1.8 (n=10) mg/Kg of DOLA•Mesyl.[3]

Results

The mean PK parameters for all patients for MDL 74,156 are summarized in Table 3. In this Table, comparisons to data from healthy adult volunteers (Protocol MCPR0081) are included.

TABLE 3
Study Protocol AN-PD-0292 (Report K-95-0372-D)

Mean[a] PK Parameters of MDL 74,156 After A Single Oral Dose of DOLA•Mesyl in Pediatric Patients and HMVs

Parameter	*Pediatric Patient Dose (Oral) All Ages (3 to 17 y) (mg/Kg)*			*Healthy Adult Volunteer Dose (Oral)[b] Protocol MCPR0081 (mg/Kg)*		
	0.6 n=9	1.2 n=13	1.8 n=10	0.65 n=17	1.3 n=16	2.6 n=17
C_{max} (ng/mL)	54.7 (38)	135.4 (52)	264.0 (58)	106.9 (20)	224.6 (24)	520.4 (26)
t_{max} (h)	1.0 (50)	0.9 (56)	0.9 (55)	0.72 (24)	0.70 (30)	0.81 (14)
AUC(0-∞) (h•ng/mL)	252.8 (46)	578.0 (72)	1085.3 (79)	613.3 (42)	1181.4 (39)	2735.1 (38)
$t_{1/2}$ (h)	5.21 (30)	6.07 (39)	6.19 (34)	7.74 (36)	7.47 (21)	8.86 (19)
CL_{app} (mL/min/Kg)	37.4 (58)	40.4 (61)	32.4 (58)	15.2 (38)	15.5 (35)	13.3 (36)

This Table corresponds to sponsor's Table 2-85 (S2, vol. 1.2, p. 244) with minor modifications.
a) Percent coefficient of variation shown in parentheses.
b) Dose normalized by individual body weight of (Doses 50, 100 and 200 mg, respectively)

- The mean MDL 74,156 plasma concentration-time profiles for the oral doses administered in this pediatric study are shown in Fig. 5.

[3] Unsatisfactory efficacy results were obtained with the 0.6 mg/Kg dose of DOLA•Mesyl; this dose was not evaluated and the protocol was amended to remove this dose.

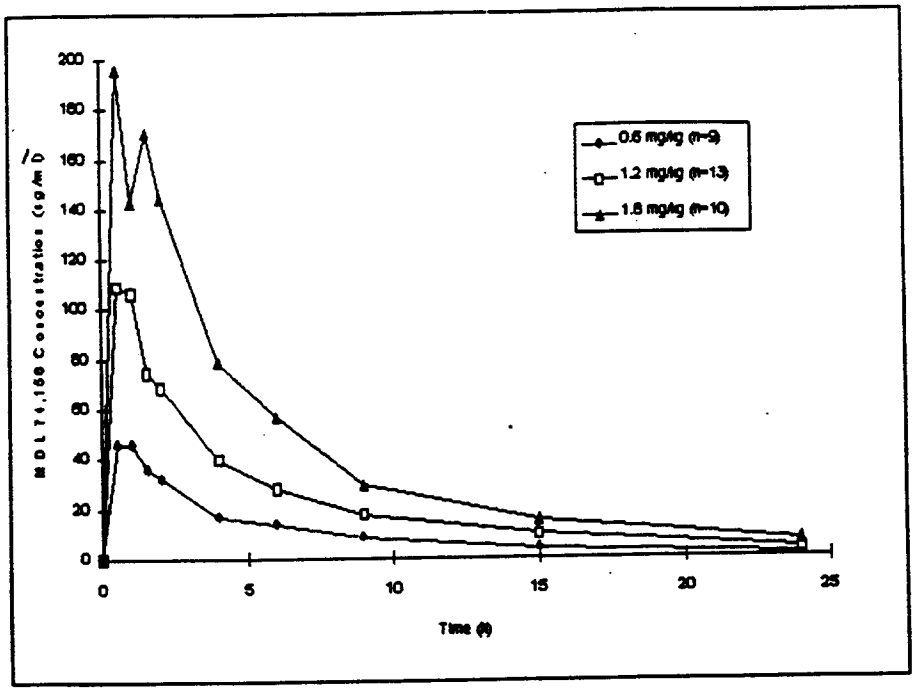

Fig. 5. - Study Protocol AN-PD-0292 (Report K-95-0372-D): Mean MDL 47,156 Plasma Concentrations After A Single oral dose of DOLA•Mesyl in Pediatric Cancer Patients.

- The mean MDL 74,156 oral clearance, half-life and time to maximum plasma concentration in three age groups are compared below.

	PEDIATRIC PATIENTS		HMV[a]
Parameter	3 to 11y (n=19)	12 to 27y (n=13	20 to 43y (n=18
Cl_{app} (mL/min/Kg)	44.24 (49)	25.52 (67)	14.7 (36)
$t_{\frac{1}{2}}$ (h)	5.50 (39)	6.39 (30)	8.04 (27)
t_{max} (h)	0.93 (56)	0.97 (52)	0.75 (23)

This Table corresponds to sponsor's Table 2-36 (62, vol. 1.2, p. 246) with minor modifications.
a) Healthy Male Volunteers, Protocol MCPR0081

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Reviewer's Comments

These evaluations in pediatric cancer patients given oral doses of up to 1.8 mg/Kg showed some differences in PK in comparison to HMVs. Due to a shorter

half-life in the younger children and a corresponding lower overall plasma concentrations, the apparent clearance increased 3-fold. The apparent clearance in children 12 to 17 years increased 2-fold. Efficacy results in pediatric cancer patients are discussed later, but as in adults, following single oral dose of DOLA•Mesyl from the main metabolite, MDL 74,156 appeared rapidly in the plasma with the maximum plasma concentrations and areas under the curve increasing with increasing dose of the drug (Fig. 5). One of the sponsor's conclusions from this study was that values for the apparent oral clearance and half-life of MDL 74,156 in pediatric cancer patients were generally unchanged with respect to DOLA•Mesyl dose.

F. PK Studies in Children Undergoing Surgery Under General Anesthesia

Study Protocol AN-PD-0993 (Report K-95-0122-CD)

This open-label, single center study was wet to evaluate the PK parameters of a single oral dose (1.2 mg/Kg) of DOLA•Mesyl solution administered 1 to 2h preoperatively to pediatric patients (between 2 and 12y of age) undergoing elective and uncomplicated surgery under general anesthesia.

- Mean plasma concentration-time plot for MDL 74,156 is depicted in Fig. 6. Mean PK parameters for MDL 74,156, that includes all patients (n=11) are given in Table 4.

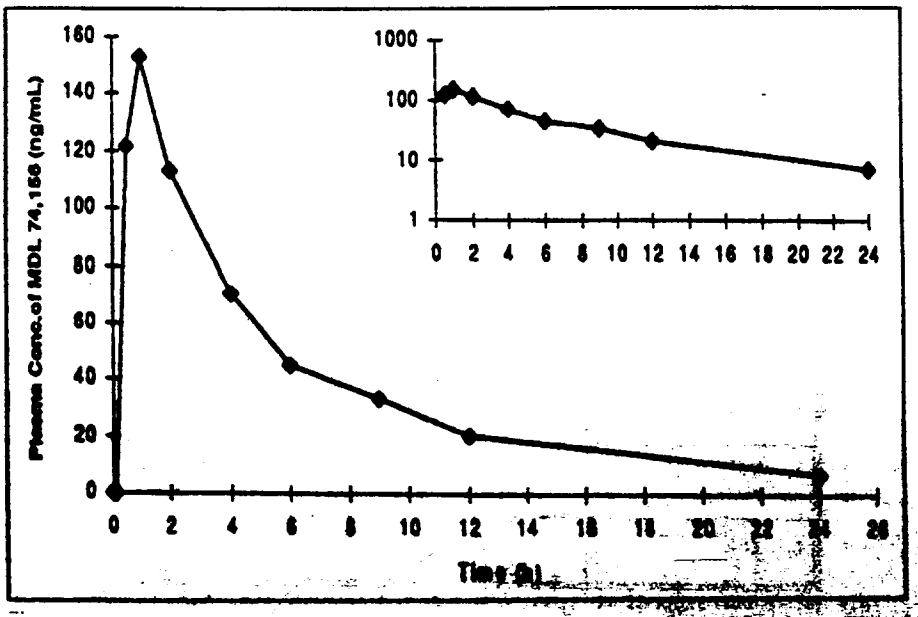

Fig. 6. - Study Protocol AN-PD-0993 (Report K-95-0122-CD). Mean Plasma Concentration vs Time Plot for MDL 74,156 Following Oral Administration of 1.2 mg DOLA•Mesyl to Children Undergoing Elective and Uncomplicated Surgery Under General Anesthesia.

TABLE 4
Study Protocol AN-PD-0993 (Report K-95-0122-CD)

Mean (%CV) Plasma PK Parameters for MDL 74,156
Following Oral Administration of 1.2 mg/Kg DOLA•Mesyl in Children
Undergoing General Anesthesia for Surgery

Variable	Mean (%CV)
AUC(0-∞ (ng•h/mL)	933 (61)
C_{max} (ng/mL)	159 (32)
t_{max} (h)	1.39 (70)
$CL_{app.po}$ (mL/min/Kg)	20.77 (49)
$t_{½}$ (h)	5.89 (24)
CV: Coefficient of variation	

This Table corresponds to sponsor's Table 2-39, with no modifications.

The sponsor's conclusions are reproduced below.

- The apparent oral clearance of MDL 74,156 for pediatric surgery patients 2 to 12y was ca. 1.3 times greater compared to adult HVs.
- Half-lifes were 21% shorter in pediatric surgical patients compared to HAVs.
- One patient received a dose that was five times (6.0 mg/Kg) greater than the 1.2 mg/Kg dose described in the protocol.
  - This patient experienced transient prolongation of the QRS and QT_c intervals.
  - Interval changes were similar in duration, onset and causality to those observed in the other children who received 1.2 mg/Kg.
  - The patient did not experience any AEs or clinically significant changes in laboratory parameters or vital signs.

G. PKs in Special Populations (Healthy Volunteers)

i) PKs in Women

Protocol AK-KW-0993 (Report K-95-0120-CD)

This open-label, randomized, one center, two-way balanced crossover design was carried out in 24 healthy female volunteers. The aims were a) to characterize PKs and bioavailability of DOLA•Mesyl and MDL 74,156 in [illegible] as compared to man and b) to measure the urinary excretion and renal clearance of DOLA•Mesyl metabolites. Each fasted subject received one of the following [illegible] in each period:

- 2.4 mg/Kg DOLA•Mesyl given as a single oral solution dose

- 2.4 mg/Kg DOLA•Mesyl given by a 12-min. i.v. infusion

- Mean plasma concentration-time plots for MDL 74,156 in women following oral and i.v. administration of 2.4 mg/Kg of DOLA•Mesyl are depicted in Fig. 7. Mean PK parameters - together with data from HMV for comparison - are summarized in Table 5.

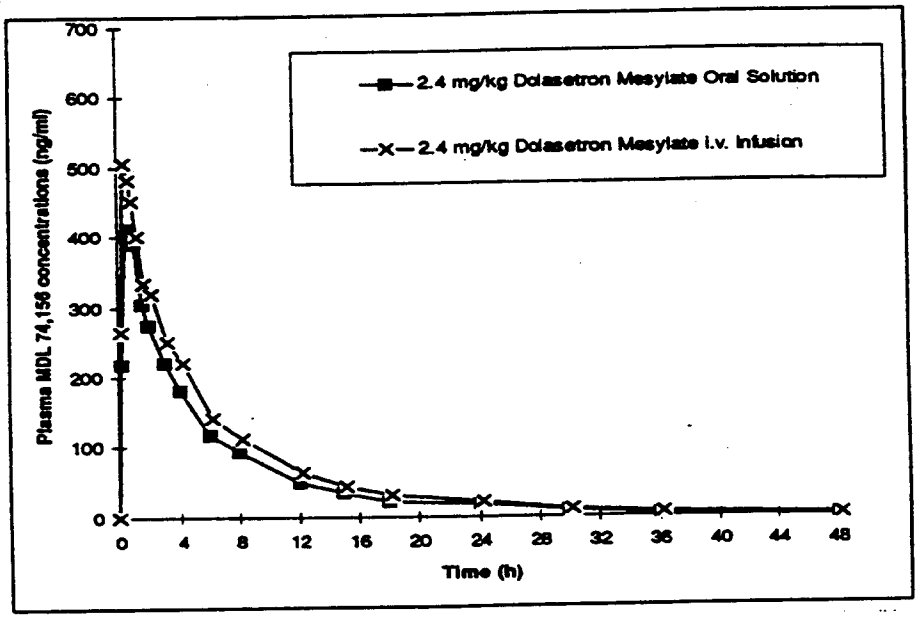

Fig. 7. - Study Protocol AK-KW-0993 (Report K-95-0120-CD): Studies in healthy female volunteers. Mean Plasma Concentration vs time-plots for MDL 73,147 (free base) following oral and i.v. administration

The sponsor's conclusions from this study are reproduced below:

- **PKs of MDL 73,147 and its major active metabolite, MDL 74,156, were similar in both men and women.**

- **MDL 74,156 was formed rapidly following oral and i.v. administration of DOLA•Mesyl in women.**

  - **As observed in previous studies, almost no MDL 73,147 was detected after oral administration.**

  - **No DOLA•Mesyl was detected in urine.**

- **Absolute apparent bioavailability as measured by MDL 74,156 for oral DOLA•Mesyl solution was 80% in women.**

TABLE 5
Study Protocol AK-KW-0993 (Report K-95-0120-CD)

Mean (%CV) PK Parameters of Total MDL 74,156 in Healthy Women and Men

Pharmacokinetic Parameter	*Women (2.40 mg/Kg)*		*Men[a] (200 mg dose, approx. 2.54 mg/Kg)*	
	iv	po	iv	po
C_{max} (ng/mL)	522 (18)	469 (18)	647 (29)	601 (35)
AUC (0-∞) (ng•h/mL)	3007 (36)	2413 (39)	3638 (33)	(2680 (30)
CL_{app} (mL/min/Kg)	11.05 (30)	14.23 (37)	9.48 (34)	12.9 (34)
$t_{\frac{1}{2}}$ (h)	8.05 (30)	9.12 (44)	7.66 (22)	8.84 (23)
BA (%)	ND	80 (12)	ND	76 (28)
Urinary Excretion of MDL 73,147	BQL	BQL	BQL	BQL
Urinary Excretion of Total MDL 74,156 (% of dose)	33.44 (37)	27.23 (48)	32.8 (28)	21.6 (31)

a) Data from MCPR0080 study (Report K-94-0734-CDS)

po Oral solution dose
i.v. 12 min. intravenous infusion for women and 10 min. infusion for men
ND Not determined BQL Below limit of quantitation

This Table corresponds to sponsor's Table 2-48 (vol. 1.2, p. 279) with minor modifications

ii) PKs in Healthy Elderly Volunteers

Study Protocol AN-EP-0992 (Report L-94-0001-C)

This randomized, open-label, one center, two-way balanced crossover trial with 18 healthy elderly volunteers (males and females) 65y of age or older was carried out to a) characterize the PK and bioavailability of DOLA•Mesyl, including its metabolite MDL 74,156 in healthy elderly volunteers and b) to measure the urinary excretion and renal clearance in this patient population.

- Each participant received in a random sequence a single dose of 2.4 mg/Kg po and i.v. DOLA•Mesyl. A 20 mg/ml, injectable DOLA•Mesyl solution (Lot #92A014) both for oral solution and i.v. infusion Txs were used in the trial. Blood and urine samples were collected prior to and 60h post dose.

- Mean PK parameters of MDL 74,156 are summarized in Table 5.

TABLE 6
Study Protocol AN-EP-0992 (Report L-94-0001-C)

Mean PK Parameters[a] of MDL 74,156 Following Single PO and I.V. Doses of 2.4 mg/Kg DOLA•Mesyl

Parameters	PO	I.V.
AUC (0-∞) ng•h/mL	3592.95±1503.30	4028.08±1583.71
$t_{\frac{1}{2}}$ (h)	7.16±2.30	6.85±1.54
CL(mL/min Kg)	9.53[b]±3.39	8.26±2.46
V (L/Kg)	5.63[c]±2.22	4.69±1.07
C_{max} (ng/mL)	661.85±182.83	619.66±190.60
t_{max} (h)	0.87±0.60	0.62±0.14
Apparent Absolute Bioavailability	0.89±0.14	---

This Table corresponds to sponsor's Table 2-47 (vol. 1.2, p. 275) with minor modifications.

a) Mean±SD
b) Apparent clearance (CL/F)
c) Apparent V (VB/F)

- The sponsor's conclusions are listed below.

  - The PKs of DOLA•Mesyl and MDL 74,156 were similar between young (19 to 40 y) and elderly (≥65 y) healthy volunteers following both oral and i.v. administration of DOLA•Mesyl.

  - DOLA•Mesyl was rapidly absorbed following oral administration and was rapidly metabolized to MDL 74,156.

  - DOLA•Mesyl was not found in urine.

  - MDL 74,156 was detected rapidly in plasma (within 10 min.) following both oral and i.v. administration.

  - Maximal plasma concentration was achieved in less than 1 h and elimination half-life was ca. 7 h.

H. PKs in Patients With Hepatic Impairment

Study Protocol 73147-2-S-085 (Report M-95-0002-D)

- This open-label, randomized, two-period crossover study was carried out at two centers

  The objectives of the trial were to provide an evaluation of the impact of hepatic impairment on the absorption and disposition of DOLA•Mesyl, as

well as on the formation and disposition of MDL 74,156 and to develop recommendations for DOLA•Mesyl dosage in patients with hepatic impairment.

- A total of 6 healthy volunteers (group I), 7 patients with hepatic impairment of Child-Pugh class A (group II), and 4 patients with hepatic impairment of Child-Pugh class B or CI (group III), participated in the study.

- Subjects received a single 150 mg oral dose and a single 150 mg of intravenous dose of DOLA•Mesyl. Used in the study were 50 and 100 mg tablets (Lot No. WN930116 and WN930114, respectively) and a DOLA•Mesyl injectable solution (Lot No. WN911105). Serial plasma samples were taken over the period 0 to 48 h after the start of dosing for both treatments. Urine samples were taken over the periods 0 to 12 h, 12 to 24 h and 24 to 48 h after dosing ror both treatments.

- Plasma PK parameters for MDL 74,156 are summarized in Table 7.

  - Mean maximum MDL 74,156 levels for both healthy and hepatically impaired subjects after i.v. dosing were within the range of those predicted from a previous dose proportionality study (study Protocol MCPR 0080, Report K-94-0734-CDS).

  - Statistical comparison of the MDL 74,156 $AUC_{0-\infty}$ data after oral dosing indicated a significant increase in $AUC_{0-\infty}$ from group I to III of ca. 70% and a smaller increase in AUC from group I to II.

  - No statistically significant differences were observed in the mean MDL 74,156 $AUC_{0-\infty}$ data after i.v. infusion between the three groups. DOLA•Mesyl was well tolerated in this study, regardless of administration route or degree of hepatic impairment.

The sponsor's conclusions from this study are reproduced below.

- **As seen in healthy volunteers, DOLA•Mesyl was rapidly eliminated in hepatically impaired subjects.**

- **In patients with severe hepatic impairment, the systemic exposure of MDL 74,156 increases ca. 1.7-fold following oral administration and remains unchanged following i.v. administration.**

- **MDL 73,147 (the free base) was detected after oral dosing in some hepatically impaired subjects and was 7% of maximum concentration of MDL 74,156 following i.v. administration.**

- **The safety and PK results suggest that no dose adjustment is necessary for hepatically impaired cancer or surgery patients.**