IV. SUMMARY AND CONCLUSIONS

Phase II clinical and pharmacologic studies demonstrated that HALDOL is an effective and safe antiemetic agent. These data provide information that indicate a parenteral dosage regimen (intramuscular) of 1.0 to 2.0 mg in patients suffering from nausea and vomiting as a result of operative procedures or gastrointestinal disorders. In these studies, Ballinger (1) noted that the injection form of HALDOL was less irritating than was injectable perphenazine. He further noted less side effects from effective doses of HALDOL than from those of prochlorperazine.

Phase III clinical evaluations were conducted double-blind in nine studies on patients with nausea and vomiting as a result of operative procedures and in seven studies of patients with nausea and vomiting as a result of gastrointestinal disorders.

The data provided by the double-blind clinical studies clearly demonstrate that HALDOL Injection is effective and safe when used in the treatment of nausea and vomiting resulting from operative procedures and gastrointestinal disorders. In addition to these studies, one investigator (Asbell) supplied information on two patients on an open evaluation.

HALDOL Injection administered at a dose level of 1.0 to 2.0 mg proved to be effective in most of these studies in controlling nausea and vomiting.

In order to obtain a clinical profile of activity of the total analyzable studies (10 or more patients per group), the global evaluations of these double-blind studies have been used as the most comprehensive measurement of clinical evaluation of

the response to the two study medications. This is summarized in the following table:

Summary of Global Evaluations

Investigator Name (No.)	No. of Pts. HALDOL	No. of Pts. Placebo	Level of Significance (P Value)	Treatment Favored
Post-Operative Use				
DeBakker, A. (739)	29	28	<.05	HALDOL
DeBakker, A. (682-1)	25	13	N.S.*	--
DeBakker, A. (682)	51	50	N.S. (<.10)	HALDOL
Cohen, P.J. (683)	32	30	<.01	HALDOL
Ritter, R./ Watson, R. (689)	59	53	<.01	HALDOL
Dannemiller, F. (733)	19	19	<.05	HALDOL
Gastrointestinal Disorders				
Leslie, R.E. (692)	23	21	<.05	HALDOL
Leslie, R.E. (713)	31	33	<.01	HALDOL
Weinstein, R. (711)	23	20	<.01	HALDOL
Christman, R.S. (695)	25	25	<.01	HALDOL
Robbins, E.L. (699)	14	14	<.05	HALDOL
Everett, S.F. (725)	10	10	N.S. (<.10)	HALDOL

*Not Significant

HALDOL, administered parenterally to patients suffering fron nausea and vomiting following operative procedures or gastrointestinal disorders has been shown to be significantly (P <.05 and in some instances P <.01) more effective than placebo in nine of the twelve studies evaluated. Four of the remaining studies (Finestone, Craythorne, Wier and LaRose) were not included above because of small populations.

The positive effects revealed by the investigators' global or overall evaluations are supported in each study by the superior responses to HALDOL over those to placebo in the specific parameters of vomiting and nausea.

In phase III studies, in which HALDOL was compared double-blind with placebo, eight patients on HALDOL were reported to have nine side effects, four of which were hypotension and two of which were nystagmus. In the patients on placebo, two were reported to have hypertension and one had nystagmus. Other side effects were either minor or related to the conditions already mentioned.

In phase II studies, a few cases of hypotension and prolonged anesthesia recovery time were reported but cannot be properly evaluated since these were either open or only partially controlled studies.

In conclusion, HALDOL Injection in well-controlled studies has been proven clearly to be an effective and safe agent for the treatment of nausea and vomiting. The doses employed (1.0 to 2.0 mg) were effective with minimal side effects.

V. SUPPORTING PUBLISHED CLINICAL DATA

Over the last thirteen years, haloperidol has been used as an antiemetic agent in many foreign countries. Results similar to those observed in the studies undertaken for this submission have been reported since 1960.

Costa and Gianasi (6)* treated 100 surgical patients aged 7 to 78 years prophylactically with 2 mg haloperidol intramuscularly. The drug was administered at the end of the surgical procedure. Of these patients, 94% did not experience episodes of vomiting. From experience, the investigators conclude that haloperidol is an effective and safe antiemetic compound.

Saarne (7) treated 1163 patients, aged 18 to over 90 years prophylactically with 2.0 to 2.5 mg of haloperidol b.i.d. administered either intramuscularly or orally. All patients were hospitalized for surgical procedures. The investigator reported that the antiemetic effect of haloperidol was very impressive. Of the entire series, 1163 patients, only 10 vomited and 3 had nausea during the 24-hour period after surgery. No extrapyramida symptoms were observed preoperatively and only two patients had slight extrapyramidal symptoms of a hyperkinetic nature postoperatively.

Dyrberg (8) studied the effectiveness of haloperidol in a double-blind evaluation against placebo prophylactically for the effect on postoperative nausea and vomiting. The prophylactic

*See References, P. 109

study consisted of 1089 male and female patients. Haloperidol 5 mg or placebo was administered intravenously during the first part of anesthesia. Both males and females in the haloperidol-treated group demonstrated significantly ($P < .001$) less nausea and vomiting six hours postoperatively than did the placebo group. At 24 hours, the females who had received haloperidol continued to differ significantly ($P < .01$) from those who had received placebo. In males given haloperidol the difference decreased from $P < .001$ at six hours to $P < .05$ at 24 hours postoperatively. During the first six hours, of 317 male patients, 14.3% on placebo, but only 2.4% on haloperidol vomited; of 772 female patients, 32.2% on placebo but only 10.8% on haloperidol vomited.

In a second group of female patients undergoing abdominal hysterectomy, the author (8) compared the effectiveness of haloperidol with that of chlorpromazine for effects against postoperative nausea and vomiting. Of 159 patients administered placebo, 38.4% vomited, while of 114 patients administered 5 mg haloperidol intravenously, only 7.9% vomited; this difference is significant ($P < .001$). Of 158 patients administered 50 mg chlorpromazine intravenously, 14.6% vomited; the difference in effectiveness between haloperidol and chlorpromazine is not significant ($P < .20$). The investigator reported that no unfavorable circulatory responses or extrapyramidal reactions occurred in patients treated with haloperidol, and tachycardia and hypotension occurred less often in those receiving haloperidol than in the control group.

Lawson and McGowan (9) administered 3 mg haloperidol intramuscularly to 300 women and intravenously to 50 women along with pethidine in the management of labor. A review of the incidence of vomiting during and after labor indicated to the investigators that haloperidol is an effective antiemetic. They reported that the administration of haloperidol intramuscularly resulted in no extrapyramidal, cardiovascular, or other side effects; whereas the intravenous administration of the drug caused some cases of bradycardia and hypotension.

Muncibi and Esposito (10) studied haloperidol in combination with atropine for the premedication of 1720 patients aged 5 to 80 years at dosages of 1 to 4 mg (mean dosage 2 mg) administered intramuscularly and in emergencies, intravenously. The authors report that haloperidol exerted a potent antiemetic effect as shown by the low percentage of cases of vomiting over a period of several hours postoperatively. Postoperative vomiting was noted in 2.3% of the patients and nausea occurred in 1.2%. Except for mild short-lasting psychomotor agitation on awakening in a small percentage of the young patients (less than 2%), none of the patients complained of side effects.

Maggi et, al, (11) in a comparative study of two groups of 70 patients each, aged 20 to 70 years, administered 4 mg haloperidol or physiological saline intravenously at the end of surgery. Haloperidol significantly reduced the incidence of postoperative vomiting in comparison with the control group.

Mainardi (12) used haloperidol 4-6 mg intramuscularly, 45 to 90 minutes preoperatively in 125 patients. The investigator

reports that the patients experienced a smooth postoperative period devoid of nausea and vomiting and were free of side effects.

Giordano and Cipriani (13) have evaluated the clinical effectiveness of haloperidol administered prior to diagnostic procedures. According to the investigators, haloperidol, 4 mg administered parenterally immediately prior to the procedures, compared very favorably with other neuroleptics and drug combinations. The incidence of vomiting in patients premedicated with haloperidol was 1%.

Casaglia (14) reported on the results of a clinical trial with haloperidol administered intravenously at doses of 2-4 mg to prevent nausea and vomiting and to provide "psychic sedation" in patients undergoing gynecologic procedures. Fifty patients were treated with haloperidol prior to the beginning of the surgical procedure and fifty other patients did not receive haloperidol. The efficacy of haloperidol in preventing emesis postoperatively was excellent in 38 of the 50 patients, good in 5 patients, fair in 4 and insufficient in 3 patients. The percentage of successful results compared to the group that did not receive haloperidol was statistically significant ($P < .01-.02$) in favor of the haloperidol group. No side effects were observed following treatment with haloperidol.

Appiani (15) administered haloperidol intramuscularly at a dose of 2 mg to 50 patients who were vomiting following vaginal or abdominal gynecologic surgery. Haloperidol was very effective as an antiemetic in this group of patients and no side effects were observed following its use.