PRODUCT MONOGRAPH

PrMEPROGEST™

Medroxyprogesterone Acetate Tablets U.S.P.

(2.5 mg, 5.0 mg and 10.0 mg Tablets)

PROGESTAGEN-PROGESTATIONAL STEROID

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PRODUCT MONOGRAPH

MEPROGEST™ (medroxyprogesterone acetate) Tablets U.S.P.

PHARMACEUTICAL CLASSIFICATION

PROGESTIN

ACTION AND CLINICAL PHARMACOLOGY

MEPROGEST™, an orally-active progestational steroid, when administered to women with adequate endogenous estrogen transforms a proliferative endometrium into a secretory endometrium. **MEPROGEST™** inhibits the secretion of pituitary gonadotropin which, in turn, prevents follicular maturation and ovulation. The anti-cancer activity of **MEPROGEST™** at pharmacologic doses, may be dependent on its effect on the hypopituitary/gonadal axis, estrogen receptors and the metabolism of steroids at the tissue level.

BIOAVAILABILITY

In a randomized cross-over study with 25 healthy post-menopausal female volunteers, the bioavailability of **MEPROGEST™** 10 mg and PROVERA® 10 mg tablets was studied following multiple oral doses in the following regimens:

A) one **MEPROGEST™** 10 mg tablet or

B) one PROVERA® 10 mg tablet at 0-hour on Days 1-6.

Each dose was administered during a fasting period which began 10 hours before and lasted until 3 hours after the dose. Treatment phases were separated by a 16-day washout period. Blood

samples were collected prior to dosing on Days 1-6, and at the following times after drug administration on Day 6: 0.5, 1.0, 1.5, 2, 2.5, 3, 4, 5, 8, 12, 24 and 36 hours. The resulting plasma samples were analyzed for medroxyprogesterone using a radioimmunoassay procedure.

Relevant bioavailability parameters are included in the following Table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

FOLLOWING ORAL ADMINISTRATION

MEPROGEST™
(6 Daily Doses of 10 mg)
From Measured Data
Geometric Mean
Arithmetic Mean (CV%)

Relevant bioavailability parameters are included in the following Table.

PARAMETER	TEST	REFERENCE***	RATIO OF MEANS
AUCr* (ng•hr/mL)	59.56 62.053 (28.2%)	60.59 62.546 (26.0%)	98.3
Cmax (ng/mL)	6.842 7.2055 (33.5%)	6.676 7.0346 (31.8%)	102.5
Cmin (ng/mL)	1.145 1.2183 (34.6%)	1.144 1.2041 (32.0%)	100.1
Fluctuation** (%)	235.87 (28.9)	226.32 (30.1)	

* T = 24 hours
** For fluctuation, the values are arithmetic mean (CV%)
*** Upjohn (Provera®) medroxyprogesterone acetate tablets. The Upjohn Company of Canada, Canada.

The principal metabolite of **MEPROGEST™** that has been identified is a 6 alpha-methyl-6 beta, 17 alpha, 21-trihydroxy-4-pregnene-3,20-dione-17-acetate, which is excreted in the urine.

INDICATION AND CLINICAL USES

MEPROGEST™ is indicated for the following conditions:

1. **for hormonal replacement therapy, to oppose the effects of estrogen on the endometrium;**
2. **functional menstrual disorders due to hormonal imbalance in non-pregnant women, in the absence of organic pathology.**

CONTRAINDICATIONS

MEPROGEST™ is contraindicated in:

1. thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions
2. known sensitivity to **MEPROGEST™, or to any of the tablet s excipients (see Pharmaceutical Information)**
3. undiagnosed vaginal bleeding
4. undiagnosed urinary tract bleeding
5. known or suspected cancer of the breast or genital organs
6. pregnancy (either for diagnosis or therapy). (See WARNINGS).

WARNINGS

1. Before prescribing **MEPROGEST™** the physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. The patient's status and need for treatment should be carefully assessed before continuing therapy.
2. Discontinue medication pending examination, if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.
3. Usage in pregnancy is not recommended. Progestational agents are also not recommended as a diagnostic test for pregnancy. **If the patient is exposed to MEPROGEST™ during pregnancy or if she becomes pregnant while taking the drug, she should be appraised of the potential risk to the fetus.**
4. Clinical suppression of adrenocortical function has not been observed at low dose levels; however, at the very high doses (500 mg daily or more) used in the treatment of certain cancers, corticoid-like activity has been reported. **In some cases it can produce cushingoid symptoms (eg., "moon" facies, fluid retention, glucose intolerance and blood pressure elevations).**
5. Detectable amounts of progestin have been identified in the milk of mothers receiving the drug. **Infants exposed to MEPROGEST™ via breast milk have been studied for developmental and behavioral effects through puberty, no adverse effects have been noted.**

6. Anaphylactic and anaphylactoid reactions have occasionally been reported in patients treated with **MEPROGEST™**.

7. Liver function tests should be performed periodically in patients who have or are suspected of having hepatic disease. The physician should be alert to the earliest manifestations of impaired liver function. Should these occur or be suspected, the drug should be discontinued and the patient's status re-evaluated.

PRECAUTIONS

1. The pre-treatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear. **This evaluation should exclude the presence of genital or breast neoplasia before considering the use of MEPROGEST™.**

2. Because this drug may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction require careful observation.

3. In cases of breakthrough bleeding, as in all cases of irregular bleeding per vaginum, organic causes should be considered. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.

4. **Patients should be advised of menstrual bleeding patterns expected with the sequential regimen. (see Dosage and Administration).**

   Upon sequential administration of MEPROGEST™ to women with adequate levels of estrogen (endogenous or exogenous), withdrawal bleeding occurs within 7 days

after stopping MEPROGEST™ treatment. Bleeding that occurs during MEPROGEST™ treatment, indicates a need for a longer duration, or a higher dose of MEPROGEST™.

5. Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. **Some patients may complain of premenstrual like depression while on MEPROGEST™.**
6. A decrease in glucose tolerance has been observed in some patients on progestogens. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving progestin therapy.
7. The age of the patient constitutes no absolute limiting factor although treatment with progestins may mask the onset of the climacteric.
8. The pathologist should be advised of progestin therapy when relevant specimens are submitted.
9. **Aminoglutethimide administered concomitantly with MEPROGEST™ may significantly depress the bioavailability of MEPROGEST™.**
10. **Rifampin can increase the metabolism of exogenously administered progestational agents. The extent to which rifampin may alter the metabolism of MEPROGEST™ remains to be determined; the possibility of an interaction should be considered.**

ADVERSE REACTIONS

1. The following adverse reactions have been associated with the use of **MEPROGEST™**:

Breast: In a few instances, breast tenderness or galactorrhea have occurred.

Reproductive System: Breakthrough bleeding, change in menstrual flow, spotting, amenorrhea, changes in cervical erosion and cervical secretions.

Central Nervous System: An occasional patient has experienced nervousness, insomnia, somnolence, fatigue, dizziness or depression, **pre-menstrual syndrome like symptoms**.

Thromboembolic Phenomena: Thromboembolic phenomena including thrombophlebitis and pulmonary embolism have been reported.

Skin and Mucous Membranes: Sensitivity reactions ranging from pruritus, urticaria, angioneurotic edema to generalized rash and anaphylaxis have occasionally been reported. Acne, alopecia, or hirsutism have been reported in a few cases.

Gastrointestinal: Rarely, nausea has been reported, **abdominal discomfort, bloating**.

Miscellaneous: **Pyrexia have, increase in weight, peripheral edema, and "moon" facies have been reported.**

2. The following laboratory tests may be affected by the use of **MEPROGEST™ U.S.P.**:

a) Gonadotropin levels

b) Plasma progesterone levels

c) Urinary pregnanediol levels

d) Plasma testosterone levels (in the male)

e) Plasma estrogens level (in the female)

f) Plasma cortisol levels

g) Metyrapone test

h) **Glucose tolerance test**

Altered test results may be an indication of an underlying condition. Discontinuation of **MEPROGEST™** may be warranted and laboratory tests should be repeated.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In female patients, overdosage may result in a period of amenorrhea of a variable length and may be followed by irregular menses for several cycles.

No cases of overdosage in male patients have been reported. However, such overdosage, if it were to occur, would not likely result in any particular symptomatology.

There is no known therapy for overdosage of medroxyprogesterone. Doses as high as 1000 mg for the therapy of endometrial carcinoma have been used without adverse effect.

DOSAGE AND ADMINISTRATION

1. **Hormone Replacement Therapy**:

   a) **Progestin Challenge Test**:

   Subsequent to the diagnosis of menopause, the progestin challenge test is recommended for amenorrheic women with an intact uterus. **MEPROGEST™** 10 mg daily should be administered for 10 days.

A negative test is identified by the absence of withdrawal bleeding, and implies the absence of endometrial stimulation due to insufficient estrogen secretion. In these women, hormone replacement therapy consisting of estrogen therapy, and concurrent **MEPROGEST™**, should be considered.

A positive test is indicated by the presence of withdrawal bleeding which occurs within 7 days after stopping **MEPROGEST™** treatment. Withdrawal bleeding implies the presence of sufficient endogenous estrogen to stimulate the endometrium. **MEPROGEST™** therapy should be administered, as above, until withdrawal bleeding no longer occurs. This cessation of withdrawal bleeding indicates the absence of endometrial stimulation due to a decline in estrogen secretion. In these women, hormone replacement therapy consisting of estrogen therapy, and concurrent **MEPROGEST™**, should be considered.

b) **Sequential Therapy**:

<table>
<tr><th colspan="3">Days of the Month
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31</th></tr>
<tr><td colspan="2">Sequential Estrogen - 25 days</td><td></td></tr>
<tr><td></td><td>Start</td><td>MEPROGEST™
5 - 10 mg/day</td></tr>
<tr><td colspan="3">Continuous Estrogens - - everyday</td></tr>
<tr><td>MEPROGEST™
5 - 10 mg/day</td><td>Stop</td><td></td></tr>
</table>

In women with an intact uterus receiving estrogen replacement therapy, **MEPROGEST™** tablets may be given in a dosage of 5 - 10 mg daily for 12 - 14 days. The recommended starting dose for **MEPROGEST™** should be 10 mg/day, administered for 12 - 14 days. A dose of 5 mg/day **MEPROGEST™** for 12 - 14 days may be appropriate for some women.

Note: The lowest dose of **MEPROGEST™** required to protect the endometrium from estrogenic-hyperstimulation should be used. A good indicator is the lowest dose of **MEPROGEST™** that will consistently result in withdrawal bleeding within 7 days after stopping **MEPROGEST™** treatment. Bleeding that occurs during the **MEPROGEST™** treatment indicates a need for a longer duration, or higher dose of **MEPROGEST™**.

2. **Functional Menstrual Disorders**

a) **Secondary Amenorrhea**:

After ruling out pregnancy, MEPROGEST™ may be employed in doses ranging from 5 to 10 mg daily depending upon the degree of endometrial stimulation desired. The dose should be given daily for 10 days beginning on the assumed 16th day of the cycle.

In patients with poorly developed endometria, conventional estrogen therapy should be given in conjunction with **MEPROGEST™**.

Withdrawal bleeding usually occurs within 3 days after combined estrogen and **MEPROGEST™** therapy.

Progestogen-induced withdrawal bleeding should occur within 3 to 7 days following discontinuation of the progestogen in the presence of an endometrium that has been previously proliferated by endogenous estrogen.

b) **Dysfunctional Uterine Bleeding**:

In dysfunctional uterine bleeding, MEPROGEST™ may be given in doses ranging from 5 to 10 mg for 10 days beginning on the assumed or calculated 16th day of the cycle.

When bleeding is due to a deficiency of both ovarian hormones, as indicated by a poorly developed proliferative endometrium, estrogens should be used in conjunction with **MEPROGEST™**. If bleeding is controlled satisfactorily, two subsequent cycles of treatment should be given. If dysfunctional uterine bleeding is not controlled by hormone therapy, appropriate diagnostic measures should be undertaken to rule out uterine pathology.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Medroxyprogesterone Acetate

Chemical Name: 1) Pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-, ( )-;

2) 17-Hydroxy-6 -methylpregn-4-ene-3,20-dione acetate

Structural Formula:

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Molecular Formula: $C_{24}H_{34}0_4$

Molecular Weight: 386.53

Description: Medroxyprogesterone acetate is a white to off-white odourless crystalline powder, stable in air, melting between 205 and 209□ C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in ethanol and methanol, slightly soluble in ether and insoluble in water.

COMPOSITION

MEPROGEST™ (2.5, 5 and 10 mg) also contain the following inactive ingredients: lactose, magnesium stearate, methylcellulose and microcrystalline cellulose. The colouring agents are D&C Red No. 30 and FD&C Blue No. 1 for the 5 mg tablet (purple) and D&C Red No. 30 and D&C Yellow No. 10 for the 10 mg tablet (peach).

STABILITY AND STORAGE RECOMMENDATIONS

Store at controlled room temperature 15-30□C.

AVAILABILITY OF DOSAGE FORMS

MEPROGEST™ tablets are available as:

- 2.5 mg (white) oval tablets, scored on one side and debossed with two opposing "C"s on the reverse side, in bottles of 100, 500 and 1000 and blister packs of 100.

- 5 mg (purple) oval tablets, scored on one side and debossed with two opposing "C"s on the reverse side, in bottles of 100, 500 and 1000 and blister packs of 100.

- 10 mg (peach) oval tablets, scored on one side and debossed with two opposing "C"s on the reverse side in bottles of 1 00, 500 and 1 000 and blister packs of 1 00.

PHARMACOLOGY

MEPROGEST™ induces responses in laboratory animals comparable to those caused by progesterone. It is more potent than progesterone. **MEPROGEST™** induces glandular development in the endometrium, maintains pregnancy, delays parturition, inhibits ovulation and suppresses estrous cycles. It is devoid of androgenic and estrogenic activity. In selected animals tests it has some adrenal corticoid-like activity and in dogs increases serum growth hormone levels.

Pharmacokinetics

The pharmacokinetics of **MEPROGEST™** were investigated in rats following oral administration of single 0.2, 1.0, 5.0, and 20.0 mg/kg doses. The resulting pharmacokinetic parameters are listed in Table 1.

TABLE 1. PHARMACOKINETIC VALUES OF MEPROGEST™ IN RATS FOLLOWING SINGLE-DOSE ADMINISTRATION

MEPROGEST™ dose (mg/kg)	**Route**	**C_{max} (ng/mL)**	**$AUC_{0-\infty}$ (ng·g/mL)**	**$t_{½}$ (h)**
0.2	i.g.	8.5	107	10.4
1.0	i.g.	45.6	545	9.7
5.0	i.g.	378	2536	10.2
20.0	i.g.	1062	8007	8.0

MEPROGEST™ was readily absorbed. Peak plasma **MEPROGEST™** levels occurred at 3, 2, 1 .5, and 3 hours for the 0.2, 1, 5, and 20 mg/kg dosages, respectively. A linear response was

observed in the plasma **MEPROGEST™** $AUC_{0-\infty}$ values over the dose range of 0.2 to 5.0 mg/kg. However, the AUC values for the 20 mg/kg dose were slightly lower than anticipated. Elimination half-lives remained essentially constant over the dose range studied.

The pharmacokinetics of **MEPROGEST™** were also determined in rats following oral administration of **MEPROGEST™** at 0.2, 5, and 20 mg/kg daily for 1 4 days. Mean C_{max}, AUC_{0-24}, concentration at 24 hours (C_{24}) and $T_{½}$ values after 14 days of dosing are presented in Table 2.

TABLE 2. MEAN C_{max}, AUC_{0-24}, and $T_{½}$ VALUES IN RATS AFTER 14 DAYS OF MEPROGEST™ TREATMENT

MEPROGEST™ dose (mg/kg)	**C_{max} (ng/mL)**	**$AUC_{0-\infty}$ (ng·g/mL)**	**$t_{½}$ (h)**
0.2	10.2	101.0	14.7
5.0	456.3	1982.4	11.0
20.0	550.2	3596.2	13.7

The peak plasma **MEPROGEST™** concentrations on treatment day 14 occurred at 1.5 hours for all doses (0.2, 5.0 and 20 mg/kg). Mean C_{max} values for the 0.2 and 5.0 mg/kg doses were higher after multiple doses than after single dose administration. However, the mean C_{max} values after multiple doses of 20 mg/kg dose was 52% of the C_{max} values after the single dose. Based on an elimination $t_{½}$ of 15 hours and a 24-hour dose interval, an accumulation factor of 1.4 is predicted for the 0.2 mg/kg dose. The day 14 AUC_{0-24} from the 0.2 mg/kg dose was similar to the $AUC_{0-\infty}$

value after single dose administration. At the 5 and 20 mg/kg doses, mean AUC_{0-24} values were less than the AUC_{0-24} from the single-dose study. The relative decrease in AUC values for the 5 and 20 mg/kg dose is likely to be due to autoinduction of **MEPROGEST™** metabolism.

The drug was given in the diet admixture in rat carcinogenicity study; therefore the absorption of the drug was investigated following a 14-day multiple dose/feed study in female rats. **MEPROGEST™** was mixed in the feed. The doses were 0.2 and 20 mg/kg/day. Mean plasma **MEPROGEST™** levels from the two sampling times for the 0.2 mg/kg/day dose were 4.9 ng/mL (PM) and 5.3 ng/mL (AM), and for the 20 mg/kg/day dose were 133.5 ng/mL (PM) and 231.0 ng/mL (AM).

If the values at these two time points are presumed to represent average plasma **MEPROGEST™** levels over the respective 12-hour cycles, the steady-state AUC values over a 24-hour period are estimated to be 122.4 and 4374 ng·h/mL for the 0.2 and 20.0 mg/kg/day doses, respectively. These values are 20% greater than the AUC values after daily doses by oral gavage, indicating good absorption from the feed.

CLINICAL PHARMACOLOGY

MEPROGEST™ is a progestational agent devoid of androgenic and **estrogenic activity.**

MEPROGEST™ in appropriate doses, suppresses the secretion of pituitary gonadotropins which in turn, prevents follicular maturation, producing an ovulation in the reproductive aged woman. This action may also account for the ability of **MEPROGEST™** to ameliorate vasomotor symptoms in the menopausal woman.

MEPROGEST™ in appropriate doses suppresses the Leydig cell function in the male, i.e., suppresses endogenous testosterone production.

A dose of either 5 or 10 mg of **MEPROGEST™** given daily for 10 days has the equivalent effect of 20 mg of parenteral progesterone given daily for 10 days in producing an optimal secretory change in an estrogen primed endometrium. Oral **MEPROGEST™** also produces typical progestational changes in the cervical mucous (inhibits ferning) and increases the intermediate cell count in the maturation index of the vaginal epithelium.

Patients with the Pickwickian Syndrome; chronic Mountain sickness and some patients with chronic obstructive pulmonary disease reduce their hypercapnia when treated with oral **MEPROGEST™** (through a centrally-mediated stimulation of ventilatory drive).

Like progesterone, **MEPROGEST™** is thermogenic. At the very high dosage levels used in the treatment of certain cancers (500 mg daily or more) corticoid-like activity may be manifest.

TOXICOLOGY

ANIMAL STUDIES

Acute Toxicity: The oral LD_{50} of **MEPROGEST™** as reported in the literature[43] is as follows:

Species	Route	Study Type	LD_{50}	Effect
rat	oral	LD_{50}	>6.4 g/Kg	Details not reported
mouse	oral	LD_{50}	>16 g/Kg	Details not reported
dog	oral	LD_{50}	>5 g/Kg	Details not reported

Sub-acute and Chronic Toxicology: MEPROGEST™ administered orally to rats and mice (334 mg/kg/day) and dogs (167 mg/kg/day) for 30 days was found to be non-toxic.

MEPROGEST™ was administered orally to dogs and rats at 3, 10 and 30 mg/kg/day for 6 months. The drug was considered to be non-toxic at these levels but with anticipated hormonal effects at the higher doses.

Reproduction Studies: **MEPROGEST™** given orally at 1, 10 and 50 mg/kg/day in pregnant beagle bitches produced clitoral hypertrophy in the female pups of the high dose animals. No abnormalities were noted in any of the male pups. Subsequent evaluation of the reproductive potential of the bitches from the litters of treated females revealed no reduction in fertility potential.

Carcinogenesis and mutagenesis: Long-term toxicology studies in the monkey, dog and rat with parenteral **MEPROGEST™** have disclosed:

1. Beagle dogs receiving 75 mg/kg and 3 mg/kg every 90 days for 7 years developed mammary nodules, as did some of the control animals. The nodules appearing in the control animals were intermittent in nature, whereas the nodules in the drug-treated animals were larger, more numerous, persistent and there were two high dose animals that developed breast malignancies.

2. Two monkeys receiving 150 mg/kg every 90 days for 10 years developed undifferentiated carcinoma of the uterus. No uterine malignancies were found in monkeys receiving 30 mg/kg, 3 mg/kg, or placebo every 90 days for 10 years. Transient mammary nodules were found during the study in the control, 3 mg/kg and 30 mg/kg groups, but not in the 150 mg/kg group. At sacrifice (after 10 years), the only nodules extant were in three of the monkeys in the 30 mg/kg group. Upon histopathologic examination these nodules were determined to be hyperplastic. The occurrence of the lesions in these two monkeys does not signify that **MEPROGEST™** is carcinogenic in women.

3. No uterine or breast abnormalities were revealed in the rat after 2 years. The micronucleus test and the salmonella/microsome test (Ames Assay) have not shown **MEPROGEST™** to be a mutagen. Animal studies have not confirmed any impairment of fertility in first or second generation studies.

The relevance of any of these findings with respect to humans has not been established.

Two Year Oral (Diet) Carcinogenicity Study - Rat

In a study conducted by Wyeth-Ayerst, **MEPROGEST™** administered in the diet to female Charles River CD rats (approximately 6 weeks of age at treatment initiation) for 104 to 106 consecutive weeks. Dosages tested were 0, 0.2, 1.0, and 5.0 mg/kg.

Many of the deaths occurring in this study were associated with spontaneous age-related changes; however, in the 5.0 mg/kg group, there was a drug-related decrease in survival, as shown in Table 3.

TABLE 3. SURVIVAL IN RATS GIVEN MEPROGEST™

	MEPROGEST™ (mg/kg)			
	0 (n = 200)	0.2 (n = 100)	1.0 (n = 100)	5.0 (n = 100)
Survival Number of Deaths	34% 132	40% 60	38% 62	20% 80

Other drug-related findings in this study included adrenal cortical atrophy, ovarian atrophy, uterine atrophy, chronic progressive nephropathy (CPN), and cardiomyopathy. The administration of **MEPROGEST™** to rats may induce atrophy of the adrenal cortex, ovaries, and uterus by acting on the pituitary gland and/or hypothalamus to reduce the production of gonadotropin and adrenocorticotropin. A significant increase in group mean body weight occurred during the first year in the **MEPROGEST™**-fed rats. A correlation exists between

early body weight gain and increased incidence of CPN and cardiomyopathy in rats.

The preneoplastic changes included uterine endometrial gland hyperplasia and islet cell hyperplasia, which occurred predominantly in the middle- and high-dosage groups in a dose-related manner. The neoplastic changes included an increased incidence of islet cell carcinoma and adenoma and a decreased incidence of islet cell carcinoma and adenoma and a decreased incidence of mammary gland tumors, as shown in Table 4. This latter finding may be linked to the significant decrease in serum prolactin concentration observed in the rats in this study[44].

TABLE 4. PERCENTAGE OF MEPROGEST™

-TREATED RATS WITH PANCREATIC LESIONS

	MEPROGEST™ (mg/kg)			
	0 **(n =196)**	0.2 **(n = 97)**	1.0 **(n =98)**	5.0 **(n = 100)**
Islet cell carcinoma	**2**	**1**	**5**	**6**
Islet cell adenoma	**5**	**3**	**8**	**18**
Islet cell hyperplasia	**1**	**1**	**3**	**10**

There is no evidence in the literature that **MEPROGEST™** causes pancreatic islet cell neoplasia. Administration of **MEPROGEST™** to women should not result in islet cell hyperplasia or neoplasia similar to that observed in the rat for the following reasons:

- The endocrine system of rats is generally more sensitive to hormonal imbalances than humans. In rodents, several different types of endocrine cells (e.g., thyroid follicular cells, adrenal medullary cells, ovarian cortical cells) are more likely to undergo neoplastic transformation in response to the long-term stimulation that results from hormonal imbalance induced by xenobiotic chemicals (especially very high doses of hormones) or physiologic perturbations than are the corresponding cell populations in human.

- When **MEPROGEST™** acetate is combined with estrogen, more progesterone receptors are produced and more receptors are available to bind

MEPROGEST™ acetate. In the absence of estrogen, fewer progesterone receptors are available to bind **MEPROGEST™**, thus leaving more **MEPROGEST™** free to bind to glucocorticoid receptors.

- The rats in the middle- and high-dosage groups developed pancreatic islet cell lesions because of continuous exposure to the drug at levels approximately 10 and 50 times greater than AUC values for women receiving a 10 mg oral dose.

The increases incidence of pancreatic islet cell hyperplasia and neoplasia may be related to the cortisol-like activity of progestogens, including **MEPROGEST™**. Cortisol increases serum glucose levels, which stimulates the beta cells of the pancreatic islets to produce insulin. Repeated stimulation of the beta islet cells may cause compensatory hyperplasia and neoplasia of the cells[45]. In humans, the diabetogenic response to **MEPROGEST™** is slight[46].

A significant drug-related decrease in mean adrenal, ovarian, uterine, and pituitary gland weights was observed in the 1 .0 and 5.0 mg/kg dose groups. With the exception of the pituitary gland, the decreased organ weight correlated with the atrophic lesion noted on microscopic examination. There was a significant drug-related increase in the mean terminal body weight in all dosage groups and also in the absolute kidney, heart, and liver weights in the 1 .0 and 5.0 mg/kg dosage groups. The increased weight of the kidney, heart, and liver correlated with the CPN, cardiomyopathy, and fatty change, respectively, as noted on microscopic examination.

All lesions except those in the pancreas were expected findings with administration of **MEPROGEST™**. Such lesions have been described in the literature[44, 45, 47-50] and are not considered to be significant safety issues.

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