APPENDIX 2

MARKETING APPLICATION FOR

DEPO-PROVERA 150 MG/ML

PRE-CLINICAL EXPERT REPORT

UPJOHN LIMITED
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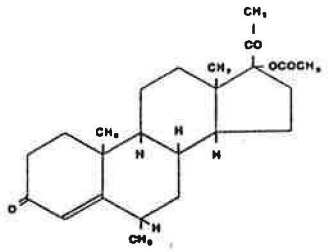
WEST SUSSEX
RH10 2LZ

MARCH 1993

PRODUCT PROFILE

Depo-Provera Sterile Aqueous Suspension contains medroxyprogesterone acetate as the active ingredient. Medroxyprogesterone acetate is a progestogen. It is designated chemically as 17 alpha-Acetoxy-6 alpha-methylpregn-4-ene 3,20-dione or Methylacetoxyprogesterone. Its structural formula is represented below.



medroxyprogesterone acetate

Depo-Provera is used extensively as a long-acting contraceptive agent, for the treatment of endometriosis, as adjunctive or palliative treatment for recurrent and/or metastatic breast, endometrial or renal carcinoma. Depo-Provera is currently licensed in the UK for long-term use only for women in whom other forms of contraception are contra-indicated or have caused unacceptable side-effects or are otherwise unsatisfactory. (150 mg/ml strength, PL 0032/0082). This application is seeking a Product Licence for Depo-Provera as a first line contraceptive agent.

Since Depo-Provera was first used clinically in the early 1960s many clinical trials have been carried out and several thousand publications concerning various aspects of its pharmacology have been published. The results of many studies of its efficacy as a contraceptive agent demonstrate that at a dose of 150 mg intramuscularly, every 90 days, it is very effective, with a method failure rate in the region of 0.22 per 100 woman years (Pearl's method). In a study of 3,905 patients enrolled at 54 centres, the 12 month continuation rate was 57.7% and 54.2% of the patients did not report any medical events. The most commonly reported medical events in this study were headache (17.5%), abdominal distress/discomfort (11.9%) and nervousness (11.6%). In this study 19.8% of patients were lost to follow-up and 14.6% dropped out for "personal reasons", these two categories apart, the most common reason for leaving the study was bleeding problems (8.4%).

The safety of Depo-Provera has been demonstrated both in clinical trials and by extensive use of the product in many countries, both for contraception and for other indications. Concern was expressed, at one time, about a toxicological study in the beagle bitch in which many of the dogs developed mammary tumours. Since that study was completed it has been agreed by most Regulatory Authorities that the dog is not an appropriate model for toxicity testing of progestogens, and that the results of the study are not relevant to women.

The most comprehensive study of relative cancer risk is the WHO Special Programme of

Research, Development and Research Training in Human Reproduction, which was initiated in 1979. This multicentre, hospital-based, case-control study was conducted at 11 research centres in nine developing and two developed countries. The main objective was to determine whether hormonal contraceptives, both oral and injectable, alter the risk of cancer of the breast, cervix, endometrium, ovary or liver.

Final reports of data from this study indicate that DMPA users are not at increased risk for cancers of the breast, cervix, endometrium, ovary or liver. (Risk of breast cancer is slightly increased in some sub-groups). In fact these data showed a protective effect of DMPA against endometrial cancer, which continues for up to eight years after discontinuation of use.

Administration of DMPA in contraceptive doses has no detrimental effect on the duration of lactation, nor does it have any adverse effects on milk volume or composition. Follow-up of children who were exposed to MPA via breast milk shows that their physical and intellectual development are entirely normal.

There is a risk of in utero exposure to MPA due to contraceptive failure or the inadvertent injection of a pregnant woman. The risk of in utero exposure due to contraceptive failure is low, since Depo-Provera is very effective. The preponderance of information suggests that in utero exposure to MPA is not associated with an increased occurrence of adverse events in infants, nor is it associated with any detrimental effects on the long-term growth or development of the infant so exposed. Precautions should be taken to ensure that women are not pregnant at the time of injection.

CONTENTS

EXPERT STATEMENT

A large volume of preclinical data on Medroxyprogesterone Acetate was submitted to the Licensing Authority, the CSM and the Panel of Persons Appointed by the Licensing Authority in the period up to 1983.

Further preclinical data has been published in the literature since that time. The results of these studies are consistent with the body of knowledge which existed in 1983. No unexpected findings in preclinical studies have been reported since 1983. The complete body of preclinical data (published and unpublished) support the conclusion that Depo-Provera is safe when used for long-term contraception.

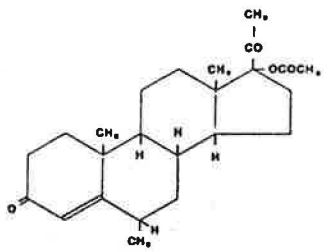
Signed: [redacted]

Position: [redacted]

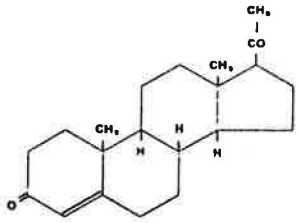
Date: [redacted]

INTRODUCTION

This report will update the toxicology, pharmacology and pharmacokinetics information of medroxyprogesterone acetate (MPA). MPA is a synthetic analog of 17α-hydroxyprogesterone and has been marketed for many years as Provera (tablets) and Depo-Provera (injectable). The structures of both MPA and progesterone appear below:



MPA



Progesterone

Because the data base is extensive from the Provera and Depo-Provera work of many years, that information will be presented in light of available pharmacokinetics information relating to oral and parenteral administration of MPA.

MPA exerts antiestrogenic, antiandrogenic, and antigonadotropic effects and has been shown to be active against hormone-dependent tumors, including hormonally dependent breast carcinoma. When administered orally or parenterally in the recommended doses to women with adequate endogenous estrogen, MPA transforms proliferative endothelium into secretory endothelium. This pharmacologic action is the basis for its development as a therapeutic agent in patients with conditions such as amenorrhea, dysfunctional (anovulatory) uterine bleeding, or endometriosis. Reported side-effects include such symptoms as fluid retention, weight gain, thrombophlebitis, CNS symptoms (depression, headache), gastro-intestinal effects (nausea, vomiting), effects on the skin (rash, pruritus, hirsutism), and vaginal spotting and discharge.

MPA is rapidly absorbed from the GI tract[146-148] and metabolized in the liver[149] to several progestin metabolites.[65,73,92,93] These metabolites are present for the most part in those animals tested in the toxicology studies and are widely distributed in the body with high concentrations in the intestine, liver, plasma, lung, skin and brain of the rat.[150] No particularly outstanding differences in metabolic profiles for different species or different routes of administration were observed.[151] MPA is excreted mainly in the feces of man and animals.[93]

Molecules of MPA bind to cytoplasmic receptor proteins and are transported to the cell nucleus where they form complexes that subsequently affect synthesis of ribonucleic acid

(RNA) and deoxyribonucleic acid (DNA).[45] In primary cultures of malignant endometrial cancer cells, MPA stimulates DNA synthesis in cells lacking both estrogen and progestin receptors while inhibiting DNA synthesis in receptor-positive cells.[47] Bojar et al[50] conclude that the mechanism of action of high-dose MPA also involves its ability to produce gross structural changes in cell membranes which alter a variety of membrane functions.

Preclinical testing of MPA began in the late 1950s leading to initiation of clinical studies in 1963 and the first marketing of the drug for contraception outside the US in 1967. Upjohn Limited has made a number of applications to the CSM for long-term contraceptive use. Questions of preclinical importance involved the relevance of the mammary and endometrial findings in dogs and monkeys have been considered by the CSM and the Panel in 1983. The theoretical risk suggested by mammary tumors in dogs and endometrial carcinoma in monkeys has not materialized in women. Recently published results of the World Health Organization (WHO) epidemiolgical study indicate no increased risk of breast or endometrial cancer from use of Depo-Provera than from use of oral contraceptives. All available data indicate that the occurrence of endometrial carcinoma in 2 monkeys at the end of a 10-year study most likely arose from an epithelial cell type found in monkeys, but not in women; thus, this finding seems irrelevant to human risk.

Preclinical animal data on MPA exists in the published literature since 1983 and consists of studies conducted to provide a greater understanding of the mechanism of action, pharmacotoxic effects and pharmacokinetics of MPA. This literature is reviewed in this document. This summary of all preclinical data and literature support the conclusion that Depo-Provera is a safe drug when used by women for contraception.

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NOTE: References are presented in Part III Volumes 2 to 4. See Part III Volume 1 page 21 for a complete reference list giving the location of each reference.

PHARMACODYNAMICS UPDATE
(Reference list follows. References are presented in Part III)

a. General Pharmacologic/Metabolic Effects

Morphological assessment of rat liver revealed that medroxyprogesterone acetate (MPA) had a beneficial effect of regeneration from carbon tetrachloride exposure. Additionally, MPA has an inducing effect on hepatic drug-metabolizing enzyme systems, and an enhancing effect on protein synthesis following chemical-induced injury. This was viewed as beneficial in treatment of liver disease.[1,2] This conclusion was supported by a study showing a beneficial effect by MPA on post injury liver collagen and prolylhydroxylase activity.[3]

MPA-induced temporal changes in (liver) drug-metabolizing enzyme systems demonstrated maximum effects on microsomal enzymes, liver wt., and protein content within 3-7 days. After cessation of MPA, values decreased to control levels within about 11 days.[4] MPA administration for 1 week also increased activity of two NADPH generating enzymes.[5]

Female rats on a protein-deficient diet had reduced cholesterol and increased liver triglyceride concentrations. MPA treatment resulted in elevated triglycerides and increased esterification of cholesterol.[6]

Steroids with estrogenic activity were much more potent than progestins in inducing liver growth and excessive DNA increase which was not associated with monoxygenase induction.[7] Specific activity of some rat liver steroid metabolizing enzymes was reduced by MPA. Plasma concentrations of luteinizing hormone, testosterone, and androstenedione were also lowered by MPA.[8] MPA treatment of rats altered bile acid composition, apparently through a direct effect on synthesis and/or secretion.[9]

Medroxyprogesterone acetate (MPA) induced mouse kidney ornithine decarboxylase, but only in strains of animals with effective androgen receptors.[10] MPA altered mouse kidney β-glucuronidase kinetics suggested an increased rate of mRNA synthesis, rather than a decreased rate of mRNA turnover.[11]

Injection of Chinese hamsters with medroxyprogesterone acetate (MPA) induced polyuria, with daily output of urine equal to about 50% of the animals' body weight. Progesterone did not cause polyuria in this species, and MPA did not induce it in other related hamster species[12]

The ability of certain adrenocortical steroids to raise arterial pressure by a novel "hypertensinogenic" mechanism, distinguishable from their classical mineral-and glucocortical (MC & GC) action, was investigated in sheep. Medroxyprogesterone acetate partially blocked the hypertensive and MC effects of ACTH infusion.[13]

The interaction between hormones and vitamins was investigated in the baboon. The authors conclude that, even though both Provera and Lo-Ovral changed concentrations of some vitamins and enzymes, the treatments "caused no physiologically significant vitamin alterations."[14]

The effects of MPA on the digestive and absorptive functions of the small intestinal epithelium was investigated in female albino rats. Sodium-dependent glucose and amino acid uptake was increased.[15]

Isolated mouse pancreatic islets were maintained in tissue culture. Medroxyprogesterone-acetate caused a 2-fold increase in insulin release during a 2-week culture period.[16]

Progesterone regulation of cellular proliferation was reviewed. As previously reported, progestins tended to inhibit uterine and stimulate mammary cell proliferation. A hypothetical model is proposed to explain these effects at the level of the gene.[17] Medroxyprogesterone-acetate, like other progestins, augment prolactin release in many species.[18]

The role of progestins in mammary gland growth and differentiation in rodents and humans was reviewed. The authors concluded that progestin effects on epithelial cells is mediated by an estrogen-dependent progesterone receptor, while the mechanism in stromal cells is different, and "remains to be elucidated."[19]

Medroxyprogesterone-acetate (MPA) mediated changes in liver prolactin receptor and serum prolactin concentration in rats was investigated. Both were reduced in the female rat. MPA counteracted an estrogen induced increased in prolactin binding.[20]

It was reported that progesterone or MPA administration increased glucose intolerance/acromegaly in dogs.[21]

b. Modulation of the Immune System

A number of steroids have been shown to possess immunomodulatory properties. Medroxyprogesterone acetate (MPA) has been demonstrated to have an inhibitory effect on response of sheep peripheral blood lymphocytes to the mitogens, phytohemogylutinin (PHA), concanavalin A, and allogenic lymphocytes (mixed lymphocyte culture). These types of response were noted with progesterone, some progesterone metabolites, androgens, corticoids, and the nonsteroidal estrogen diethylstilbesterol, as well. The effects were noted during the early prereplicative phase and not attributed to cytotoxicity.[22,23] MPA also inhibited human lymphocyte response to PHA, when incubated at a concentration of 100 ng/ml.[24]

Medroxyprogesterone acetate (MPA), 2 mg daily, significantly retarded skin transplant rejection, both within and between species in deer mice. Near-term

fetal and placental sizes and weights were not detectably influenced by daily 1-mg MPA injections given to the mother from the 5th through the 19th day of pregnancy.[25]

Highly inbred male CBA mice were administered one mg subcutaneously of MPA, twice a week, for 2 or 4 weeks. Thymus weight was reduced; other lymphoid organs were not effected. Humoral and cellular immune responses were normal, as was stem-cell differentiation capacity.[26]

Progestins (MPA included) were less potent than estrogens in causing rat thymus involution.[27]

MPA did not affect Ig production in the paraaortic lymph nodes draining the pregnant uterus, when administered (1 mg, subcutaneously) to mice.[28]

c. **Effects on the Central Nervous System**

The effects of medroxyprogesterone acetate (MPA) on sexual behavior in the male has been examined. Autoradiography of cynomolgus monkey brain was used to identify binding sites. Unmetabolized MPA was concentrated, one hour following injection, in neurons in regions of the brain known to be implicated in regulating sexual behavior, and pituitary function.[29,30] Pretreatment with progesterone reduced binding of MPA (82-95%). Pretreatment with dihydrotestosterone did not. These results were interpreted as suggesting that MPA binds predominantly to progestin, and not androgen receptors, in the brain of the male primate.[31]

Intact male CF_1 mice were given daily injections of either medroxyprogesterone acetate (MPA), tamoxifen (TAM) or a combination of the two, and tested for aggressive behavior. MPA reduced seminal vesicle and testis wt., but aggressive behavior was unaffected by drug treatment in this model.[32]

New Zealand white female rabbits were injected with depo MPA (0.3 ml of 50 mg/ml) weekly for four weeks. No significant changes were noted in nonadrenergic and perivascular (basilar artery) nerves with 5-HT-like immunoreactivity. The authors suggest that for women prone to migraine attacks, contraceptive pills with progesterone alone or with low estrogen content should be preferred to those with high estrogen content.[33]

An hypothesis suggesting a role of progestins in potentiation of endorphinergic modulation by estrogens associated with the male preponderance for cluster headache was reviewed.[34]

d. **Mechanism of Action**

An extensive body of literature examining the mechanism of action of steroid hormones continues to accumulate. These include binding studies with partially

purified *in vitro* cellular fractions, biochemical mechanistic studies, or various forms of *in vivo* bio-assay. They utilize both naturally occurring and synthetic steroids with different spectra of biological activity, in various tissues from a number of different species. These studies are especially relevant for determining relative potency and specificity. They also contribute to understanding mechanism of action, when metabolism and tissue distribution are approximately considered.[35-63]

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PHARMACOKINETICS UPDATE (see attached Table I on page 16 - 18)
(Reference list follows. References are presented in Part III)

a. Absorption

In adult female rhesus monkeys, peak drug concentrations in peripheral circulation occurred earlier and were greater after intraperitoneal administration (i.e., 149 ng/ml at 1 hr) as compared to oral drug administration (i.e., 67 ng/ml at 4 hr).[1] Results from a study in monkeys suggested that, after single-dose intramuscular administration of 25-100 mg drug per kg body weight to pregnant animals, the sustained drug concentrations in peripheral circulation could partly explain the observed embryotoxicity.[2] Similar studies in pregnant rats showed that, after single-dose intramuscular administration of 45-360 mg drug per kg body weight, fetal serum drug concentrations were 30-70% of the respective maternal values.[3]

Studies in rabbits showed a well-defined triphasic disappearance of intact drug from peripheral circulation, after single-dose intravenous administration of 0.1; 0.5 or 1 mg MPA per kg body weight as a solution in dimethylsulfoxide. A delay in the time required to reach maximum plasma drug concentrations was observed in animals treated with the aqueous suspension. Model-independent pharmacokinetic analysis showed a significant dependence of plasma drug clearance and mean residence time on the dose of drug administered.[4]

b. Distribution

Plasma concentrations of intact drug as well as the amounts of drug-related materials in brain, intestine, liver and lung were higher in rats treated with SKF-525A and slightly lower in phenobarbital-treated animals as compared to saline-treated rodents. Approximately equal amounts of radioactivity were eliminated via urine and feces in control animals, while induction of drug metabolism enhanced excretion in urine and inhibition of drug metabolism enhanced elimination via the intestinal tract.[5] Studies in cynomolgus monkeys demonstrated that, in addition to lowering plasma levels of tritium-labeled testosterone, pre-treatment with multiple doses of MPA inhibited the uptake of testosterone and dihydrotestosterone by cell nuclei in the brain and genital tract.[6]

c. Biotransformation

Although MPA had been shown to be an inducer of hepatic microsomal cytochrome P-450 in both humans and rats, it did not produce a significant induction of either α_1-acid glycoprotein or hepatic cytochrome P-450 activity in dogs as measured by antipyrine clearance.[7]

The 3α-hydroxysteroid dehydrogenase of rat brain cytosol was purified and shown to have several properties in common with the enzyme purified from rat liver

cytosol. MPA was found to be a potent inhibitor of the enzyme.[8] The specific activities of 5α-reductase and 3β-hydroxysteroid dehydrogenase were reduced in rat liver microsomes and liver homogenates after treatment with MPA. Plasma concentrations of luteinizing hormone, testosterone and androstenedione were reduced also by MPA treatment.[9] Changes in the activities of microsomal enzymes involved in hepatic steroid metabolism in the rat (viz., 3α- and 3β-hydroxysteroid dehydrogenase and 5α-reductase) were reported also after administration of androgenic, estrogenic, progestational, anabolic and catatoxic steroids.[10] Results from studies in normal and phenobarbital-treated animals suggested that MPA and phenobarbital differ in their effects on the NADPH-producing system in rat liver.[15]

Studies of the time course of hepatic changes produced by intraperitoneal administration of MPA to female rats showed that maximum effects were attained in 3-7 days and returned to control values in about 11 days.[11] In rats, the liver/plasma concentration ratio of MPA was decreased in liver injury.[12] Treatment with MPA induced drug metabolizing enzymes in liver to about the same extent in both protein deficient and normal pair-fed rats.[13] Single-dose intramuscular administration of MPA caused a dose-dependent reduction in maternal body weight gain of rats in late pregnancy but the response was not accompanied by any measurable changes in hepatic or placental drug metabolizing activity.[14] Quantitative structure-activity studies on the effects of various steroids on growth and monooxygenases of rat liver showed that estrogens induced hepatic effects more potently than progestins.[16]

d. Excretion

Little, if any, new information was reported, during 1983-1991, on the excretion of MPA and/or drug-related materials in urine and feces of animals.

TABLE I: ADME STUDIES UPDATE IN ANIMALS WITH MEDROXYPROGESTERONE ACETATE

Species	Species Strain	Number Sex	Mode of Administration	Dose (mg/kg)	Form of Drug	Purpose of Study	Reference No. *
Dog	Beagle	6M	P.O.	25-400 mg	Provera® tablets	Induction of hepatic microsomal enzymes	7
Monkey	Macaca Mulatta	3F	I.P. P.O.	40 mg		Comparison plasma drug concentration after I.P. and P.O. drug administration	1
Monkey	Cynomol-gus	12F	I.M.	25-100 mg/kg	Aqueous suspension	Relationship between maternal serum drug concentrations and embryotoxicity	2
Monkey	Cynomol-gus	4M	I.M.	40 mg/wk x 16	Depo-Provera® aqueous suspension	Effect of MPA on nuclear uptake of ^{3}H-testosterone by brain, pituitary gland and genital tract	6
Rabbit	New Zealand White	30F & M	I.V.	0.1-1.0 mg/kg	Depo-Provera® aqueous suspension and as solution in DMSO	Pharmacokinetics in rabbit after I.V. drug administration	4

* Pharmacokinetic Update Reference Number

TABLE I: ADME STUDIES UPDATE IN ANIMALS WITH MEDROXYPROGESTERONE ACETATE (continued)

Species	Species Strain	Number Sex	Mode of Administration	Dose (mg/kg)	Form of Drug	Purpose of Study	Reference No. *
Rat	Sprague-Dawley	F	I.M.	0-360 mg/kg	Aqueous suspension	Relationship between maternal serum drug concentrations and embryotoxicity	3
Rat		100M	—	—	—	*In vitro* characterization of 3α-Hydroxysteroid dehydrogenase	8
Rat	Wistar	70F	I.P.	100 mg/kg	Drug in Lutopolar® vehicle	Hepatic enzyme changes produced by MPA	11
Rat	Wistar	4F 4M	I.P.	600 mg/kg	Drug in olive oil	Effect of MPA on liver steroid reductases	9
Rat	Wistar	75M	I.P.	10 mg/kg	1.2-^{3}H labeled drug in corn oil: p-dioxane (8:2)	Disposition of MPA *in vivo* with and without enzyme induction and inhibition	5
Rats	Sprague/ Dawley	M castrates F castrates & intact F	S.Q.	5 mg	Drug in sesame oil/benzoyl Benzoate (4:1 v/v)	Changes in activities of microsomal enzymes after drug administration	10
Rats	Wistar	24F	I.P.	100 mg/kg	Lutopolar®	Effect of microsomal enzyme activity on hepatic drug metabolism	12

* Pharmacokinetic Update Reference Number

TABLE I: ADME STUDIES UPDATE IN ANIMALS WITH MEDROXYPROGESTERONE ACETATE (continued)

Species	Species Strain	Number Sex	Mode of Administration	Dose (mg/kg)	Form of Drug	Purpose of Study	Reference No. *
Rats	Wistar derived	F	I.M.	35 mg/kg	Depo-Provera®	Effect MPA on hepatic drug metabolizing enzymes in normal and protein-deficient animals	13
Rats	Sprague/ Dawley	F	I.M.	0-360 mg/kg	Microcrystalline suspension in saline	Effect MPA on hepatic and placental drug metabolism	14
Rats	Wistar	7M	I.P.	100 mg/kg	Lutopolar®	Effect of MPA on liver NADPH-generation on enzyme activities	15
Rats	Wistar	5F	S.Q.	200 mg/kg/ D x 7	Drug in castor oil/benzyl benzoate (3:2)	Effect of MPA on liver growth and monooxygenases	16

* Pharmacokinetic Update Reference Number

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TOXICOLOGY UPDATE
(Reference list follows. References are presented in Part III)

a. Effects Related to Reproductive Effects

A brief description is provided here of pertinent reproductive effects of medroxyprogesterone acetate (MPA) noted in the open literature. These effects are consistent with those noted in controlled, toxicologic trials and are highlighted here for completeness. Carroad et al, reported that single IM doses of medroxyprogesterone acetate administered to pregnant Sprague Dawley rats at 45, 90, 180 or 360 mg/kg caused a dose-related increase of uro-genital changes in male and female fetuses.[1] In females, the effects were increased ano-genital distance and displacement and narrowing of the urethra. In males, decreased ano-genital distance occurred at doses of 90 mg/kg and greater, and effects of hypospadia, urethral narrowing, and decreased perineal prominence and scrotal swelling were noted. In baboons (Prahalada et al), single doses of 2.5, 25, or 100 mg/kg MPA administered on Day 27 of gestation caused malformations in external genitalia at the two higher doses, and adrenal gland hypoplasia at 100 mg/kg.[2] There were no effects at 2.5 mg/kg. These doses represented 1, 10 and 100 times the equivalent human contraceptive dose. Similarly, a study by Prahalda et al, revealed that a single dose of MPA given intramuscularly at 25 or 100 mg/kg to pregnant cynomolgus monkeys caused alterations in external genitalia at both dose levels and smaller adrenal glands at the high dose.[3] In all of these studies, maternal serum MPA levels correlated well with pharmacolgic effects in a dose-related fashion. Carbone et al studied the effects of subcutaneous implants containing MPA on gestation in mice.[4] This study was conducted at doses of 5, 50 or 500 mg/kg and indicated that there was no increase in non-genital abnormalities. The high dose, equivalent to 2550-fold the human dose, was embryotoxic and resulted in 100% resorption of implants. In particular, the investigators measured limb development and determined that it was not affected even at doses which caused an inhibition of endochondral bone growth.

In a rather loosely controlled study in mice, subcutaneous doses of 2 or 4 mg/kg administered at approximately four days prior to delivery, MPA seemed to reduce aggressive behavior in male mice.[5] Aribarg showed that azoospermia could be induced in male rabbits when MPA was injected for at 10 or 20 mg/kg for 7 to 10 weeks in combination with 5 mg/kg testosterone enanthate.[6]

MPA and Ogen were administered orally to female rats at doses of 0.125 to 1 times the anticipated human dose for 3 weeks. This was a dose finding study in which fewer than half of the rats in each group displayed a change in estrous cycling and/or vaginal epithelium appearance. It was concluded that the 1X anticipated human dose of MPA (0.1 mg/kg/day) and Ogen (0.025 mg/kg/day) could be used as the low dose for a carcinogenicity study in the rat.[7]

Depo-Provera (MPA) was administered at about day 30 of gestation to pregnant

baboons (Papio cynocephalus) at approximately three[8] or at 1, 10 or 40[2] times the human contraceptive dose equivalent based on body weight. MPA was judged not to have any adverse effects on fetal development when administered at 1 or 3 times the human dose. Some changes in external genitalia and adrenal hypoplasia (target organs) were noted in the 10 and 40 time dose groups.

b. Effects Related to Tumorigenesis

Lanari et al, have shown that doses of MPA administered as 40 mg subcutaneously every 2 months for one year induced mammary tumors in virgin BALB/c mice.[9,10]. These doses represent approximately 300-600 times the human contraceptive dose (150 mg every 3 months) based on mice weighing 25 g between (22.8-28.1 g at 84-252 days old).[11] In this study, the doses were greatly exaggerated, particularly for a potent hormone, thus, the effect on the mammary tissue is not surprising. The World Health Organization (WHO) conducted a multinational epidemiological study of neoplasia and steroid contraceptives in over 1,000 women who had used MPA over long periods of time.[12] The results of the study indicated that women who have used MPA for a long time and who initiated use many years previously are not at increased risk of breast cancer. The results of this WHO study also gave support to the elimination of the FDA requirement for a 7-year beagle dog study and its replacement with 2-year chronic toxicity/carcinogenicity studies in rats and mice for the registration of steroidal contraceptives. This decision was based on the human results of the multinational study suggesting the effects of Depo-Provera in dogs are not predictive of its effects in humans.[13]

Noel et al reported in an abstract that MPA administered to Sprague Dawley rats had a co-carcinogenic effect with DMBA when administered at the same time as DMBA and was protective if administered before DMBA.[14]

c. Effects Related to Bone

Cortical bone remodeling was compared in paired control-Depo Provera (MPA) treated spayed Beagle dams.[15] Analysis of static and dynamic parameters indicated that continuous treatment with MPA (100 mg every 2 months) resulted in more Basic Multicellular Units being activated, exhibiting shortened resorption and formation times. The authors suggested that progesterone "may play a role in the prevention or slowing down of cortical bone loss in females following menopause oophorectomy."

TOXICOLOGY UPDATE REFERENCES

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CONCLUSIONS

The nonclinical animal data suggest:

1. Medroxyprogesterone acetate (MPA) is a derivative of progesterone and has actions and uses similar to progesterone.

2. MPA is rapidly absorbed from the GI tract and metabolized in the liver to several progestin metabolites. These metabolites are widely distributed in the body and are present for the most part in those animal species tested in the toxicology studies as well as the human.

3. No particularly outstanding differences in metabolic profiles for different species or different routes of administration were observed.

4. MPA is excreted mainly in the feces of animals and humans.

5. MPA exerts antiestrogenic, antiandrogenic and antigonadotropic effects and in humans it has been shown to be active against hormone-dependent tumors.

6. The acute oral LD_{50} of MPA in rats was greater than 10,000 mg/kg, a dose which did not elicit any clinical sign of toxicity. These data provide at least a 1,000-fold margin of safety for toxic effects when administered orally in high therapeutic doses (500 mg/day) to humans.

7. MPA orally or parenterally at dosages up to 50 times a 30 mg/day therapeutic human dose is nontoxic when administered to dogs and rats over a 6-month period, to rabbits over a 1-year period, and to monkeys over a 28-month period. Expected hormonal effects were noted, however.

8. MPA is an antifertility drug. When administered in its depot form in repeated doses, return to normalcy is prolonged over an indefinite time period.

9. MPA is not teratogenic in rats or mice.

10. MPA elicited corticoid and teratogenic effects (cleft palate) in rabbit offspring. This effect is known to occur in rabbits administered corticoid products and "probably does not indicate an unusual human risk for cleft palate."

11. MPA is not mutagenic.

12. MPA is not carcinogenic in mice and rats.

13. The dog is an unsuitable species for the carcinogenesis testing of progestogens due to an extreme sensitivity to the action of progestogens with mammary tumors formed easily. Therefore, minimal consideration is given to the data derived from dogs.

14. The occurrence of endometrial cancer in 2 replacement monkeys administered Depo-Provera at 150 mg/kg/90 days for up to 10 years does not indicate this lesion would occur in women. In fact, this form of MPA is active against endometrial cancer and is used therapeutically in the treatment of this disease.

15. Based on all the nonclinical animal data presented, MPA is safe for human use within the established therapeutic regimen for the approved indications.