CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-180

PHARMACOLOGY REVIEW(S)

NDA 21-180
ORTHO EVRA (norgestimate/ethinyl estradiol) Tablets

3S

R.W. Johnson

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7-4260
HFD-580

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Pharmacology Section

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: 17-deacetylnorgestimate (norelgestromin), ethinyl estradiol, transdermal patch, contraception
Reviewer Name: Krishan L. Raheja, D.V.M., Ph.D.
Division Name: DRUDP
HFD#: 580
Review Completion Date:

Review number: 001
IND/NDA number: NDA 21-180
Serial number/date/type of submission: 000/12-21-2000/original submission
Information to sponsor: Yes ( ) No ( )
Sponsor (or agent): The R.W.Johnson Pharmaceutical Research Institute, Raritan, NJ
Manufacturer for drug substance: EVRA Transdermal Contraceptive System is manufactured by:

Ortho-McNeil Pharmaceutical, Inc.
Drug Delivery Division, Redwood City, CA

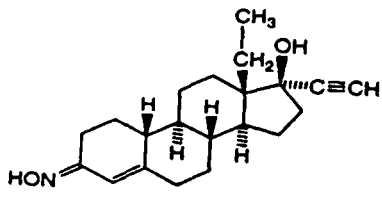
Drug:

Code Name: norelgestromin (progestin) and ethinyl estradiol (estrogen)
Generic Name: 17-deacetylnorgestimate and ethinyl estradiol
Trade Name: Ortho-Evra
Chemical Name: (17-a)-17-Hydroxy-13-ethyl-18,19-dinorpregn-4-en-20-yn-3-one-3-Oxime or 18,19-Dinopregn-4-en-20-yn-3-one, 13-ethyl,17-hydroxy,3 -oxime,(17-a) for 17-deacetylnorgestimate

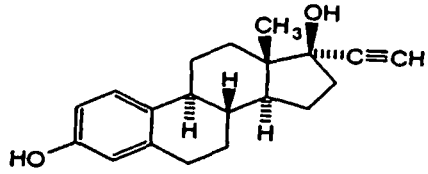
19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17a)- or
19-Nor-17a-pregna-1,3,5(10)-trien-20-yne-3, 17-diol 0r
17-ethinyl-3,17-estradiol for ethinyl estradiol
CAS Registry Number: 53016-31-2 for 17-deacetylnorgestimate
57-63-6 for ethinyl estradiol
Molecular Formula/ Molecular Weight: $C_{21}H_{29}NO_2$/327.47 for 17-deacetylnorgestimate
$C_{20}H_{24}O_2$/296.41 for ethinyl estradiol

Structure:

17-deacetylnorgestimate



Ethinyl estradiol



Relevant INDs/NDAs/DMFs [redacted]; NDAs 19-653 and 19-697.

Drug Class: Progestin (17-deacetylnorgestimate) and estrogen (ethinyl estradiol)

Indication: Prevention of pregnancy

Clinical formulation: Ortho-Evra consists of the norelgestromin as the progestin and ethinyl estradiol as the estrogen. Ortho Evra is a combination transdermal contraceptive patch with a contact surface area of 20 cm^2. It contains 6.0 mg of norelgestromin and 0.75 mg ethinyl estradiol and releases 150 ug of norelgestromin and 20 ug of ethinyl estradiol per 24 hours.

Quantitative composition of the patch is as shown in the table 1 below:

Table 1

Component	Role	Weight/patch % w/w	weight/patch,mg
Drug substances			
Norelgestromin	Progestogen	2.00	6.00
Ethinyl estradiol, micronized	Estrogen	0.25	0.75
Excipients			
Polyisobutylene/polybutene (PIB) adhesive solution	Adhesive	[redacted]	
[redacted]			
Lauryl lactate[b]	Solvent/vehicle		
Crospovidone, micronized NF and EP	Hydrophilic filler		
Total adhesive matrix			)
Polyester non-woven	Structural support		
Polyester backing film laminate	Backing, protection		)
Total patch weight			)
Polyester release liner	Protection		5

[a] evaporated during the manufacturing process

[b] quantity refers to lauryl lactate mixture in the final product

[redacted] and crospovidone are compendial components

[redacted], polyisobutylene/polybutene adhesive, polyester release liner, polyester backing film laminate, lauryl lactate and polyester non-woven are non-compendial components for which specification numbers were provided.

Lauryl lactate has not been used previously in any approved-marketed drug product. Lauryl lactate is also known as Dodecyl 2-hydroxypropanoate; 2-hydroxypropanoic acid; dodecyl ester; and propanoic acid, 2-hydroxy-, dodecyl ester.

Route of administration: transdermal application once a week for 3 consecutive weeks followed by one patch-free week.

Proposed clinical protocol or Use: contraceptive

Previous clinical experience: 17-deacetylnorgestimate is the primary active metabolite of norgestimate, the progestin component of the oral contraceptive products ORTHO-CYCLEN and ORTHO-TRICYCLEN approved by FDA on 12-29-1989 and 07-03-1992, respectively.

Furthermore, sponsor's clinical program included 24 studies: 3 principal Phase3 efficacy and safety studies, five specialized safety, dose-ranging, and/or supportive efficacy studies, 4 dermal safety studies, and 12 PK and bioavailability studies. Two additional PK and bioavailability studies are said to be ongoing. A total of 6,254 women participated in the EVRA clinical investigations, including 3,330 safety-evaluable subjects who wore EVRA transdermal contraceptive system in Phase 3 studies with a planned duration of 6 or 13 cycles (total 22,177 treatment cycles).
Results of these studies demonstrated that the transdermal contraceptive system is highly effective, with an overall Pearl Index of 0.88 compared to overall Pearl Index of 2.18 for Triphasil (levonorgestrel/ethinyl estradiol tablets). Also the cycle control was comparable to Triphasil or Ortho-Cyclen (norgestimate/ethinyl estradiol tablets).

Four PK studies with transdermal contraceptive system were conducted under Protocols # NRGEEP-PHI-003, 004, 005 and 006. One multiple dose PK study was conducted with Ortho-Cyclen (protocol NRGMON-OC-402) and another multiple dose study with Ortho Tri-Cyclen (Protocol NRGTRI-OC-115). Results of these studies are briefly summarized here to show that the systemic exposure to both 17d-NGM and EE with transdermal contraceptive system was lower than that reported with oral approved contraceptive containing NGM + EE. Also only 17d-NGM and norgestrel were reported in both transdermal administration of 17d-NGM and oral administration of NGM, suggesting that metabolites produced by the 2 routes of administration are same and skin does not produced any different or additional metabolites.

Protocol NRGEEP-PHI-003 (single application for one week) volume 35, page 1

Analyte	Cmax
17d-NGM (ng/ml)	0.65
Norgestrel (ng/ml)	0.68
EE (pg/ml)	38.1

Protocol NRGEEP-PHI-004 (single application with 1-week washout between treatments) volume 36, page 1

	C_{max}
17d-NGM (ng/ml)	0.88
Norgestrel (ng/ml)	1.32
EE (pg/ml)	58.7

Protocol NRGEEP-PHI-005 multiple applications) volume 38, page 1

	C_{max}		
	1-8 days	9-15 days	9-18 days
17d-NGM (ng/ml)	0.85	0.93	0.84
Norgestrel (ng/ml)	0.45	1.43	1.46
EE (pg/ml)	42.9	50.7	45.0

Protocol NRGEEP-PHI-006 (dose proportionality study, 10, 15 and 20 cm^2 patch) volume 39, page 1

Patch size cm^2	10	15	20
		C_{max}	
17d-NGM (ng/ml)	0.54	0.71	0.95
Norgestrel (ng/ml)	0.88	1.28	1.84
EE (pg/ml)	34.0	47.8	70.7

Protocol NRGMON-OC-402 (multiple dose study with Ortho-Cyclen) volume 41, page 1

	Day 1 of cycle 1	Day 21 of cycle 3
	C_{max}	
17d-NGM (ng/ml)	1.78	2.19
Norgestrel (ng/ml)	0.649	2.65
EE (pg/ml)	92.2	147.0

Protocol NRGTRI-OC-115 (multi-dose study) volume 43, page 1

	Day 7 0.180 mg (1-7 day)	Day 14 0.215 (8-14 day)	Day 21 0.250 mg (15-21 day)
17d-NGM (ng/ml)	1.80	2.12	2.66
Norgestrel (ng/ml)	1.94	3.00	3.66
EE (pg/ml)	127	128	126

Stated advantages of the transdermal contraceptive system over oral contraceptives were as follows:

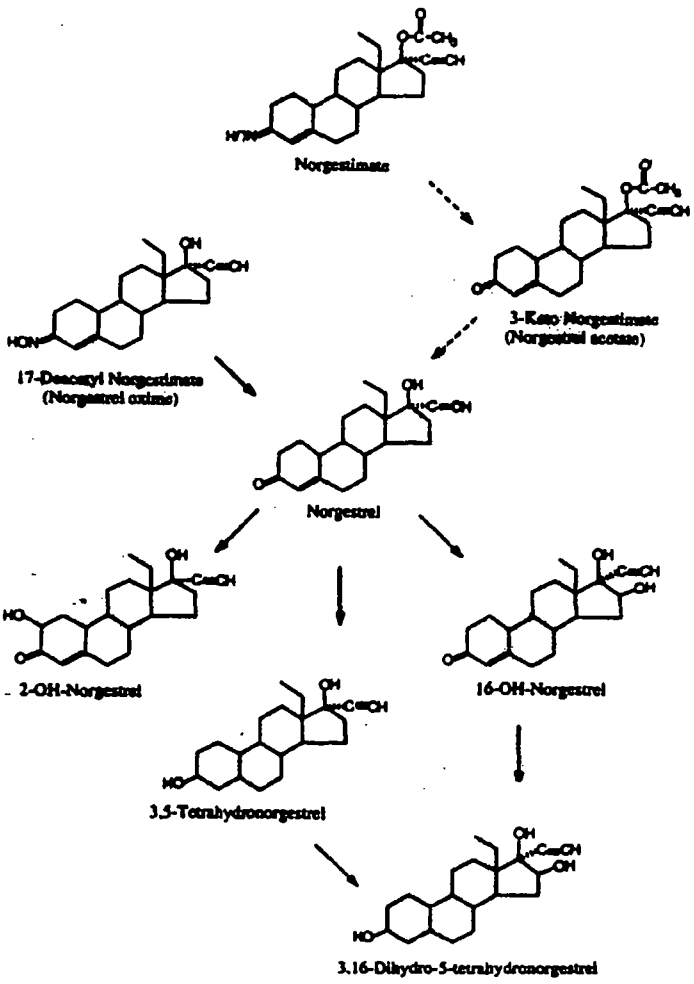
- Weekly transdermal administration of contraceptive hormones provides an alternative to daily oral administration of contraceptive pills;
- With transdermal administration, absorption of 17 d-NGM and EE would not be affected by GI disturbances, such as GI viruses or dysentery-type illnesses;
- More convenient to use and may increase subject compliance relative to oral contraceptive use;
- Compared to daily oral administration of contraceptive pills, use of the patch provides delivery of contraceptive hormones that does not stop immediately upon reaching the 7^{th} day of dosing. Since the daily dose of hormones decreases gradually over the next few days if the patch remains in place beyond 7 days, no backup contraception is required if the patch is changed one day late;
- Unlike long-acting contraceptive methods i.e., implants, injectables and sterilization, transdermal application provides sustained contraceptive efficacy that is easily reversible and user controlled.

Disclaimer -- use of sponsor's material

Introduction and drug history: Norelgestromin is the active progestin largely responsible for the progestational activity that occurs in women following application of Ortho Evra. Norelgestromin is also the primary active metabolite produced from norgestimate by one-step enzymatic conversion (deacetylation) following oral administration of norgestimate, the progestin component of the oral contraceptive products ORTHO-CYCLEN and ORTHO-TRICYCLEN. This conversion of norgestimate to 17-deacetylnorgestimmate is reported to be extensive and occurs in the gut wall and liver during first-pass metabolism when norgestimate is administered orally. Since norgestimate has been approved under NDAs 19-653 and 19-697, the safety and efficacy of norelgestromin is established.
17-deacetylnorgestimate was chosen as the progestin included in EVRA system mainly because complete metabolism of norgestimate to 17-deacetylnorgestimate could not be assured with transdermal administration.

The metabolic scheme for the production of 17-deacetylnorgestimate from its parent compound norgestimate is shown in the following figure:

Figure # 1.



There is no non-oral contraceptive system available that contains a combination of progestin and estrogen. The transdermal contraceptive system will have the advantage that it may allow the use of lower doses of steroids than oral contraceptives, and be more convenient to use. Also since it can be worn for 7 days, it could increase patient compliance relative to oral contraceptive use. Also side effects related to ingestion and hepatic metabolism may be reduced.

Studies reviewed within this submission: Since most of the pharmacology, pharmacokinetic/toxicokinetic and toxicology of 17-deacetylnorgestimate has been supported based on results of pre-clinical toxicity studies previously submitted for approval of oral norgestimate and ethinyl estradiol combination contraceptive products, Ortho-Cyclen and Ortho-Tricyclen under NDAs 19-653 and 19-697 respectively, only a limited toxicology program was proposed by the sponsor and agreed upon by the division.

Toxicity studies conducted with 17-deacetylnorgestimate included the following:

- A primary dermal irritation study in rabbits
- A contact sensitization study (Buehler assay) in guinea pig
- A 28-day dermal toxicity study in rabbits
- Since NGM is not extensively metabolized to 17 d-NGM in rabbits, a developmental toxicity study was conducted in rabbits with 17 d-NGM using SC administration
- Battery of genotoxicity studies consisting of in vitro bacterial plate assay, HGPRT point mutation, and chromosomal aberration assays and in vivo bone marrow micronucleus test.

Additional long-term studies with 17-deacetylnorgestimate were not conducted in light of the long history of clinical use of norgestimate/ethinyl estradiol. However, bridging studies were conducted to determine the exposure to 17-deacetylnorgestimate which occurred at doses utilized in the original rat carcinogenicity study and 10-year study in monkeys with norgestimate/ethinyl estradiol combination. Systemic exposures in these rat and monkey studies were used to calculate animal/human exposure ratios.

Studies <u>not</u> reviewed within this submission: All studies reviewed under [redacted], for 17-deacetylnorgestimate has not been reviewed here. Instead copies of pertinent reviews have been appended and summary of the reviews is provided. These include the following:

1. Original submission dated 4-30-1996, serial submission number (SS#) 000.
This submission provided general information about 17-deacetylnorgestimate and ethinyl estradiol and the dosage formulation used. Also discussion in this submission pertained to non-clinical pharmacology, pharmacokinetics and results of the primary skin irritation in rabbits with the proposed transdermal formulation. In the rabbit irritation study, both the test and control materials were mildly irritating to the skin.

2. SS# 003, dated 7-17-1996 (volume 12, page 338)

This submission contained results of dermal sensitization study in guinea pigs (Report # X6C002G). It was concluded from this study that neither test material (17-deacaetyllnorgestimate/ethinyl estradiol patch) nor placebo control were contact sensitizers.

3. SS# 014 and 015 dated 4-10-1997.
Under this submission a study (# 4400896:1) was conducted in rabbits to determine serum concentrations of norgestimate and its metabolites following a single oral administration of 300 ug/kg norgestimate/ethinyl estradiol. The levels of norgestimate and its metabolites were below the limit of quantification ——— Based on these results, sponsor concluded that their proposal to use the Segment 2 oral norgestimate study in rabbits to support the transdermal contraceptive patch would be invalid. Sponsor suggested that SC administration of 17-deacetylnorgestimate would be appropriate if testing 17-deacetylnorgestimate in combination with ethinyl estradiol were not required. Pharmacology agreed with the sponsor's proposal.

Also in this submission sponsor determined serum concentrations of norgestimate and its metabolites in female Long-Evans rats following single oral administration of 250 ug/50 ug/kg of norgestimate/ethinyl estradiol (study # 425809:1) to support a 2-year carcinogenicity study in rats with norgestimate/ethinyl estradiol.
The multiples of human exposure obtained in this study for 17-deacetylnorgestimate were only 1.5 and 2.3, respectively based on C_{max} and AUC values.
In another rat carcinogenicity study conducted in Europe, sponsor had used dose levels of 0.15, 0.60 and 3.0 mg/kg/day of NGM/EE (5:1). Pharmacology recommended that the sponsor repeat the above PK study using the high dose of 3 mg/kg/day to determine if rats were adequately exposed to 17-deacetylnorgestimate.

Serum concentrations of 17-deacetylnorgestimate and norgestrel were also determined in female white rabbits following a single application of a transdermal contraceptive delivery system of 17-deacetylnorgestimate/ethinyl estradiol for one week (Study # 425842:1). Although rabbits were systemically exposed to 17-deacetylnorgestimate, the multiple of human exposure was only 3.6.

4. Under SS# 019, dated 5-19-1997 sponsor evaluated norgestimate, norgestimate metabolites and ethinyl estradiol as reversible and mechanism-based inhibitors of human cytochrome P450 isoforms (study # DM95334). Results of this study demonstrated that norgestimate and its metabolites and ethinyl estradiol function as reversible inhibitors of major P450 enzymes expressed in human liver microsomes. Competitive inhibition was seen with norgestimate for CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5; with D-norgestrel for CYP2A6, CYP2C9, CYP2C19 and CYP3A4/5; with norgestrel acetate for CYP2C9, CYP2D6, and CYP3A4/5; with 17-deacetylnorgestimate for CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5. Ethinyl estradiol competitively inhibited CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5. D(-) norgetrel and 17-deacetylnorgestimate respectively inhibited CYP3A4/5 by 26% and 44%. D(-) norgetimate also inhibited CYP2C19 by 13%.
Sponsor concluded that the possibility that these steroids could impede the clearance of other drugs metabolized by cytochrome P450 with its clinical and toxicological consequences was insignificant, based on the fact that the C_{max} of these steroid was too low relative to K_I to cause clinically significant inhibition of cytochrome P-450 activity.

5. Under SS# 034 dated 5-29-1998, one month dermal toxicity study with 17-deacetylnorgestimate/ethinyl estradiol transdermal contraceptive system applied topically to female NZW rabbits was determined (Study # 96007). Patches measuring 10, 15 or 20 cm^2 and containing 17-dNGM/EE as 3 mg/0.0375 mg, 4.5 mg/0.56 mg and 6 mg/0.76 mg, respectively were used for 5 rabbits in each group. Control groups had a placebo patch. Patches were applied weekly for a combined total of 28 days with continuous exposure 24 hours/day. Serum samples were drawn to evaluate drug absorption (volume 13, page 54).

Results showed higher ALT and GGT activities in a high dose and in 2 mid dose rabbits. Ovarian weight was significantly increased in a dose-related manner. Uterine enlargement was observed in 12/15 treated rabbits and 0/5 control rabbits. Parovarian cysts (cysts in the oviduct or bursa) were noted in 1/5 placebo, 0/5 in low dose and 3/5 each in mid and high dose rabbits. Compound related uterine changes included multifocal decidualization and enlargement with discoloration (myometrial hypertrophy, stromal thickening, increased vascularity and luminal dilatation). Smooth muscle hypertrophy was observed in the vagina and cervix. There were no microscopic changes to explain increased ovarian weight. There was treatment-related thymic lymphoid depletion and minimal to mild deposition of apparent amyloid in spleen in all rabbits, suggested to be due to estrogen administration. No compound-related differences were found at the skin patch sites. Although the doses administered ranged from 29 to 40 times the maximum projected clinical dosage on body weight basis, the systemic exposure was similar to that reported with clinical patch under SS# 035 dated 6-19-1998.(see table 4)

6. Under SS# 050 dated 10-7-1998, results of 3 in vitro mutagenicity tests (Ames test, HGPRT point mutation assay using CHO cells, chromosomal aberration assay using cultured human peripheral lymphocytes) and under SS# 060 dated 2-26-1999 results of rat bone marrow micronucleus assay were submitted. These in vitro and in vivo tests demonstrated no mutagenic potential for 17-deacetylnorgestimate. (volume 14, page 257 and volume 15, pages 1, 103 and 187).

To support the carcinogenicity study in rats sponsor had to determine norgestimate and its metabolites at steady state after oral norgestimate administration. To this end sponsor used norgestimate/ethinyl estradiol doses of 300 ug/60 ug, 600 ug/120 ug and 3000 ug/600 ug, which were used in the European rat carcinogenicity study. After a single or 14 daily oral doses of norgestimate/ethinyl estradiol, PK of norgestimate and its metabolites was determined under SS# 051 dated 10-22-1998.

Results of this study were very variable. $T_{1/2}$ based on only 2 points was extremely variable. T_{max} and AUC on Day 14 were less than half compared to those on Day 1. Despite these variables, sponsor concluded that steady state had been reached, but this interpretation was disputed by the Division. Sponsor submitted letters from [redacted] to support their contention that steady state had been reached. These consultants suggested that there was a slower rate of absorption of the parent drug on Day 14 compared to Day 1. They concluded however, that based on estimated $T_{1/2}$, observed dose proportionality on Day 14, and similar though variable C_{min} on day 13 and 14, steady state was presumed to have reached.

Pharmacology sought a consult from Clinical Pharmacology and Biopharmaceutics Review Division of Pharmaceutical evaluation. It was concluded by Dr. Jarugula that the study cited was not adequately designed to evaluate steady state conditions for 17d-NGM and did not provide adequate evidence to prove that study state was reached although one can argue that steady state is expected by Day 14. A copy of Dr. Jarugula's review is appended.

Based on Dr. Jarugula recommendations, sponsor's data was accepted.

PHARMACOLOGY:

Mechanism of Action: In combination, 17-deacetylnorgestimate (a progestin) and EE (an estrogen) prevent pregnancy by inhibiting ovulation through the suppression of gonadotropins. Other factor contributing to inhibition of pregnancy include changes in the cervical mucus and endometrium, and motility and secretion, which increase the difficulty of sperm entry into the uterus and reduce the risk of implantation.

Drug Activity Related to Proposed Indication: Contraception

Ancillary Pharmacology Studies:

Antiovulatory activity: The antiovulatory activity of 17 d-NGM was compared to that of NGM in rats. Groups of 5 to 10 rats were dosed orally or SC in the morning of metestrus, diestrus and proestrus. The dose levels used by each route were 0, 0.062, 0.125, 0.25, 0.5 and 1.0 mg/kg. The day following the last dose the rats were killed and the oviducts examined for the presence of ova. As shown in table below, inhibition of ovulation in at least 50% of the rats occurred following SC doses of 0.125 mg/kg and oral doses of 0.5 mg/kg of either compound. Ovulation was inhibited in all rats given 0.25 mg/kg or greater of NGM or 17 d-NGM subcutaneously. Results thus showed that based on dose response, the potency of 17 d-NGM to inhibit ovulation was equivalent to that of NGM.

Table 2

		Number of rats ovulating/10 rats treated					
	Mg/kg	0	0.062	0.125	0.25	0.50	1.0
	17 d-NGM	10	-	8	8	3	3
Oral	NGM		-	10	9	4	2
	17 d-NGM	10	8	5	0	0	-
Subcutaneous	NGM		10	5	1	0	-

Progestational activity (Biological Research # 1466, volume 12, page 1): Using immature estrogen primed rabbits (Clauberg progestational assay), the progestational potency of 17-deacetynorgestimate was found to be similar to norgestimate, whereas those of 3-keto-norgestimate and levonorgestrel were respectively 3.4 and 4.9 times greater when compared to norgestimate.

Androgenic activity: (BR # 1459) Using rat ventral prostate assay for androgenic activity, the activity of 17-deacetylnorgestimate was not significantly different from that of norgestimate when administered by either SC (0.007 times that of testosterone propionate) or oral route (0.01 times that of methyl testosterone). Levonorgestrel and 3-keto-norgestimate were both significantly more androgenic than norgestimate when given by either route, and both were more potent androgens when given by SC than when given orally. With SC administration

Levonorgestrel and 3-keto-norgestimate were about 0.1 times as potent androgen compared to testosterone propionate.

Progestin receptor binding: (BR# 1459, volume 12, page 36) Norgestimate and 17-deacetylnorgestimate had similar binding affinities as progesterone for the rabbit uterine progesterone receptors as measured by displacement of ^{3}H-R50200 (a synthetic progestin ligand). The test was run in the presence of BSA to prevent binding to glassware. The IC_{50} (the concentration of test substance corresponding to 50% inhibition on the linear regression response curve) for 17 d-NGM, NGM, 3-keto-NGM, LNG and progesterone was 2.82, 5.01, 0.83, 0.71 and 1.87 nM, respectively.

Neither norgestimate nor 17-deacetyl norgestimate showed significant binding to SHBG and neither in vitro studies displaced ^{3}H testosterone from SHBG, suggesting that the concentration of circulating testosterone would not increase due to the presence of norgestimate and 17-deacetyl norgestimate in the blood.

Androgen receptor binding: (BR# 1459) was measured by the displacement of radiolabeled 5a-dihydrotestosterone from isolated androgen receptors from rat ventral prostates. Test was run in the presence of 0.1% BSA to prevent binding of test substance to glassware. The IC_{50} (nM) for 17 d-NGM, NGM, 3-keto-NGM, LNG and dihydrotestosterone was 156, 857, 78, 11 and 2.2, respectively.

Summary of pharmacology: The antiovulatory activity of 17 d-NGM was similar to NGM when dosed orally or subcutaneously.

The response and potency of 17 d-NGM (norgestrel oxime) for progestational activity was similar to that of NGM, while 3-keto-NGM (norgestrel acetate) and LNG (D-norgestrel) were more potent than NGM.

Androgenic activity of 17 d-NGM was slightly higher than NGM. 3-keto-NGM and LNG were significantly more androgenic than NGM.

SAFETY PHARMACOLOGY: Only dermal safety studies were conducted with the proposed transdermal patch.

Neurological effects: Studies to examine the CNS effects of 17 d-NGM have not been conducted. However, the effect of NGM has been investigated on CNS activity and alterations in autonomic functions in rats. Rats were administered a single oral dose of 1, 5 and 25 mg/kg. Controls were given sesame oil only. Animals were observed and examined over the next 24 hours. Sponsor reported no effect on CNS depression and stimulation, grip strength, skeletal muscle tone, catalepsy, anesthesia, respiration rate, pupil size, analgesia, diarrhea, diuresis, palpebral size, exophthalmus, lacrimation, salivation, piloerection, vasodilatation, blanching, hypo/hyperthermia, or reflexes.

Cardiovascular effects: The cardiovascular and autonomic effects of NGM were determined in dogs administered an IV dose of 0.5 mg/kg. It was stated that there was no effects on heart rate or any of the following stimuli: tilt head-up, norepinephrine, dimethylphenylpiperazine, peripheral vagal stimulation, acetylcholine, tyramine, histamine, or isoproterenol. It was pointed out that the fact that NGM did not block the tilt reflex in the dogs suggests that the drug does not interfere with CV reflex mechanisms associated with the CNS.

Pulmonary effects: none submitted
Renal effects: none submitted
Gastrointestinal effects: none submitted
Abuse liability: none mentioned
Other: NGM did not inhibit growth of any of the 8 microorganism tested.
Conclusions: Although no studies were conducted with 17 d-NGM, results of studies with NGM would suggest that 17 d-NGM has no neurological or cardiovascular effect.

Summary: Since NGM, the parent compound of 17 d-NGM did not show any neurological or cardiovascular effect, it is assumed that these findings also apply to 17 d-NGM.

PHARMACOKINETICS/TOXICOKINETICS:

17-dNGM is formed from NGM by a one-step enzymatic conversion (deacetylation). This metabolism occurs in both the intestinal wall and the liver. As such, oral doses of NGM are almost completely deacetylated during oral absorption (first-pass effects). 17d-NGM can therefore be considered the primary active metabolite of NGM.

As mentioned before although 17-dNGM has not been used previously in a contraceptive product, it is the primary active metabolite of NGM, which is marketed in United States as Ortho-Cyclen and Ortho-Tri-Cyclen. Both these products contain ethinyl estradiol as the estrogenic component, the estrogen most frequently used in combination oral contraceptives and which is also the estrogenic component in the proposed contraceptive transdermal patch, EVRA.

Studies with 17d-NGM and EE, which have been performed to support the EVRA program include the following:

1 TK studies in rabbits, following single or multiple application of the transdermal patches, and in rats and rabbits following single or multiple SC doses of 17d-NGM
2 Studies with NGM that were included in the previous NDAs for Ortho-Cyclen and Ortho-Tri-Cyclen. These studies were performed in a variety of animals (rats, rabbits, dogs, and monkeys) mostly by the oral route, the intended route of administration for Ortho-Cyclen and Ortho-Tri-Cyclen. Studies were also conducted by the IV route and in vitro.
3 New studies that were performed to update the package of information that supports the two oral products. The objectives of these studies were to provide additional information on 17d-NGM, NGM and their metabolites and to document the exposure in laboratory animals used in toxicity testing.

In addition since lauryl lactate was the only non-compendial compound in the AVRA transdermal contraceptive system, which is not used in any approved product, sponsor has provided information on the safety of this compound.

PK parameters: Five PK/TK studies with 17 d-NGM (alone or in combination with EE) were performed. These were:

1. a single (7 day) application of the 17 d-NGM/EE patch to NZW rabbits, which monitored the absorption and PK of 17 d-NGM, norgestrel and EE

2. a TK study in rabbits which assessed the absorption and PK of 17 d-NGM, norgestrel and EE following multiple applications of the patch
3. single and multiple SC toxicokinetic studies in rats and NZW rabbits, to provide information on the systemic exposure of 17 d-NGM and its metabolite, norgestrel, after SC dosing and to determine if exposure was related to dose and daily administration.
4. Studies that supported development program of NGM. These studies determined the PK of 17 d-NGM, NGM and norgestrel in Long-Evans and SD rats, NZW rabbits and rhesus monkeys, following single and multiple oral or IV administration of NGM (alone or in combination with EE). These were carried out to provide retrospective TK data for safety studies in the rat, rabbit and monkey.
5. Effect of dose and the duration of dosing on systemic exposure and comparison of the relative exposure of 17 d-NGM in laboratory animals and humans.

The results of these all PK/TK studies are reviewed below:

Rat – Single and multiple doses 17 d-NGM (study # DM98402, volume 30, page 169)

This study was designed to support a Bone Marrow Micronucleus study by providing information on the systemic exposure of 17 d-NGM and norgestrel in SD male and female rats, after SC administration for 1 or 3 days.
Results expressed as mean (+/-SD) serum concentrations (ng/ml) for 17 d-NGM and norgestrel in male and female rats (N=5) are shown in table 3 below:

Table 3

Dose[a]	Analyte	Gender	Day 1[b]	Day 3[b]	Final[c]
Low	17 d-NGM	Male	179 (229)	246 (46.3)	182 (24.6)
		Female	211 (12)	516 (159.0)	272 (59.8)
Mid	17 d-NGM	Male	127 (29)	359 (96.2)	273 (48.5)
		Female	309 (65)	694 (169.9)	477 (157.3)
High	17 d-NGM	Male	196 (78)	587 (200.2)	388 (86.9)
		Female	455 (199)	1198 (387.7)	1067 (679.3)
Low	Norgestrel	Male	1.74 (0.83)	6.67 (1.72)	5.36 (0.70)
		Female	2.37 (0.51)	8.93 (1.73)	7.07 (1.52)
Mid	Norgestrel	Male	2.40 (0.45)	11.10 (2.01)	9.98 (1.38)
		Female	6.46 (4.59)	20.12 (5.21)	16.36 (1.83)
High	Norgestrel	Male	3.83 (1.3)	15.24 (2.70)	16.54 (3.77)
		Female	5.09 (1.90)	32.24 (16.63)	34.02 (22.30)

a 25 mg, 75 mg and 125 mg/kg 17 d-NGM for low, mid and high dose respectively
b Days 1 and 3 samples collected 1.5 hr postdose
c Final samples collected 24 hours following last dose (Day 3)

Results showed that serum levels of 17 d-NGM and norgestrel increased with increasing doses. The mean $C_{t.5h}$ for 17 d-NGM and norgestrel were approx. 1.2 to 3.0 times higher than those seen in males. Also multiple dosing resulted in approx. 3.2 to 6.4 fold increases in mean $C_{1.5h}$ for 17 d-NGM and 3.2 to 6.4 fold increase for norgestrel.

In 5 clinical PK studies with EVRA, the mean $AUC_{0\text{-}24h}$ determined after 1 to 3-week application was 19.01 ng.h/ml. As shown in Table 9, comparing rat values with AUC in women, the exposure in rats exceeded that in humans by approximately 497, 739 and 1430-fold, respectively.

Rabbit – Single patch 17d-NGM plus EE (study No. DM96347, vol 21. Page 1)

This study was designed to assess systemic exposure of 17 d-NGM and norgestrel after single application of EVRA (20 cm^2 containing 6 mg 17 d-NGM and 0.6 mg EE) to 3 non-fasted NZW female rabbits for 7 days. Cmax for both analytes occurred at 24 hours. The mean serum AUC (0-192 hours) were 78.16 and 41.79 ng.h/ml, and Cmax 0.7 and 0.42 ng/ml, respectively for 17d-NGM and norgestrel. Using 19 ng.h/ml as AUC for human with the proposed patch, the exposure in rabbits was from 2.70 to 5.56 times the human exposure.

Multiple 17 d-NGM plus EE patch study was conducted using 20 female rabbits in 4 groups of 5 each (study No. DM96350). Group one was applied 20 cm^2 placebo patch, group 2: low dose, 3 mg 17 d-NGM plus 0.375 mg EE, 10 cm^2 patch; group 3: mid dose, 4.5 mg 17 d-NGM plus 0.56 mg EE, 15 cm^2 patch; group 4: high dose, 6 mg 17 d-NGM plus 0.75 mg EE, 20 cm^2 patch. Patches were worn for a total of 28 days with continuous exposure for 24 hours/day. Blood samples were collected pre-dose and then 4, 8, 24 and 48 hours following initial patch application. On day 7, 14, 21 and 28, a single blood sample was drawn from each rabbit/dosage group. Serum 17d-NGM was determined using LC/MS assay and EE using GC/MS assay.

Results: Max concentration of 17 d-NGM and EE were observed on Day 1 at 24-48 hours. Levels then decreased up to 150 hours and then increased again to the end of study. Serum norgestrel was measurable only in 10% of mid and high dose groups and ranged from 0.19 to 0.57 ng/ml. It was stated that there was variability in the adherence of each individual patch and as a result the data were very variable as shown in table 4 below. Values are C_{max} expressed as mean +/-SD.

Table 4

	Low dose	Mid dose	High dose
17d-NGM (ng/ml)	0.34+/-0,27	0.32+/-0.22	0.67+/-0.38
EE (pg/ml)	66.3+/-41.5	49.3+/-34.4	120.3+/-80.0

Rabbit - Single and multiple SC doses of 17 d-NGM (study No. DS98311, DM98334 vol.21 page 138)

This study was conducted to support a developmental toxicology study in rabbits (DS98311). One hundred twenty presumed pregnant NZW rabbits were randomized into 5 groups of 24 each and administered daily SC doses of 0, 1, 2, 4, or 6 mg/kg (0.1 ml/kg) of 17 d-NGM. Blood was obtained from 6 rabbits/group on gestation day 7 and again from same rabbits on gestation day 19 at 1.5 hours postdose.
Mean (SD) serum concentrations (ng/ml) for 17 d-NGM and norgestrel on gestation days 7 and 19 are given in table 5 below:

Table 5

Dose group	Gestation day	17 d-NGM	Norgestrel
Control Group 1	7 19	0.00 0.00	0.00 0.00
1mg/kg/day Group 2	7 19	56.7 (42.0) 47.8 (23.0)	4.3 (1.8) 5.0 (0.8)
2 mg/kg/day Group 3	7 19	74.0 (20.4) 92.6 (42.2)	6.2 (3.0) 6.2 (1.3)
4 mg/kg/day Group 4	7 19	96.3 (36.0) 129.3 (73.7)	7.8 (3.2) 13.0 (5.1)
6 mg/kg/day	7	119.9 (25.8)	10.6 (3.2)

Group 5	19	159.3 (19.1)	15.6 (4.1)

Vehicle used was 95% ethyl alcohol.

Results showed that values increased in less than dose-proportional manner and values were generally higher on Day 19.

Note: In rabbits the SC route was used since after single oral dose of 300 ug/kg NGM plus 60 ug/kg EE, serum concentrations of NGM and its active metabolites were all below the LOQ. However, after a single IV administration of 20 mg NGM, small amounts of NGM were found in the plasma in 2/3 rabbits up to 1 hour post-dose, but at lower concentrations than its metabolites. The concentrations of 17 d-NGM (syn + anti, geometric isomers) generally being higher than norgestrel as shown in table 6 below:

Table 6

Time (min)	17-d-NGM Syn	17-d-NGM Anti	NGM	Norgestrel
0	0	0	0	0
20	0.378	0.805	0.193	0.328
45	0.154	0.502	0.047	0.253
60	0.101	0.293	0.030	0.180
120	ND	0.131	ND	0.127
180	ND	0.061	ND	0.072
240	ND	ND	ND	ND

ND= not determined. values are as ug/ml.

Rat – Single and multiple oral doses NGM plus EE (study # DM97355, page 246)

This study using female Long-Evans rats was designed to provide information on the systemic exposure of 17 d-NGM, NGM, and 3-ketonorgestimate after either single or multiple (14 days) oral doses. The dose groups were 300 ug/kg NGM plus 60 ug/kg EE (low dose), 600 mg/kg NGM plus 120 ug/kg EE (mid dose) and 3000 ug/kg NGM plus 600 ug/kg EE (high dose). These doses were used in the 2-year chronic oral toxicity study with NGM and adequate 17 d-NGM systemic exposure is necessary to support the safety of EVRA since no carcinogenicity study was conducted with 17 d-NGM.

Mean (SD) serum PK parameters for 17 d-NGM, NGM, norgestrel, and 3-ketonorgestimate (N=10) following administration of single or 14 daily oral doses of NGM/EE is shown in table 6 below:

Table 7

Dose group	Analyte	C_{max} (ng/ml)	T_{max} (h)	C_{min} (ng/ml)	AUC (0-24 h) (ng.h/ml)
Single dose					
Low	17 d-NGM	7.89 (3.36)	1.7 (0.95)	0.0 (0.0)	53.33 (19.10)
Mid	17 d-NGM	14.18 (4.39)	2.0 (1.15)	0.05 (0.16)	113.33 (27.03)
High	17 d-NGM	103.08 (37.63)	2.3 (0.95)	1.05 (2.80)	769.61 (201.40)
High	NGM	6.14 (11.75)	1.2 (1.03)	0.23 (0.72)	24.40 (54.84)
High	Norgestrel	1.68 (0.48)	4.0 (1.63)	0.0	14.82 (4.13)
Mid	3-ketoNGM	0.0 (0.0)	0.0 (0.0)	0.0	0.0
High	3-ketoNGM	1.0 8(0.42)	1.0 (1.08)	0.0	3.12 (1.94)
Multiple dose					
Low	17 d-NGM	4.08 (1.44)	2.9 (2.18)	0.0	38.63 (10.30)
Mid	17 d-NGM	10.04 (4.74)	4.4 (2.76)	0.15 (0.24)	87.39 (36.64)
High	17 d-NGM	36.40 (9.07)	4.2 (2.20)	1.64 (1.56)	356.81 (87.32)
High	NGM	1.26 (1.31)	2.4 (2.75)[b]	0.3 (0.67)	11.54 (23.42)

High	Norgestrel	1.10 (0.33)	4.3 (2.75)	0.13 (0.26)	13.73 (5.21)
Mid	3-ketoNGM	0.35 (0.08)	2.65 (3.04)	0.0	1.39 (0.79)
High	3-ketoNGM	1.00 (0.45)	3.15 (2.71)	0.7 (0.16)	5.99 (3.93)

b N=7

Results showed that at both dose and time points, 17 d-NGM was the main component in serum and the systemic exposure to it increased with increasing dose. However, it should be pointed out that the levels decreased significantly after multiple dosing. In the highest dose group after both single and multiple doses, NGM, norgestrel and 3-ketoNGM were also detected in the serum, but in the low and mid dose groups, in most cases the concentrations of these analytes were below the level of quantification. The mean T1/2 of 17 d-NGM and norgestrel in the highest dose were 5.27 +/- 1.36 and 12.41 +/- 7.35 hours, respectively.

Monkey – Single and multiple oral doses of NGM plus EE

The single dose pilot study (#DM94329) was conducted using 4 cycling female monkeys. A single dose of 250 ug NGM + 35 ug EE was administered orally in hydroxypropylmethyl cellulose (HPMC) suspension. Blood samples were collected pre-dose and up to 24 hours post-dosing.

C_{max} (ng/ml) and T_{max} (h) for NGM, were 3.2+/-5.9 and 0.6+/-0.6 (mean +/-SD) respectively. Data was insufficient to calculate AUC.

C_{max}, T_{max} , AUC and T1/2 values for 17d-NGM were 35.0+/-13.1, 1.3+/-0.5, 172.7+/-19.8, and 5.0+/-3.5, respectively. For norgestrel, C_{max}, T_{max}, AUC and T1/2 were 15.4+/-9.1, 2.8+/-1.5, 67.0+/-110.2 and 9.1+/-7.7, respectively. Norgestrel acetate was detected only in 2/4 monkeys with C_{max} and T_{max} values of 0.1+/-0.2 and 0.5 respectively.

Results 17d-NGM and norgestrel are the primary metabolites after oral administration of NGM/EE.

In the multiple dose study (#EDMS-USRA-3293371:3.0), two groups, each with 4 monkeys received 5 ug/kg NGM plus 0.7 ug/kg EE, and 250 ug/kg NGM plus 35 ug/kg EE, respectively for 21 consecutive days. These dose levels were equivalent to the low and high dose levels that were being used at the end of a chronic monkey toxicology study with oral norgestimate. The results of this study are intended to support the safety of 17 d-NGM. Serum concentration of NGM and three metabolites (17 d-NGM, norgestrel and 3-ketoNGM) were determined using LC-MS/MS assay and results are shown in table 8 below:

Table 8

Analyte	Dose	Study day	C_{max} (ng/ml)	T_{max} (h)	AUC(0-24h) (ng.h/ml)
Low		Low	0.4 (0.1) 0.6 (0.2)	1.3(0.5) 1.3 (0.5)	1.6 (0.8) 2.0 (0.4)
Norgestrel	Low	1 21	0.6 (0.1) 0.8(0.2)	2.0(1.4) 2.0(1.4)	4.3 (1.7) 4.3 (3.0)
EE	Low	1 21	0.03 (0.01) 0.01 (0.01)	0.5(0.0) 0.25(0.29)	C C
17 d-NGM	High	1 21	22.6 (4.8) 28.6 (9.6)	1.5(0.6) 2.3(1.3)	151.9 (34.7) 140.3 (8.6)
NGM	High	1 21	0.2 (0.08) 0.3 (0.2)	0.4 (0.3) 1.0 (0.8)	C C
Norgestrel	High	1 21	19.0 (7.1) 11.4 (3.5)	3.5 (3.0) 3.0 (1.2)	219.7 (106.6) 88.2 (37.1)
EE	High	1	0.5 (0.1)	0.6 (0.3)	1.2 (0.8)

		21	0.1 (0.1)	0.8 (0.3)	0.5 (0.2)

c= Insufficient data

Results showed that 17 d-NGM and norgestrel were present in both groups following single and multiple doses. By contrast, NGM was detected in low concentrations in the high dose group and 3-ketoNGM was not detected in the serum from either group. EE was detected in serum of all monkeys in the high dose group after multiple dosing, but only in the serum of 2 monkeys in the low dose group after multiple dosing. Cmax occurred between 0.4 to 3.5 hours for 17 d-NGM, NGM and norgestrel and at 0.25 to 0.8 hours for EE following single and multiple doses. Comparing the results from Days 1 and 21 showed a significant decrease (40-80%) in AUC and Cmax for norgestrel and EE in the high dose group following multiple doses. Sponsor suggested this is due to possible induction of the metabolism of norgestrel and EE during multiple dose administration.

Exposure comparison between animals and humans

The animal exposure data were from a rat study supporting a bone marrow micronucleus test, and 2 rabbit SC toxicokinetic studies supporting the reprotoxicology program. The AUC data for 17 d-NGM, after oral administration of NGM in rats and monkeys were also used since they employed essentially the same doses as those used in the chronic toxicity studies in these species.

Comparative exposure of 17 d-NGM in rats and rabbit following SC administration of 17 d-NGM with that of human subjects following application of EVRA is shown in a table 9 below (item 5, vol. 1.page 260, table 4-24):

Table 9

Species	Dose 17 d-NGM (mg/kg)	Duration of dosing	C_{avg} (ng/ml)	AUC_{0-24h} (ng.h/ml)	Human AUC_{0-24h} (ng.h/ml)	Ratio (animal/human)
Rat (F)	25	3 days	394[c]	9456	19.01	497
	75		585.5[c]	14052	19.01	739
	125		1133[c]	27180	19.01	1430
Rabbit (F)	0.025	13 days	0.525[d]	12.60	19.01	0.663
	0.05		1.61d	38.52	19.01	2.03
	0.1		5.45[d]	130.8	19.01	6.88
	0.2		6.23[d]	149.4	19.01	7.86
	0.4		10.1[d]	242.4	19.01	12.8
	0.8		21.88[d]	525.0	19.01	27.6
Rabbit (F)	1.0	13 days	19.45[d]	466.8	19.01	24.6
	2.0		55.60[d]	1334	19.01	70.2
	4.0		81.15[d]	1948	19.01	102
	6.0		99.35[d]	2284	19.01	125

[a] $AUC_{0-24h}=C_{avg} \times 24$

[b] Human AUC_{0-24h} is the mean of 5 clinical studies

[c] Day 3 $C_{avg}= (C_{1.5h} + C_{24h})/2$

[d] Gestation Day 19 $C_{avg}= (GD\ 19\ C_{1.5h} + GD19\ C_{24h})/2$ where $GD19C_{24h}=(GD19C_{1.5h} - GD7C_{1.5h})$

Comparative exposure of 17 d-NGM in rats following oral administration of NGM plus EE with that of humans subjects following EVRA application or therapeutic doses of oral contraceptive products, Ortho-Cyclen and Ortho-TriCyclen (250 ug NGM/35 ug EE) gave a rat/human ratio of 16.0 and 15.1 for transdermal and oral products, respectively. The AUC_{0-24h} for oral products for humans was 19.8 ng.h/ml. The monkey/human ratios were 7.5 and 7.2 when compared to transdermal and oral contraceptive products, respectively.

Absorption, Distribution and excretion: No pre-clinical absorption, distribution and excretion studies have been performed with 17-d-NGM. However, studies have been performed with orally administered lebeled NGM, which is completely metabolized to 17d-NGM by the first-pass effect.
In rats after a single oral dose of 0.6 mg/kg of labeled NGM, average C_{max} of 69.9 ng equiv/ml was reached in 4.8 hours. An average of 5.45 % and 47.9% of the administered radioactivity was excreted in urine and feces in 3 days and only 1% more was recovered the following day.
The highest tissue concentrations of ^{14}C were found in the liver and in decreasing order in the adrenals, adipose tissue and the pituitary. Lower concentrations were found in the kidney, ovary, skin, lungs, oviduct and uterus. Lowest concentrations were found in the brain, muscle and vagina. Peak concentration occurred in most tissues in 3 hours.

Metabolism: The in vitro metabolism of 17d-NGM was investigated in rat hepatic S9 fraction and in human liver microsomes. As shown in table 10 below, in the rat system, hydroxylated metabolites of 17d-NGM were formed and in human microsomes, norgestrel was the metabolite identified.

Table 10

Species	Assay matrix	Metabolites Detected	% detected
Rat	Hepatic S9	17d-NGM	85
		M1, OH-17d-NGM	7
		M2, OH-dihydro 17d-NGM	4
		M4, 3-ketoNGM	3
		M3, OH-norgestrel	<1
Human	Liver microsomes	Norgestrel	11.3
		Uncharacterized metabolites	27.4

In the human liver microsome experiment it was reported that there was a significant correlation (r=0.97) between the extent of 17d-NGM metabolism and cytochrome P450 content which s uggested that cytochrome P 450 is involved in the metabolism of 17d-NGM.

The in vitro and in vivo metabolism of NGM in various animal species and in humans demonstrated that 17d-NGM is the primary metabolite of NGM in rats, monkey and humans. Also differing levels of norgestrel were found in these species, together with small amounts of 3keto-NGM.
Comparative metabolism of NGM in rats, guinea pigs, rabbits, dogs and monkeys is shown in table 11 below:

Table 11

Species	Assay matrix	Metabolite detected	% detected
Rat	Hepatic S9	NGM	72
		M1, 17d-NGM	20
		M2, OH-dihydro-17d-NGM	3
		M4, 3-keto-NGM	2
		M3, OH-norgestrel	2
Rat	Hepatocytes	17d-NGM	108
		norgestrel	1.6
		3-keto-NGM	9.8
Guinea pig	Hepatocytes	17d-NGM	35
		norgestrel	13
		3-keto-NGM	8.2
Rabbit	Hepatocytes	17d-NGM	72

		norgestrel 3-ketoNGM	10 2.1
Dog	Hepatocytes	17d-NGM norgestrel 3-ketoNGM	6.2 10 2.1
Monkey	hepatocytes	17d-NGM norgestrel	78 34

% Detected results are expressed as AUC (ug.min/ml)

Studies conducted in humans using GI mucosa, liver microsomes, endometrial tissue, normal breast cells demonstrated that the major metabolite of NGM was 17d-NMG followed by norgestrel and 3-ketoNGM. The % of 17d-NGM observed with endometrial cancer cell line and malignant breast cell culture were higher and that of norgestrel lower when compared with normal tissue.

In vivo studies with NGM

17d-NGM, 3-ketoNGM and norgestrel were reported in rat serum.
In rabbit serum 14 metabolites were observed. M8 (NGM glucuronide) was 10-30% and M9 (17d-NGM glucuronide) was 5-10%. All other metabolites were less than 5%. In rabbit urine M8 (NGM glucuronide) was 5-10% and M9 (17d-NGM glucuronide) was 10-30% while 17d-NGM, M11 (OH-17d-NGM glucuronide), M12 (oxo-17d-NGM glucuronide) and M13 (norgestrel glucuronide) were less than 5%.
In an other study, rabbit plasma showed only norgestrel (M5) and 17d-NGM (M1, 2 isomers) and Monkey serum contained 17d-NGM, norgestrel and 3-ketoNGM.
Human serum contained 17d-NGM and norgestrel.

Excretion: No excretion studies have been performed following administration of 17d-NGM in animals or in humans. Since both NGM and 17d-NGM are extensively metabolized before they are excreted, results of excretion study after oral administration of labeled NGM are applicable to 17d-NGM. The results expressed as mean percent of radioactive dose recovered post-dose in urine and feces in the rat, rabbit and dog administered a single oral dose of NGM are shown in table 12 below:
Table 12

Total radioactivity

Species	N	Days Post-dose	Urine	Feces	Total
Rat	4	7	5.5	47.9	53.3
Rabbit	4	7	44.0	14.9	58.8
Dog	2	8	14.0	52.2	66.2

In humans a higher percentage was excreted in urine than in feces.

Protein binding: No animals studies have been performed to characterize protein binding of 17-d-NGM, norgestrel and EE. However, protein binding of 17-d-NGM and norgestrel in serum assessed ex-vivo in women dosed with 3 cycles of either Ortho-Cyclen or Ortho-TriCyclen, showed both progestogens to be highly bound to serum proteins (98.3 to 99.0%). The binding of 17-d-NGM did not change significantly during dosing, since it does not bind to SHBG. However, for norgestrel there was statistically significant increase in the percent protein bound from 98.28

to 98.77% following dosing with Ortho-Cyclen and from 98.35 to 99.01 following dosing with Ortho-TriCyclen. The increase was attributed to an increased binding as a result of contraceptive therapy causing increased level of SHBG.

Enzyme inhibition: The ability of 17d-NGM, norgestrel and EE to inhibit the major P450 enzymes in human liver microsomes in relation to their potential to inhibit the metabolism of co-administered drugs was evaluated in vitro. The results expressed as inhibition constants (Ki, uM) are shown in table 13 below:

Table 13

Cytochrome P450 enzyme	17d-NGM	Norgestrel	EE
CYP1A2	34.1	>90	17.7
CYP2A6	>90	40.3	15.8
CYP2C9	11.1	40.6	5-15
CYP2C19	5.9	42.8	14.8
CYP2D6	10.4	>90	11.9
CYP2E1	>90	>90	>90
CYP3A4/5	11.3	51.2	5.78
CYP4A9/11	>90	>90	>90

Note: under pharmacokinetics, steady state concentration of 17d-NGM following dermal application of EVRA in human was reported to be 0.82 ng/ml (table 4-14, item 5/item volume 1/page 240). A value of 0.82 ng/ml represents 2.77 nM. The lowest K_i for 17d-NGM for CYP2C19 is 5.9 uM which is 2130 times greater compared to 2.77 nM. As such under therapeutic conditions there does not seem any possibility of inhibition of a co-administered drug.

Summary:

TOXICOLOGY: All toxicology of 17d-NGM was supported by the toxicity studies conducted for NGM and submitted for the approval of Ortho-Cyclen and Ortho-TriCyclen. These studies consisted of oral subchronic, chronic and carcinogenicity studies in rats, dogs and monkeys. Reproduction studies in rats and rabbits and mutagenicity studies i.e., bacterial and mammalian point mutation assays, chromosomal aberration assay and in vivo micronucleus assay.

Since the only non-compendial component in the AVRA transdermal system is Lauryl lactate, which has not been used previously used in any approved marketed drug product, sponsor was asked to provide information about the safety of lauryl lactate. Sponsor has provided the following published-literature and battery of genotoxicity studies conducted to support safety of lauryl lactate.

Published literature:

A review by the Cosmetic Ingredient Review Expert Panel entitled " Final report on the safety assessment of glycolic acid, ammmonia, calcium, potassium, and sodium glycolates, methyl, ethyl, propyl, and butyl glycolates, and lactic acid, ammonium, calcium, potassium, sodium, and TEA-lactates, methyl, ethyl, isopropyl, and butyl lactates, and lauryl, myristyl, and cetyl lactates.

International Journal of Toxicology 17(Suppl. 1):1-131, 1998. Findings on lauryl lactate are briefly summarized below:

It was reported that lauryl lactate functions as a skin-conditioning agent-emolient. Product formulation data submitted to the FDA in 1997reported that lauryl lactate was used in 13 cosmetic formulations with lauryl lactate concentrations ranging from 0.1% in eye cream to 5% in face cream. Acute oral toxicity of body freshener formulations containing lauryl lactate, LD_{50} in female rats was greater than 7 g/kg. Primary irritation in rabbits using single insult occlusive patch produced minimal to mild irritation with formulation containing 2 to 5% lauryl lactate. In the guinea pig allergic contact sensitization test (Magnusson-Kligman maximization test), it was reported that 72 hours after challenge, none of the animals had reacted to 5% concentration and the irritation index was 0; with the 25% challenge, 30% of the animals reacted (had scores > or = 1), and the irritation index was 1.3. In vivo ocular irritation with 0.1% eye cream was minimal. All the studies described were conducted by ———

Genotoxicity studies: The following studies were conducted the ———— ——— in accordance with FDA Good Laboratory Practices (GLP) regulations.

1. Study DS99035: Evaluation of a Lauryl lactate (as supplied for use in EVRA) in the ———— in the presence and absence of induced rat liver S-9
2. Study DS99037: In vivo test of Lauryl lactate (as supplied for use in EVRA) for the induction of micronucleated polychromatic erythrocytes in mouse bone marrow cells.
3. Study DS99036: Evaluation of Lauryl lactate (as supplied for use in EVRA) in the L5178Y TK +/- mouse lymphoma mutagenesis assay with colony size evaluation in the presence and absence of induced rat liver S-9

The above studies have been reviewed under genotoxicity section.

CARCINOGENICITY: No carcinogenicity studies were conducted with 17d-NGM. Instead in agreement with the Division a PK study was conducted with doses used in the previous rat carcinogenicity study which was conducted to support the approval of Ortho-Cyclen and Ortho-Tri-Cyclen. Results of the PK study demonstrated that rats were adequately exposed to 17d-NGM during the administration of NGM. Also PK study in monkeys using doses similar to that which were used in the 10 year NGM toxicity study demonstrated that monkeys were adequately exposed to 17d-NGM following administration of NGM.

- Overall Interpretation and Evaluation
- Adequacy of the carcinogenicity studies and appropriateness of the test model: Since the rat carcinogenicity study conducted using oral dosing with NGM was accepted for the approval of NGM as Ortho-Cyclen and Ortho-Tri-Cyclen and as adequate exposure to 17d-NGM has been demonstrated with similar dosage in the PK studies, no new carcinogenicity studies with 17d-NGM were requested.

IMMUNOTOXICOLOGY: no studies submitted

REPRODUCTIVE TOXICOLOGY:

Study title: **Developmental toxicity study of RWJ-10553-097 (17-deacetylnorgestimate) administered subcutaneously to female New Zealand white rabbits**
Study No: DS98311, volume 14, page 1
Site and testing facility: R.W.Johnson Pharmaceutical Research Institute, Spring House, PA
GRP compliance: Yes
QA- Reports Yes (*) No ( ):
Lot and batch numbers: RWJ-10553-097
Protocol reviewed by Division Yes ( ) No (*):

Methods:

- Species/strain: Rabbit/NZW
- Doses employed: 0, 1, 2, 4 and 6 mg/kg/day, corresponding to 0, 11, 22, 44, and 66 mg/m^2, respectively based on 2.6 kg rabbit.
- Route of Administration: SC
- Study Design: as shown in table 14 below:

Table 14

Group	Treatment[a]	Dose level[b] mg/kg/day	Concentration mg/ml	# of females
1	Control	0	0	24
2	17d-NGM	1	10	24
3	17d-NGM	2	20	24
4	17d-NGM	4	40	24
5	17d-NGM	6	60	24

[a] administered once daily on gestation days 7-19 at a volume of 0.10 ml/kg
[b] administered in 95% ethyl alcohol
[c] number of naturally mated females (day of mating = day 0 of gestation)

Justification of dose level selection: In an earlier developmental toxicity study NGM and EE in a ratio of 5:1 were administered by gavage at NGM doses of 12, 60 and 300 ug/kg. The only drug-related effect was a high rate of fetal resorption in the mid and high dose. However, systemic exposure to NGM, 17d-NGM and NG after a single oral dose of 300ug NGM + 60 ug/kg EE was below the limit of quantification. Therefore, a dose range-finding study with 17d-NGM using SC route of administration was used. The transdermal route of administration was not used because of the inconsistent absorption due to rapid hair growth and as peak blood levels would not be achieved until at least 24 hours. In the SC dose-finding study doses of 17d-NGM up to 800 ug/kg/day were used and except for possibly increasing irritation at the injection sites, the study did not reveal any maternal toxicity or reproductive effects. However, systemic exposure to 17d-NGM was observed in all pregnant rabbits at all dose levels. Therefore, in the main study as outlined above in the table 14, dose levels of 1, 2, 4 and 6 mg/kg/day were used. The high dose was limited by the solubility of 17d-NGM in alcohol, and the effort to minimize the exposure to ethanol.

- Number of animals/sex/dosing group: as given in table
- Parameters and endpoints evaluated: Clinical observation, mortality, body weight, and food consumption. Post-mortem observation for F_0 females (pre- and post-implantation loss, number of corpora lutea, total implantations, live fetuses by sex and total, number and percent of dead fetuses, number and percent of early, late and total resorptions) and fetal observations (body weight and fetal alterations).

- Statistical evaluations: Bartlett, Dunnett's, Kruskal-Wallis, Dunn's and Fisher's exact tests.

Results:

- Clinical signs: Discoloration, eschar formation, edema and erythema at the injection sites occurred in control and all drug treated groups with no dose-response relationship. Sponsor suggested the irritation due to the vehicle (95% ethyl alcohol) and stated that since the concentrations employed in the main study did not induce a dramatic increase in irritation, where the drug concentrations were much higher than those used in the dose-finding study, the effects seemed likely related to the vehicle and depth of injection.

Mortality: No drug-related deaths were observed.

Body weight: Body weight gains were reduced for the 6 mg/kg dose group during Days 10 through 13 of gestation. Adjusted body weight losses (Day 29 adjusted minus Day 7 body weight) for the drug treated groups were significantly less than that of control group for the 4 and 6 mg/kg groups. There was not dose response relationship and sponsor stated that reason for the differences is not clear. The mean body weight on gestation day 29 was 3752, 3769, 3775, 3742 and 3626 g, respectively for group 1 – 5.

- Food consumption: Food consumption for the 6 mg/kg dose group was significantly reduced for Days 13-16, 7-20 and 7-29 compared to control group.
- Toxicokinetics: given under Pharmacokinetics sub-section (Table # 9)
- Terminal and Necroscopic evaluations:

- In-life observations: are shown in table 15 below:

Summary of reproductive outcome

Table 15

Dose level	0	1	2	4	6
Number of females naturally mated	24	24	24	24	24
Number of females pregnant	24	24	24	23	23
Number of females which aborted	0	2	1	1	0
Number of females that died	0	0	0	0	1
Number of females that delivered early	0	0	0	0	0
Number of females with all resorptions	0	0	0	0	3
Number of females with viable litters	24	22	23	22	19

Summary of reproductive data of adult females is given below:

Table 16

Dose Mg/kg/d	N	Corpora lutea	Implantations	% pre-implantation loss	Live fetuses male	female	total	% Resorptions Early	Late	total	Post-implantation loss
0	22	8.5	8.2	5.4	3.8	4.1	8.0	1.6	1.4	3.0	3.0
1	22	8.4	8.2	2.7	3.6	4.3	7.9	3.3	0.0	3.3	3.3
2	23	8.4	8.1	3.4	3.9	3.7	7.7	3.8	0.9	4.7	4.7
4	22	8.6	8.4	2.4	3.8	3.9	7.7	6.0	2.3	8.2	8.2
6	19	9.4	8.8	7.5	2.6	2.7**	5.4**	32.6**	5.9	38.5**	39.4**

Values are expressed as means for N shown.

- Necroscopic evaluations:
-
- Postmortem examination of adult females showed that while 5/24 and 15/24 females in groups 4 and 5 had placentae firmly adhered to the uterus, none in groups 1, 2 and 3 had this condition.

Fetal parameters:
Fetal body weight: The body weight of both male and female fetuses was lower in the 4 and 6 mg/kg groups. The mean weight (g) for the males fetuses was 43.5, 41.6, 40.7, 35.6** and 31.6**, respectively for groups 1-5. For female fetuses the values were 41.7, 41.2, 39.3, 34.8** and 29.2** g respectively (** $p<0.01$).

Fetal alterations:

Embryo-fetal toxicity was indicated by decreased live fetuses and increased resorptions at 6 mg/kg and dose-related decreased fetal weight at 2 mg/kg and above. In addition embryo-fetal toxicity was indicated by increased fetal variations (reduced ossification of the pubis bone) at all drug-treated levels, and increased malformations at 4 mg/kg and above (cleft palate and paw hyperextension, and paw hyperflexion at 4 and 6 mg/kg dose level. These findings are summarized in table 17 below. Values are expressed as litters (fetuses) affected.

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ON ORIGINAL

Table 17

Group	1	2	3	4	5
Dose level mg/kg/day	0	1	2	4	6
# of litters (fetuses) examined	22 (175)	22 (174)	23 (176)	22 (169)	19 (102)
External observations					
Limbs					
A paw hyperextension	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
A paw hyperflexion	0 (0)	0 (0)	0 (0)	1 (1)	2 (3)
Mouth/Jaws					
A cleft palate	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)
Trunk					
A spina bifida	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
A umbilicus hernia	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Number of litters (fetuses) affected	1 (1)	1 (1)	0 (0)	1 (1)	4 (5)
Soft tissue observations					
Blood vessels					
A innominate absent	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
A malpositioned carotid branch	0 (0)	1 (1)	3 (5)	1 (1)	3 (4)
Heart					
A innominate absent	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Kidneys					
A dilated renal pelvis	1 (1)	3 (6)	1 (1)	4 (4)	2 (2)
Ureters					
A convoluted ureter	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
A retrocaval ureter	0 (0)	0 (0)	2 (2)	1 (1)	0 (0)
# of litters (fetuses) affected	2 (2)	4 (7)	5 (7)	5 (5)	7 (8)
Skeletal observations					
Pelvis					
Incompletely ossified pubis	1 (1)	5 (7)	8 (12)	11 (27)	13 (34)
Unossified pubis	1 (1)	1 (1)	0 (0)	2 (3)	4 (7)
Skull – Bent hyoid	4 (5)	3 (3)	5 (7)	4 (8)	9 (14)
Unossified hyoid	9 (0)	0 (0)	2 (2)	2 (2)	6 (9)
Split palatine	0 (0)	0 (0)	0 (0)	0 (0)	3 (3)

It was concluded that NOAEL for adult females and fetuses is 2 mg/kg and lower than 1 mg/kg, respectively. Malformations were seen at 4 mg/kg and above.

Note: Sponsor stated that the absence of malformations in the fetuses of rats and rabbits dosed with NGM/EE as opposed to findings of malformation caused by 17d-NGM in rabbits is probably the result of the low dose levels tested in the NGM/EE studies and suggested that there is no reason to suspect that 17d-NGM has a greater potential for causing malformations than NGM. On the other hand, one could infer that NGM will be tratogenic at higher doses than those tested previously.

Sponsor has stated citing published literature in labeling under Warning section item # 6 "Hormonal contraceptive use before or during early pregnancy" that extensive epidemiological studies have revealed no increased risk of birth defects (cardiac anomalies and limb reduction defects) in women who have used oral contraceptives prior to pregnancy or during early pregnancy.

GENETIC TOXICOLOGY: 17d-NGM was tested in three in vitro mutagenicity assays (bacterial plate incorporation mutation assay, CHO/HGPRT mutation assay, chromosomal aberration assay using cultured human peripheral lymphocytes) and in one in vivo mutagenicity test (mouse micronucleus assay). 17d-NGM was considered not mutagenic or clastogenic. These studies were reviewed under IND [redacted], respectively. Copies of the reviews are appended.

Genotoxicity studies with lauryl lactate

Study title: In vivo test of lauryl lactate (as supplied for use in EVRA) for the induction of micronucleated polychromatic erythrocytes in mouse bone marrow cells.

Study No: DS99307
Study type (if not reflected in title)
Conducting laboratory and location: [redacted]
Date of study initiation: 1-7-2000
GLP compliance: Yes
Drug, lot #, radiolabel, and % purity: [redacted] Lot:Q0153, AZKO Lot: A-5722 and RWJPRI Lot: 9179N. [redacted]
QA reports : yes (*) No ( )
Formulation/vehicle: liquid dosing form administered i.p.

Methods:

Strains/species/cell line: mouse/CD-1

Dose selection criteria: Maximum tolerated dose

Basis of dose selection: Based on dose finding study findings

Range finding studies: Conducted suing dose levels of 05, 1 and 2 ml/kg body weight, once daily on 3 consecutive days.

Test agent stability: expiration date July 18, 2000

Metabolic activating system: NA

Controls:

Vehicle: The test agent was in liquid form and so no vehicle was required. Vehicle for cyclophosphamide was distilled water.

Negative controls: untreated mice

Positive controls: Cyclophosphamide 80 mg/kg (8.0 mg/ml x 10 ml/kg) by oral gavage

Comments: In the dose finding study, by the end of 3-day observation period, body weight was decreased in female mice by 0.0 %, 17.4%, 17.4% and 18.2% in the untreated, 0.5, 1 and 2 mg/kg dose groups, respectively. The decrease in males was 0.0, 16.1, 19.4 and 13.8%, respectively. The results showed that 2/3 animals of each sex died at the dose level of 2 ml/kg and 2/3 males at the 1 mg/kg dose levels also died. Clinical signs consisted of inactivity, closed eyes, and/or piloerection. All animals treated with test article had 21.6 to 39.5% decreases in PCE

Exposure conditions:

Incubation and sampling times: Mice in the test article group were sacrificed 24 hours after the last dose administration. Those in the positive control group were sacrificed 24 hours after dose administration

Doses used in definitive study: Based on results of dose-finding study, dose levels of 0.125, 0.25 and 0.5 ml/kg body weight was selected for both male and female mice.

Study design: 5 mice/s were used in 5 groups (negative control, test article (0.125, 0.25 and 0.5 ml/kg) and positive control.

Analysis:

No. of replications:

Counting method: number of polychromatic erythrocytes (PCE) and normochromatic erythrocytes (NCE) among 200 erythrocytes (PCE +NCE) per animal was determined. The number of micronucleated polychromatic erythrocytes (MPCE) was determined for 2000 PCE per animal.

Criteria for a valid assay:

1. In the vehicle control, the average number of MPCE/2000 PCE should not exceed 10.
2. In the positive control, the increase in the average number of MPCE/2000 PCE over the average number of MPCE for the vehicle control should be statistically significant
3. At least 5 animals from each sex must be alive at the time of sacrifice.

Criteria for positive results: Test article was considered positive if:

1. The test article showed a positive dose-response trend and a statistically significant increase in the number of MPCE at one or more dose levels over that of the concurrent control
2. In the event there was no positive dose-response trend, at least 2 consecutive test doses must have produced a statistically significant increase in the number of MPCE.

Summary of individual study findings: At the high dose of 0.5 ml/kg, there was there was reduction in the % of PCE by 39.5% for males and 27.1% for females, showing toxicity of the test article.

The mean number of MPCE in 2000 PCE were as shown in table below:

Table 18

Treatment	Mean numbers of MPCE in 2000 PCE	
	24 hours in males	24 hours in females
Negative control	0.4	0.2
Test article doses (0.125-0.5 ml/kg)	0.0-0.2	0.0-0.2
Positive control (CP 80 mg/kg)	25.2*	21.8*

* statistically significant

Study validity: seems valid

Study outcome: lauryl lactate was negative in the micronucleus assay

Study title: Evaluation of a lauryl lactate (as supplied for use in EVRA) in the Salmonella typhimurium/Escherichia coli plate incorporation mutation assay in the presence and absence of induced rat liver S-9

Study No: DS99035

Study type (if not reflected in title)

Conducting laboratory and location: same as for mouse micronucleus assay

Date of study initiation: 11-16-1999

GLP compliance: yes

Drug, lot #, radiolabel, and % purity: drug lots and purity were same as stated for mouse micronucleus assay. The expiration date was 6-18-2000

QA reports : yes (*) No ( )
Formulation/vehicle: Solution in DMSO/DMSO

Methods:

Strains/species/cell line: Salmonella typhimuarium strains TA98, TA100, TA1535 and TA1537. Escherichia coli strain WP2uvrA

Dose selection criteria: Toxicity was evaluated based on 1) decreased reversion frequency, 2) decreased number of viable colonies, and 3) integrity of background lawn i.e. thinning or absence of microcolonies compared to control

Basis of dose selection: based on results of range finding study

Range finding studies: were conducted using strains TA100 and WP2uvrA using 7 doses of test article ranging from ——— ug/plate (one plate/dose), with and without S-9

Test agent stability: not determined

Metabolic activating system: S-9

Controls:

Vehicle: DMSO

Negative controls: DMSO

Positive controls: 2-nitrofluorene, sodium azide, 2-aminoanthracene and methyl methanesulfonate

Exposure conditions: incubated at 37+/-! ^{0}C for approximately 68 hours.

Incubation and sampling times:

Doses used in definitive study: Based on the results of the dose-range finding study, in the first mutation assay following concentrations of test article were used:
Salmonella without activation: 2, 5, 7.5, 10 and 50 ug/plate
Salmonella with activation: 10, 25, 50, 75, and 100 ug/plate
E. coli with and without activation: 100, 200, 500, 750 and 1000 ug/plate

Since the results of the first study were negative, second mutation assay was run using the same treatment method, but with higher doses to confirm results of first assay:
Salmonella without activation: 25, 50, 75, 100 and 250 ug/plate
Salmonella with activation: 50, 75, 100, 250 and 500 ug/plate
E.coli with ad without activation: 500, 750, 1000, 2500 and 5000 ug/plate

Study design: For spontaneous reversion frequency: 500 ul of sterile water or 500 ul of S-9 cofactor mix was added to tubes containing 2.0ml of top agar supplemented with 1X histidine-biotine or 1X tryptophan solution. Immediately thereafter, 100 ul of TA100 or WP2UVRA was added, followed by 100 ul of appropriate test article dose or solvent. Tubes were vortexed, contents poured into agar plate. When top agar was solidified, plates were inverted and incubated at 37+/-1 C for about 68 hours.
Mutation assays were run as above except all Salmonella tester strains and WP2uvrA were used. Positive controls were treated with 100 ul of appropriate stock solution.
To determine viable cells delivered to the assay plates, 250-500 cells were added to top agar supplemented with 10X histidine-biotine or 10X tryptophan solution, processed and incubated as above.

Analysis:

No. of replications:

Counting method: Automatic colony counting for plates with no precipitation and hand count if precipitate interfered with automatic counting. Relative cloning efficiency was determined by comparing corrected viability counts for each dose with the respective solvent control viability counts.

Criteria for positive results: A response was considered to be positive if either strain TA98 or TA100 exhibited a mean reversion frequency that was at lest double the mean reversion frequency of the corresponding solvent control in at least one dose, or if either strain TA1535, TA1537 or WP2uvrA exhibited a 3-fold increase in the mean reversion frequency compared to solvent control in at least one dose. Also response must be dose-dependent.

Summary of individual study findings: Results of both the first and second mutation assays indicated that lauryl lactate did not induce any increase in the number of revertant colonies for any of the tester strains in the presence or absence of induced rat liver S-9.

Study validity: seems valid

Study outcome: Under the conditions of the study, lauryl lactate was negative in the Salmonella typhimurium/Escherichia coli plate incorporation mutation assay (Ames test)

Study title: Evaluation of lauryl lactate (as supplied for use in EVRA) in the L5178Y TK +/- mouse lymphoma mutagenesis assay with colony size evaluation in the presence and absence of induced rat liver S-9.

Study No: DS99036
Study type (if not reflected in title)
Conducting laboratory and location: same as for 2 above genotoxicity studies
Date of study initiation: 12-28-1999
GLP compliance: yes
Drug, lot #, radiolabel, and % purity: same as for above 2 genotoxicity studies
QA reports : yes (*) No ( )
Formulation/vehicle: solution/DMSO

Methods:

Strains/species/cell line: L5178Y TK +/- mouse lymphoma cells, clone 3.7.2C

Dose selection criteria: Cytotoxicity- Coloning efficiency (av. # of colonies per viable count plate x 200/number of cells seeded 200) and relative suspension growth (suspension growth of treated cultures/av. of suspension growth of solvent controls x 100)

Basis of dose selection: Range finding study results

Range finding studies: The concentration of lauryl lactate used in the range finding study were 0.1, 0.5, 1.0, 5.0, 10, 50, 100, 500, 1000 and 5000 ug/ml with and without S-9 activation in order to determine concentrations which would produce 0-100% cytotoxicity. Lauryl lactate was toxic at concentration of 50 and greater in the non-activated system and at concentrations of 500, 1000 and 5000 ug/ml in the activated system.

Test agent stability: not given

Metabolic activating system: S-9

Controls:

Vehicle: DMSO

Negative controls: DMSO
Positive controls: Hycanthone without S-9; dimethylbenz[a]anthracene with S-9
Comments:

Exposure conditions:

Incubation and sampling times: 4 hour treatment in the first assay and 24 hour treatment period in the second confirmatory assay

Doses used in definitive study: Based on the results of the range finding study, mutation assay was performed (4 hour treatment period) at the following lauryl lactate concentrations:

Without activation: 10, 15, 20, 25, 30, 35, 40, 45 and 50 ug/ml
With activation: 20, 40, 60, 80, 100, 125, 150, 200 and 300 ug/ml

Since all responses were negative in this test and Relative total growth (RTG) for the non-activated cultures ranged from ' , and that for the S-9 activated cultures ranged from a confirmatory assay was conducted without S-9 activation with 24-hour treatment period at the following concentrations:
1.0, 10, 15, 20, 25, 30, 35, 40, 45 and 50 ug/ml.
All responses were negative and the RTG for the cultures cloned for mutation selection ranged from

Study design: Cultures were adjusted to $0.3x10^6$ cells/ml. Only cultures having an RSG of approx. 10% or greater were cloned. The mutant frequency (MF) of each culture that was successfully cloned was determined as a function of viable cells forming colonies and calculated as follows:

$MF/10^6$ viable cells = Average No. mutants per (RM) plate/Average No. of colonies in the corresponding VC plates x 200.
The induced mutant frequency was calculated as follows:

IMF = MF of treated cultures – Average MF of solvent control cultures.

Analysis:

No. of replications: 3 plates/dose for colony counting

Counting method: colonies were counted using colony counter. Mutant frequency was calculated as shown above.
Colony sizes were determined by varying the size-setting potentiometer on an colony counter to have 15 size groups.

Criteria for positive results: A response was considered positive if at least one culture had a MF that was 2 times or greater than the average MF of the corresponding solvent control cultures and the response was dose dependent.

Summary of individual study findings: The mutant frequency for the 2 studies was as follows:

		Study # 1	Study # 2
Without activation	Solvent control	11-14	63-66
	LL treated	13-24	39-61

With activation	Solvent control	24-42	
	LL treated	10-50	
Positive control	solvent DMSO	18-19	30-43
	HYC	173-214	244-263
	Acetone solvent	24-28	
	DMBA	77-120	

In study #1 treatment duration was 4 hours while that in study # 2 it was 24 hours.

It was reported that the size distribution for the cultures treated with the positive control, HYC, exhibited an acceptable positive response and colony size distribution i.e. there was greater than 3 times the small size as well as the total number of colonies in the HYC treated cultures in comparison to solvent control cultures.

Study validity: seems valid

Study outcome: Results indicated that under the test conditions, lauryl lactate produced a negative response in cultures treated either in the absence or presence of exogenous metabolic activation and was not considered mutagenic in the mouse lymphoma assay.

Genetic toxicology summary: Both in vivo and in vitro assays demonstrated that lauryl lactate was not clastogenic or mutagenic under the conditions of the asays performed.

Genetic toxicology conclusions: Lauryl lactate is not genotoxic

SPECIAL TOXICOLOGY STUDIES: One month dermal toxicity study using transdermal contraceptive system in rabbits and sensitization study in guinea pig. The rabbit toxicity and guinea pig sensitization studies were reviewed under IND respectively. Copies of the review are appended.

In addition toxicity of lauryl lactate, Lot 3890 was studied by acute oral administration in rats, and primary eye irritation in rabbits. It was reported that a dose of 5 ml/kg was not considered toxic in male and female albino rats.

In the rabbits lauryl lactate was tested at 10% dilution with propyl glycol. A single intraocular application of 0.1 ml of sample produced no irritation in rabbit treated eyes when compared to contra-lateral untreated eyes.

OVERALL SUMMARY AND EVALUATION:

Introduction: Ortho-Evra is a combination transdermal contraceptive patch, which contains norelgestromin (17D-NGM) as the progestin and ethinyl estradiol as the estrogen. It is to be applied once a week for 3 weeks followed by one patch-free week.

17-deacetylnorgestimate is the primary active metabolite of norgestimate, the progestin component of the oral contraceptive products Ortho-Cyclen and Ortho-Tricyclen which were approved by FDA on 12-29-1989 and 7-3-1992 under NDAs 19-653 and 19-697, respectively. 17d-NGM rather than NGM was chosen as the progestin in EVRA system mainly because complete metabolism of norgestimate to 17d-NGM could not be assured with transdermal application.

Clinical studies have demonstrated that EVRA transdermal contraceptive system is highly effective, with an overall Pearl Index of 0.88 compared to overall Pearl Index of 2.18 for Triphasil (LNG/EE tablets). Since NGM has been approved under 2 NDAs for contraception, the safety of 17d-NGM is established.

Safety Evaluation: Based on extensive clinical experience with both NGM/EE and 17d-NGM/EE, there is no obvious safety concern. Only adverse finding was teratogenic effect of 17d-NGM observed in rabbits.

Clinical Relevance of Safety Issues: Although 17d-NGM exhibited teratogenic potential in rabbits, it was observed at dose levels, which gave a very high systemic exposure compared to that observed with EVRA. This safety concern is further mitigated by the extensive clinical experience with NGM/EE.

Other Clinically Relevant Issues: none

Conclusions: Pharmacology studies with NGM/EE and 17d-NGM indicate that the pharmacological effects of EVRA are equivalent to those of NGM/EE. EVRA did not induce sensitization in guinea pig and 17d-NGM did not show mutagenic potential in a series of mutagenicity studies. 17d-NGM did cause dose-related malformations in fetuses of rabbits exposed to high subcutaneous doses, which gave high multiples of systemic exposure compared to that observed with application of EVRA. Although no toxicity and carcinogenicity studies were conducted with 17d-NGM, PK bridging studies demonstrated that animals were adequately exposed to 17d-NGM in studies conducted with NGM/EE to support the safety of Ortho-Cyclen and Ortho-TriCyclen, which were approved on 12-29-1989 and 7-3-1992 under NDAs 19-653 and 19-697, respectively. Also the metabolism, distribution and excretion profiles of EVRA in women were considered to be comparable to those observed after oral administration of NGM/EE. Thus the studies in animals on 17d-NGM/EE and NGM/EE along with clinical experience with EVRA and oral use of NGM/EE demonstrate that the use of EVRA at the proposed contraceptive dose is safe.

Communication Review:

- Labeling Review (NDA): The label needs to be modified to reflect the following changes:

The title Carcinogenesis should be changed to Carcinogenesis, Mutagnesis, Impairment of Fertility.

It should be stated that no carcinogenicity studies were conducted with 1-deacetylnorgestimate. However, bridging PK studies were conducted using doses of NGM/EE which were used previously in the 2-year rat carcinogenicity study and 10 year monkeys toxicity study to support the approval of Ortho-Cyclen and Ortho-TriCyclen under NDAs 19-653 and 19-697, respectively. These studies demonstrated that both rats and monkeys were to a good multiples of the human exposure with the proposed AVRA transdermal contraceptive system.

17-deacetylnorgestimate was tested in in-vitro mutagenicity assays (bacterial plate incorporation mutation assay, CHO/HGPRT mutation assay, chromosomal aberration assay using cultured human peripheral lymphocytes) and in one in vivo mutagenicity test (mouse micronucleus assay) and found to have no genotoxic potential.

Under the subtitle Pregnancy, it should be stated that 17-deacetylnorgestimate was tested for its reproductive toxicity in a rabbit developmental toxicity study by the SC route of administration. Doses of 0, 1, 2, 4 and 6 mg/kg body weight, which gave systemic exposure of 20 to 120 times the human exposure with EVRA, were administered once daily on gestation days 7-19. Malformations (paw hyperextension and hyperflexion) at 4 and 6 mg/kg and cleft palate at 6 mg/kg were reported.

- Investigator's Brochure/Informed consent review (IND):

RECOMMENDATIONS: Based on the pre-clinical and extensive clinical experience with Ortho-Cyclen and Ortho-TriCycle (NGM/EE combination) as oral contraceptives and preclinical and clinical studies conducted with 17-deacetylnorgestimate, Pharmacology recommends approval of 17-deacetylnorgestimate/EE transdermal contraceptive system, EVRA.

Internal comments: none
External Recommendations (to sponsor):
Draft letter Content for Sponsor: as stated under labeling review
Future development or NDA issues: none
Reviewer signature/team leader signature [Concurrence/Non-concurrence]

Reviewer (Krishan L. Raheja) Team leader (Alex Jordan)

cc:

Original NDA 21-180
HFD-580
HFD-580/A.Jordan/K.Raheja/J.Mercier

Draft date (# of drafts):
Memorandum of Non-concurrence (if appropriate, attached):
Addendum to review (if necessary):
Appendix/attachments: Copies of appropriate IND reviews

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Krishan L. Raheja
11/7/01 03:14:46 PM
PHARMACOLOGIST

Laurie McLeod
11/7/01 03:43:48 PM
PHARMACOLOGIST
signing on behalf of Alex Jordan

APPEARS THIS WAY
ON ORIGINAL

PHARMACOLOGIST REVIEW OF GLP EIR
(CP 7348.808)

FIRM NAME: Ortho-McNeil Pharmaceutical, Inc.
(dba: The R. W. Johnson Pharmaceutical Research Institute)
CITY, STATE: Spring House, PA

QUARTER/FYASSIGNED: 3rd QTR/FY'99
EI DATE(S): 1/16-29/01

CFN: 2522433
DISTRICT OFFICE: Philadelphia, HFR-CE150

INVESTIGATOR(S):
1. Mike M. Rashti, HFR-CE150
2.
3.

INSPECTION TYPE:	X	ROUTINE SURV.	__	DIRECTED
FDA-483 ISSUED:	X	NO	__	YES
LETTER TO ISSUE:	X	NONE	__	PI LETTER
	__	WARNING LETTER	__	REJECTION OF STUDY

DATE EIR REC'D DSI: 02/26/01
DATE EIR REC'D BY REVIEWER: 02/28/01
1ST DRAFT REVIEW COMPLETED: 05/01/01

This review evaluates the referenced Establishment Inspection Report (EIR) and determines the FDA's final classification. CDER's Division of Scientific Investigations (HFD-45), CDER review divisions, and FDA field personnel use this information both for determining action on the audited non-clinical toxicity studies and for monitoring this nonclinical testing facility.

The master schedule collected during the inspection was used by Investigator Rashti to select the following studies for review:

STUDIES AUDITED DURING THIS INSPECTION:

1. IND: [redacted]
   DRUG: as stated in title of study
   REV DIV: HFD-580
   STUDY #: DS98311
   STUDY TITLE: Developmental Toxicity Study of RWJ-10553-097 (17-Deacetylnorgestimate) Administered Subcutaneously to Female New Zealand White Rabbits (Study DS98311)
   FINAL REPORT DATE: 09/15/99

2. IND: [redacted]
   DRUG: RWJ-270201-162
   REV DIV: HFD-530
   STUDY #: DS99318
   STUDY TITLE: Seven-Day Intravenous Toxicity Study of RWJ-270201-162 in Rats (Study DS99318)
   FINAL REPORT DATE: 02/25/00

BACKGROUND:

Ortho-McNeil Pharmaceutical, Inc., is a Delaware corporation, with the website http://www.ortho-mcneil.com This website describes Johnson & Johnson as "our parent company".

The R. W. Johnson Pharmaceutical Research Institute is a division of Ortho-McNeil Pharmaceutical, Inc. In addition to this Pennsylvania nonclinical testing facility, The R. W. Johnson Pharmaceutical Research Institute has another such facility in New Jersey.

The last three GLP inspections at this Pennsylvania facility known to CDER resulted in the following final classifications:

FY	DONE	TYPE	CLASS.	CENTER
1/90	11/06/89	S&C	VAI-1	CDER
4/93	11/16/93	S&D	VAI	CDER
1/96	06/02/97	S	NAI	CDER

DISCUSSION:

The EIR consists of a summary of findings, discussion of the audited studies, and reviews of the firm, its personnel, in house quality assurance unit, facilities, equipment, facility operations, master schedule, computer usage, analysis of test and control articles, care of test and control articles, and maintenance of records and reports. To the EIR are appended 32 exhibits, including the master schedule, protocols and final reports for the two audited studies, selected standard operating procedures (SOPs), a list of contract laboratories, and an organizational chart for the firm.

As no studies were ongoing during the inspection, Investigator Rashti could not observe animal care first hand. He inspected SOPs for animal care and inspected and collected as exhibits the minutes of the last two meetings of the Institutional Animal Care and Use Committee.

If the master schedule was created as an electronic record, this electronic record is the raw data. The master schedule for the last two years was collected as a hardcopy printout. I cannot determine whether this is a printout of the entirety of the electronic record, or whether it is a report showing selected fields of the electronic record. If at the next inspection the investigator chooses to collect hard copy rather than collecting the electronic record itself, it would he helpful if such information is supplied.

No departures from protocols or GLPs were noted during the facility inspection and the review of the selected studies.

No FDA-483 was issued.

RECOMMENDATIONS:

1> The two studies that were audited are acceptable for review in support of regulatory decisions by the Agency.

2> Routinely reinspect in two years.

RECOMMENDED HQ CLASSIFICATION:

Reviewer: /S/

Charles A. Snipes, Ph.D.
Pharmacologist

Supervisory Concurrence:

Concur: CTV Date: 5/3/01

Nonconcurrence: _____: Date: _____
(See attached supervisory memorandum)

CFN : 2522433
FEI : 2522433
Inspection Conclusion : NAI (No action indicated)
District Recommendation : NAI
Final HQ Classification : NAI

cc:

HFA-224
HFD-45
HFD-48/Fujiwara(3)/Snipes/CF

HFR-CE100
HFR-CE150/Rashti
DSI/GBIB: CAS: RWJ-1-Rev
Draft: CAS: 05/01/01
Review: TKF: 05/02/01
Review: CTV: 05/03/01
Final: CAS: 05/03/01

APPEARS THIS WAY
ON ORIGINAL

NDA 21-180

ORTHO EVRA®
(norelgestromin/ethinyl estradiol) Transdermal Patch

R.W. Johnson Pharmaceutical Research Institute
1, 4S

PM: Jennifer Mercier
HFD-580
7-4260

Submission Date: December 21, 2000
Primary Goal Date: October 21, 2001
Secondary Goal Date: December 21, 2001

/S/

CAC/ECAC Report

N/A