Chronic Maternal Blues Raise Childs' ADHD Risk

BY DIANA MAHONEY New England Bureau

BOSTON — A diagnosis of maternal depression any time between 1 year before and 9 years after giving birth is a risk factor for attention-deficit/hyperactivity disorder in school-age children, according to a study presented at a meeting of the Society for Research in Child Development.

In addition, the likelihood of an attention-deficit/hyperactivity disorder (ADHD)

ACTIVELLA®

1.0 mg/0.5 mg 0.5 mg/0.1 mg

thindrone acetate) tablets

diagnosis in children is directly related to the chronicity of depression in the mother, said Anne Guevremont, M.Ed., a research fellow at the Manitoba Centre for Health Policy at the University of Manitoba, Winnipeg

Although previous studies have linked maternal depression to ADHD in children, none have specifically investigated whether and to what degree the timing of maternal depression has an impact on the relationship, Ms. Guevremont said.

Through computerized health care user files from the Manitoba health department, Ms. Guevremont and senior researcher Marni Brownell, Ph.D., reviewed data on 12,323 children born between April 1993 and March 1994 whose mothers were living in Manitoba the year before the child's birth and for whom follow-up information was available until the child was 7-9 years old.

The investigators ascertained the presence of maternal depression by hospital or physician claims for this diagnosis and cat-

antity and quality of breast milk. Detectable amounts of estrogens have been identified in the milk of thers receiving this drug. Caution should be exercised when Activella is administered to a nursing

quartity and quality of breast milk. Detectable amounts of estrogens have been identified in the milk of mother: **H. Pediatric Use** Activelia is not indicated in children. **L. Geratric Use** Activelia is not indicated in children. **L. Geratric Use** Activelia is not indicated in children. **L. Geratric Use** Activelia is not indicated in children. **L. Geratric Use** Activelia is not indicated in children. **L. Geratric Use** Activelia is not indicated in children. **L. Geratric Use** Activelia is not indicated in children. **L. Geratric Use** Activelia is not indicated in children. **L. Geratric Use** Activelia is not indicated in children. **L. Geratric Use** Activelia is not indicated in children. **L. Geratric Use** Activelia is not indicated in children. **L. Geratric Use** Activelia is not indicated in the estrogen-ubject opeasit substudy of the Women's Health Initiative (WH) study. 44% (n–7.320) were 65–74 years of age, Nille 6.6% (n=1.095) were 75 years and over. There was a higher relative risk (CMPM sy splacedo) in on-fatal stroke and invosive breast cancer in women 75 and over compared to women is seath inflative Memory Study (WHIMS), a substudy of WH, a population of 4.522 hysterectomized women, aged 65 to 79 years, was randomized to DE/MPA (p255 mgl.25 mgl.20 hysterectomized women, aged 65 to 79 years, was randomized to DE/MPA wsplacebol of probable dementia was 2.05 (p5% G 1.21-3.48), the absolute risk (DE/MPA vsp. placebol) or posabil dementia was 2.05 (p5% G 1.21-3.48), wore myler of subjects in the estrogen-alone substudy of WHI.46% (n=-4.943) were 65 years and over, while 71% (n=-767) were 75 years of age compared to women 75 years and ower. He estrogen-alone WHIMS substudy, a population of 2.947 hysterectomized women, aged 65 to 79 years, was randomized to C5 (D25 mg daily or placebo. After an arearge follow-up of 52 years, the relative risk (Cz xsplacebo) of probable dementia was 1.46 (FS% (G 0.0352.66)). T

Women, (See BOXED WARNINGS and WARNINGS, Dementia.) AUCRESE REACTONS See BOXED WARNINGS, and WARNINGS, Dementia.) AUCRESE REACTONS See BOXED WARNINGS, MANNINGS and PRECAUTIONS. Because clinical trials are conducted under widely avaying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse vents that appear to be related to drug use and for approximating rates. Adverse events product with Activella 1.0 mg/0.5 mg by investigators in the Phase 3 studies regardles of causality assessment are shown in Table 6. roximating rates. ents reported with Activella 1.0 mg/0.5 mg by investigators in the Phase 3 studies regardless assessment are shown in Table 6.

TABLE 6: ALL TREATMENT-EMERGENT ADVERSE EVENTS REGARDLESS OF RELATIONSHIP

	Endome	etrial	Vasomotor		Osteoporosis	
	Hyperplasia Study		Symptoms Study		Study	
	(12-Mol			(3-Months) (2 Year		
	Activella	1 mg E2	Activella	Placebo	Activella	Placebo
1	1.0 mg/0.5 mg	1 mg ca	1.0 mg/0.5 mg	1 100000	1.0 mg/0.5 mg	1 10000
	(n=295)	(n=296)	(n=29)	(n=34)	(n=47)	(n=48)
Body as a Whole	. ,	. ,		. ,	. ,	
Back Pain	6%	5%	3%	3%	6%	4%
Headache	16%	16%	17%	18%	11%	6%
Digestive System						
Nausea	3%	5%	10%	0%	11%	0%
Gastroenteritis	2%	2%	0%	0%	6%	4%
Nervous System						
Insomnia	6%	4%	3%	3%	0%	8%
Emotional Lability	1%	1%	0%	0%	6%	0%
Respiratory System						
Upper Respiratory Tract						
Infection	18%	15%	10%	6%	15%	19%
Sinusitis	7%	11%	7%	0%	15%	10%
Metabolic and Nutrition						
Weight Increase	0%	0%	0%	0%	9%	6%
Urogenital System						
Breast Pain	24%	10%	21%	0%	17%	8%
Post-Menopausal Bleedi		15%	10%	3%	11%	0%
Uterine Fibroid	5%	4%	0%	0%	4%	8%
Ovarian Cyst	3%	2%	7%	0%	0%	8%
Resistance mechanism						
Infection Viral	4%	6%	0%	3%	6%	6%
Moniliasis Genital	4%	7%	0%	0%	6%	0%
Secondary Terms						
Injury Accidental	4%	3%	3%	0%	17%*	4%*
Other Events	2%	3%	3%	0%	6%	4%

Juding one upper extremitly fracture in each group prese events reported with Activella 0.5 mg/0.1 mg by investigators during the Phase 3 study ardless of causality assessment are shown in Table 7. TABLE 7: ALL TREATMENT-EMERGENT ADVERSE EVENTS REGARDLESS OF RELATIONSHI REPORTED AT A FREQUENCY OF ≥ 5% WITH ACTIVELLA 0.5 MG/0.1 MG

	Activella	Placebo	
	0.5 mg/0.1 mg		
	(n=194)	(n=200)	
ody as a Whole			
Back Pain	10%	4%	
Headache	22%	19%	
Pain in extremity	5%	4%	
igestive System			
Nausea	5%	4%	
Diarrhea	6%	6%	
espiratory System			
Nasopharyngitis	21%	18%	
rogenital System			
Endometrial thickening	10%	4%	
/aginal hemorrhage	26%	12%	

The following adverse reactions have been reported with estrogen and/or progestin therap **1. Cenitourinary system** Changes in vaginal bleeding pattern and abnormal withdrawal b or flow, breakthrough bleeding, spotting, dysmenorthea, increase in size of uterine leionry vaginits, including vagina's change in anounch to cervical secretion; changes in estropion; premenstrual-like syndrome; cystilis-like syndrome; ovarian cancer: endometric advonterid

Calopenti, pointease andometrial cancer. 2. Breasts Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes

2. breast cancer.
3. Cardiovascular Deep and superficial venous thrombosis: pulmonary embolism; thrombophlebitis; myocardial infaction, stoke; increase in blood pressure.
4. Gastrointestinal Nausea, vomiting; changes in appetite; cholestatic jaundice; abdominal pain/cramps; finaturence; bloading; increased incidence of galibladder disease; pancreatitis; enlargement of hepatic hemannings. Italiumice, wooming, and the many persist when drug is discontinued; erythema multiforme; **5. Skin** Chicasma or melasma that may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; seborrhea; hirsutism; itching; skin rash:

pruritus. 6. Eyes Relinal vascular thrombosis, intolerance to contact lenses. 7. Central nervous system Headache, migraine, dizzinese, mental depression; chorea; insomnia nervousness, mood disturtances; initiability; exacerbation of epilepsy, probable dementia. 8. Miscellaneous increase or discrease in weight; aggravation of portphylic; edema; leg cramps; changes in libiotic, fatigue; reduced carbohydrate loterance; anphylactohidranaphylactic reactions; hypocalexemia; exacerbation of asthma; increased triglycerides; back pain; arthralgia; mylagia.

IDDCalational, order closen to essential, increase vegation of a close of ACTIVELLA is a registered trademark of Novo Nordisk FemCare AG

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egorized the depression into one of five groups according to the child's age at the time of the mother's diagnosis: within 1 year before birth, within 1 year after birth, between 1 and 3 years old, 4-6 years old, and 7-9 years old.

Approximately 36% of the mothers in the study had a diagnosis of depression during at least one time period, Ms. Guevremont reported in a poster presentation. Among the children, approximately 5% had a physician diagnosis of ADHD when they were 7-9 years old, she said.

With respect to chronicity, the investigators considered each time period in which a mother had a diagnosis of depression and counted the total number of years that the mother had the diagnosis outside of that time period, according to Ms. Guevremont. "Approximately 16% of the mothers had a depression diagnosis in 1 year only, while 8% of the mothers received a depression diagnosis in 2 years and 12% in 3 or more years," she said.

In analyses of the effect of the timing and chronicity of maternal depression on child ADHD, children with depressed mothers were approximately 1.5-2 times more likely to have an ADHD diagnosis than children of nondepressed mothers, said Ms. Guevremont, noting that the odds ratio was highest, at 2.18, for mothers diagnosed with depression in the year before the child's birth. This finding "confirms the need to look for maternal depression at every stage of motherhood, including the prenatal period," she said. "The prenatal period is an excellent time to screen for depression, as the vast majority of mothers seek prenatal care before their child's birth."

In addition, the chronicity of depression was significant in each model, and the odds of a child being diagnosed with ADHD were higher for each additional year a mother was diagnosed with depression, regardless of the timing of the diagnosis, said Ms. Guevremont. The interaction between chronicity and timing was significant among children whose mothers were diagnosed in the year before birth, in the year after birth, or when the child was between 1 and 3. Children whose mothers were diagnosed during these periods and who had longer durations of depression were most vulnerable to an ADHD diagnosis, the results showed.

"Clearly, the number of years with a depression diagnosis is particularly important, and should be taken into consideration by clinicians caring for both mothers and their children," Ms. Guevremont said. "The earlier depressed mothers are recognized and treated, the better for the health of both the mother and her children. Intervention at multiple time periods is possible and needed." For example, in addition to prenatal screening, "another opportunity for screening is when mothers seek physicians for the children's behavior problems," she said.

The study is limited by the potential for underreporting of both maternal depression and child ADHD, Ms. Guevremont noted. "Some physicians may not know a mother is depressed and therefore would not diagnose the condition if symptoms are not reported," she stated.

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Rx Only (For full Pres scribing Information and Patient Information, visit www.activella.com.) CARDIOVASCULAR AND OTHER RISKS Estrogens with or without progestins should nob used for the prevention of cardiovascular diseases or dementia. (See CUINCIAL STUDIES in prescribing information and WARNINGS, Cardiovascular disorders and Dementia). The estrogen plus progestin substudy of the Wonner's Health initiative (WH) reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary entoli, and dee yean thrombosis in postmenopausal women (SD to 79 years of age) (Juring 56 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with methoxyprogestence acatelle (WH2 CS and per visit, relative to facebos, Csee CUINCIAL STUDIES in prescribing information and WARNINGS, Cardiovascular disorders and Malignant neoplasms, *Breast Cancer*.) The estrogen-alone substudy of the WH reported increased risks of stoke and deep yean thrombosis (IOV) in postmenopausal wome (S0 to 79 years of age) during 6.8 years and 7.1 years, respectively of treatment with oral conjugated storgens (CE 0.625 mg) er day, relative to placeho, Csee CUINCIAL STUDIES in prescribing information and WARNINGS, Cardiovascular disorders.) The Women's Health Initiative Memory Subuty (WHINS), a substudy of the WH study, reported increase) risks of developing probable dementia in postmenopausal vomen 65 years of age or day ed uning 4 years of treatment with CE 0.625 mg anomined with MPA 2.5 mg and during agelies to yourger postmenopausal women. (See CUINCIAL STUDIES) in prescribing information whether this finding agelies to yourger postmenopausal women. (See CUINCIAL STUDIES) in prescribing information whether this information age or day end and years of the dement with CE 0.625 mg anomined with MPA 2.5 mg and during agelies to yourger postmenopausal women. (See CUINCIAL STUDIES) in prescribing intervices in prescribin intervices in prescribing intervices in prescrib CARDIOVASCIII AR AND OTHER RISKS

substudy of the WH study, reported increased risk of developing procease dementia in postmenopause women 65 years of age or older during 4 years of treatment with CE 0.625 mg alone, relative to placebo. It is unknown whether this finding applies to yourgen postmenopause) women. (See CLINCEAL STUDIES in prescribin information, WARNINGS, Dementia and PRECAUTIONS, Geriatric Use.) Other does do roal conjugate estogens with medroxyprogestereme actuate, and other combinations and docage forms of estogens and progestims were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these trials, estrogens with or without progestims should be prescribed at the lowest effective doces and for the shortest duration consistent with treatment quals and risks for the individual woman. NDICATIONS AND USAGE Activella 1.0 mg/0.5 mg and 0.5 mg/0.1 mg are indicated in women who have a utenus for the:
 Treatment of moderate to severe vasomotor symptoms associated with menopause.
 Prevention of postmenopausal obsoporosis. When prescribing solely for the prevention of postmenopausal edisconcrisis themas hould not be considered for the prevention of postmenopausal edisconcrisis.

Tave a utenus for the: 1. Treatment of moderate to severe vascondor symptoms associated with menopause. 2. Prevention of postmenopausal osteoprorsis. When prescribing solely for the prevention of postmenopausal osteoprovisa, the ray should only be considered for women at significant risk of osteoprorsis and non-estrogen medications should be carefully considered. The mainstays for decreasing the risk of postmenopausal osteoprovisa are weight bearing exercise, adequate calcium an vitamin D Intake, and when indicated, pharmacologic therapy. Postmenopausal women require an average of 1500 mg/day of elemental calcium. Therefore, when not contraindicated, calcium supplementation may be height for women with suboptimal diletary intake. Vitamin D supplementation of 400-800 U/day may also be required to ensure adequate daily intake in postmenonausal women.

Support mentation of non-our lower may work to be a support of the should be considered. <u>CONTRAINDICATIONS</u> Activella should not be used in women with any of the following conditions: 1. Undiagnosed atomormal genetal bleeding. 2. Known, or suspected, or history of cancer of the breast. 3. Known or suspected estrogen-dependent neoplasia. 4. Active deep wini thrombosis, pulmorary embolism, or history of these conditions. 5. Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial interaction).

Infarction). 3. Liver dysfunction or disease. 7. Known hypersensitivity to the ingredients of Activella 1.0 mg/0.5 mg or Activella 0.5 mg/0.1 mg. 8. Known or suspected pregnancy. There is no indication for Activella in pregnancy. There appears to be tittle or no increased risk of birth defects in children bom twomen who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy. **Gee PRECAUTIONS**.)

WARNINGS See ROXED WARNINGS.
1. Cardiovascular disorders Estrogen-plus-progestin therary has been associated with an increased risk of myocardial infarction as well as stroke, venous thrombosis and pulmonary embolism. Estrogen-alone therary has been associated with an increased risk of stroke and deep vein thrombosis (D/T). Should any of these evenils occur or be suspected, estrogens should be discontinued immediately. Risk harbs for an terih vascuid mässes (e.g., hypertension, diabetes mellits). Koacous use, hypercholesterolemia, and obeshy and/or venous thromboentolism (e.g., personal history or family history of VTE, besky, and systemic Luues erytheratiouss) should be maraged appropriately.
a. Stroke in the estrogen plus progestin substudy of the Women's Health Initiative (WH), a statistically significant increased risk of stroke vene reported in women receiving CEMPA Occursching information.
In the estrogen alone substudy of the WHI, a statistically significant increased risk of stroke vene streported in women receiving DeLeMPA of U.Y. Statistically significant increase in risk was demonstrated after the firstly arean downstrated in year one and persisted.
Decompany heart disease in the estrogen-plus progestin sub-study of WHI, no statistically significant increase in CHB enersiste in first ward and examinated in year one and terestid.
L. Oromary heart disease in the estrogen-plus progestin sub-study of WHI, no statistically significant increase in cellewing estimated in year one, and terestid.
L. Oromary heart disease in the estrogen placebo (29 vs. 33 pr 10,000 women-years). The increase in relative risk was demonstrated in year one and terestid.
L. Oromary heart disease in the ventomer exerciving placebo (24) west sported in women receiving estrogen substudy of WHI, no setallist (20) west sported in women receiving estrogen alone compared to placebo (29 vs. 33 pr 10,000 women-years). An increase in relative maximum and thand than than there to ward esce

ie estrogen-atone substudy of WHI, no overall effect on coronary disease (CHD) events was reported in receiving estrogen alone compared to placebo. (See CLINICAL STUDIES in prescribing matrice).

In review recent recently excepted rative compared to practice, See Currents Structures and the compared to practice of the presention of configuration of the compared to practice of the compared to the

and go trajuspective function that in their to increase the risk on finitial importance interval interval of the tempolarity of tempolarity of the tempolarity of te

DefDUS to provinge a minimumation. **2. Maignant neoplasms a. Breast cancer** in some studies, the use of estrogens and progestims by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the CE/MPA substudy of the WH study (see CLINICAL STUDIES in prescribing information). The results from observational studies are generally consistent with

STUDEs in prescribing information. The results from observational studies are generally consistent with those of the WH clinical trial. Observational studies have also reported an increased risk of breast cancer for estrogen-plus-progestin combination threagy, and a smaller increased risk for expension the area of use. For both findings, the excess risk increased risk duration of use, and appeared to return to baseline over adout free years after stopping treatment (only the observational studies) have exubantial data on risk after stopping). In these studies, the risk of breast cancer was greater, and became apparent earlier, with estrogen-plus-progestin combination therapy as compared to estrogen-alone therapy. However, these union disputies are trained in the risk of breast cancer more different estrogeners or among different estrogener plus-progestin combinations, doess, or routes of administration. In the estrogen-plus-progestin combination in the risk of breast cancer among different estrogener an increased risk of breast cancer. In this substudy, prior use of estrogen alone or estrogen-plus-progestin combination hormore therapy was reported by 20% of the women. The relative risk of imaxies breast cancer was 12.4 (69% NG 1.10-1.54), and the absolute risk was 41 vs. 32 cases per 10.000 women-years. If oscillation rolowers and the risk of imaxies breast cancer was 1.86, and the absolute risk was 46 vs. 25 cases gene 10.000 women-years for esting only the redistive risk of imaxies breast cancer vas 1.08, and the absolute risk was 40 vs. 36 cases per 10,000 women-years in the progest in combination breases the progest in combination breases the progest in combinetion brease therapy. The redistive risk of imaxies breast cancer vas 1.80, and the absolute risk was 40 vs. 25 cases per 10.000 women-years of the strong-years of absolute risk vas 41 vs. 36 cases per 10,000 women-years in the relative risk of imaxies breast cancer vas 1.80, and the absolute risk was 45 vs. 25 cases per 10,000 women-

estrogen plus progestin compared with placebo. In the WH trial, invasive breast cancers were larger and diagnosed at a more advanced stage in the estrogen-plus-progestin group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognetic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups. In the estrogen-ations substudy of WH at an average of 71 years of follow-up, CE (0.625 mg daily) was not associated with an increased risk of invasive breast cancer (RR 0.80, 55% nO 0.52-1.04). In a con-year trial among 1, 176 women who received either unopposed 1 mg estadol or a combination of 1 mg estradol plus one of three different doses of NET 0, 10, 253, and 0 5 mg), seven new cases of breast cancer were diagnosed, two of which occurred among the group of 256 women treated with 1 mg estradiol().1 mg NETA.

estradiol().1 mg NETA. The use of estrogen alone and estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a health care provide and perform monthly breast self-examinations. In addition mammography examinations should be scheduled based on patient age, risk factors, and prior

examinations by a nearly call provider and period minimum groups an examination shown in adultable mammography examinations should be scheduled tassed on patient age, risk factors, and prior mammography examinations should be scheduled tassed on patient age, risk factors, and prior mammography examinations should be scheduled tassed on patient age, risk factors, and prior scheduler tassed in the scheduler tassed on patient age, risk factors, and prior scheduler tassed in the scheduler tassed on patient age, risk factors, and prior scheduler tassed in the scheduler tassed in the scheduler tassed task in the scheduler with a scheduler tassed in the scheduler tassed task in the scheduler with an increased risk of robot 20 to 210 dig treater than in nonzess associated with prior scheduler tassed in the scheduler tassed task in the scheduler with an increased risk of 15- to 24-hold for five to ten years or more. This risk has been shown to persist for at least 8 to 15 years after scheduler paties in a different endomertial risk profile than synthetic scheduler tassed treating endometrial scheduler tassed scheduler tassed task in the prior scheduler tassed treating scheduler patiest in a different endometrial risk profile than synthetic scheduler tassed treating scheduler persiste tor recomming abornal vaginal bledning. There is no evidence that the use of natural schedulers results in a different endometrial risk profile than synthetic scheduler tassed tassed tassed tassed tassed tassed the scheduler tassed task in the scheduler task in the extreme scheduler tassed task in the scheduler tassed task in the scheduler task in the sc

Cl 121-349. The abouter risk of probable dementia for CEMPA vs. placebo was 45 vs. 22 cases per 10.000 vormer-years. In the estrogen-alone substudy, after an average follow-up of 52 years. 29 vormen in the estrogen-alone group and 19 vormer in the placebo you you were diagnosed with probable dementia. The relative risk of probable dementia for CE alone vs. placebo was 1.49 (950, 00.032). (b) he about the risk of probable dementia the CE alone vs. placebo was 1.49 (950, 00.032). (b) he about the risk of probable dementia the VE alone vs. placebo was 1.49 (950, 00.032). (b) he about the risk of probable dementia the VE alone vs. placebo was 1.76 (950, 01.032). (b) he about the risk of probable dementia was 1.76 (950, 01.192-260). Since both substudies were conducted in vormen ayees 50 vg. 1 to you whether these inflings apply to younger postmeropausal women. (See **DOXED WARNINGS and PPECAUTIONS, Geriatric Use.) 4. Calibladder classes** A two-16 our to foll increase in the risk of gailbalder disease requiring surgery in postmeropausal women relative risk of protable distrom may lead to sever hypercalcenain in patients with threast cancer and bone metastases. If hypercalcenain the vestion will were for severe hypercalcenain in patients with threast cancer and bone metastases. If hypercalcenain the vestion and bone metastases is the for discuss the server noticuted in galanters receiving estrogens taken to reduce the server. Acidition level. **4. Systal anormalities** Relina vascular thrombosis has been reported in patients working estrogens residued profile to scaled partial or complete hyser division, or a sudden nore of proglosis. dipopia, or migraine. If examination reveals papiliedema or retinal vascular lesions, estrogens should be permanently discontinued. **PERCENTIONS**

Iteoris, estrogents should be permanently discontinued. **PERCALIDOS A Ceneral 1. Addition of a progestin when a woman has not had a hysterectomy** Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasis than would be induced by estrogen treatment alone. Endometrial hyperplasis may be a procursor to endometrial forgeneral to estrogen-alone treatment. These induce passible increased risk of breast cancer. **2. Elevated blood pressure** in a small number of case reports, substantial increases in blood pressure have been attributed bi idiolynozite accistons to estrogenes. In a large, radionates, flacebo-controlled dimical trial, a generalized defact of estrogens on blood pressure was not seen. Blood pressure shall be associated with extending of the strogen use. **3. Hypertrigiveridemia** in patients with preveating hyperhigiverariates along thereavers that oblical parameters **4. Inspiratio Hieror function and past history of cholestatic jaundice 5. Strogetrigiveridemia** in patients with preveating hyperhigiveraines learing the strogen see. **5. Hypotryoidisen Strogen** aniom trait of cholestatic jaundice Estrogens may be poorly metabolized in patients with impared liver function. For patients with a history of cholestatic jaundice sasociated with past estrogen aniom 1. Serum concentrations in the normal range. Patient dependent on through homome reglocement therapy who are also receiving estrogen may require increased does **6. Fluid relations** that might relation and comparate therapy and may be also the strogen many require increased does **6. Fluid relations** that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful doesnation that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful doesnation that might be estrogen ange reselving defined to a marginal their free thy

cardful observation when estrogens are prescribed.
 7. Hypocachemic Estrogens should be used with caution in individuals with severe hypocachemia.
 8. Ovarian cancer The strogens-plus-progestin substudy of WH reported that after an average follow-up of 6.5 years, the relative risk for variant cancer for settingen plus progestin x placebo was 1.58 (95%) Cl 0.77 – 3.24), but was not statistically significant. The absolute risk for estrogen plus progestin x placebo was 2.4 ys. 2.7 cases per 10,000 wornen-years. In some epidemiologic studies, the use of estrogen-type association with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associated with an increased risk of ovarian cancer. Other epidemiologic studies have not fourt these association with a spectra stromy with estrogen-strome transp. For patients how to be exacethet with with administration of estrogens. Malignant transformation of progestin should be considered.
 10.52 coerchaftion of other conditions. Estrogens may cause an exacetable with an individual endomethois post-hysterectomy, with caution in women with these conditions.
 8. Patient Information Physicians are advised to discuss the contents of the Patient Information Residence advised with advisor how mit these conditions.
 8. Patient Information Physicians are advised to discuss the contents of the Patient Information Residence advised with patients for the onthis strogens and stoud be used the lowest dose approved for the indication and then guided by clinical response, rather than by serum hormone levels (e.g., estradial), 820.

FSH, Drug/Laboratory Test Interactions 1. Accelerated prothermitin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VI antigen, VII coapulant activity, IX, XI, VII-X complex, increased platelet count; increased factors II, VI antigen, VII coapulant activity, IX, XI, VII-X complex, and bete: thromboplochim; decreased levels of anti-factor X and antithrombil. III, decreased antithrombin III activity, increased levels of anti-factor X and antithrombil. III, decreased antithrombin III activity, increased levels of the factor X and antithrombin III, decreased antithrombin III activity, increased levels of the factor X and antithrombin III, decreased antithrombin III activity, increased levels of the factor to the standard transmission, or T, levels X and internucessary. T resit to platels is decreased reflecting the elvels to Tacibint Tachard TBG. Free T, and free T, concentrations are unattered. Patients on thyroid replacement therapy may require higher doses of thyroid hornone.

1, concentrations are unlared. Yatients on unyrou replacement u energy may requere imprer wow on thyroid hormone.
3. Other binding porteins may be elevated in serum (i.e., controsteroid binding globulin (CSB), SH60, Hearing to increased total circulation controsteroid and are seretoris, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/remnin substrate, aptina-1 antitypsin, ceruloplasmin).
4. Increased trade including to including and the set serior is respectively. Free hormone concentration, increased tridyperide levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.
E. Carcinogenese, Mutagenesis, Impairment of Fertility Long-term continuous administration of estrogen, with or without progestin, in women with or without a uterus, has shown an increased risk of endometrial cance, treast cancer, and varian cancer. (See BOXED WARNINGS, WARNINGS, and PRECUTIONS.)

ious administration of natural and synthetic estrogens in certain animal species

tes the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver, nancy Activella should not be used during pregnancy. (See **CONTRAINDICATIONS**.) sing Mothers Estrogen administration to nursing mothers has been shown to decrea