Chapter 4

Hormone Products and Prescription

Contents

Page

INTRODUCTION 63
MARKET INFORMATION 63
Labeling 63
Generics 66
PRESCRIBING PRACTICES 66
Estrogens 68
Progestins and Combined Hormone Therapy 68
PROMOTION OF HORMONE THERAPY 70
SUMMARY 71
CHAPTER 4 REFERENCES 71

Boxes

Box *Page*

4-A. Bioequivalence for Generic Conjugated Estrogens 67
4-B. Prescribing Practices in California 69

Tables

Table *Page*

4-1. Estrogens and Progestins Used for Hormone Therapy 65
4-2. New Prescriptions (Rx) of Premarin by Specialty, 1990 68
4-3. Premarin Prescriptions (Rx), 1990 68
4-4. Estrogen Therapy by Geographic Region, January-December 1991 70

Chapter 4
Hormone Products and Prescription

INTRODUCTION

Doctors can choose from a variety of different brand-name products, drug formulations and dosages, and possible treatment regimens when they prescribe estrogen therapy (ET) or combined hormone (i.e., estrogen combined with a progestin) therapy (CHT) for postmenopausal women. In the United States, nearly 20 estrogen products are on the market and approved for use in treating menopausal symptoms; two products have the additional indication of prevention of osteoporosis. There are also progestin products that, although not officially approved for use in CHT, are commonly prescribed for it. A number of pharmaceutical manufacturers compete in the estrogen and progestin marketplace and conduct research and development on new formulations, routes of administration, and combination products. Until 1991, when the Food and Drug Administration (FDA) withdrew its approval, several generic formulations of conjugated estrogens were also on the market.

The effects of long-term use of hormone therapy for the prevention of osteoporosis and cardiovascular disease have received much attention in recent years. Drug labeling for estrogen has been changed to include the osteoporosis indication, and the FDA is currently considering adding cardiovascular disease information to estrogen labeling. Doctors employ estrogen and progestin in many different ways; e.g., they may prescribe the use of unopposed estrogen or combination forms (cyclic, sequential, or continuous/combined) of both products. There is little agreement on the optimal prescription for CHT, although for women with intact uteri, some regimen of continuous estrogen combined with progestin is the approach favored by most physicians.

This chapter considers information relevant to the commercial market for hormone therapy, the products that are used, and promotion practices. It addresses the labeling of approved estrogen and progestin products and discusses efforts that have been made to change the labeling to include indications for long-term preventive use. The chapter also describes the attempts to gain approval for generic estrogens and discusses prescribing information.

MARKET INFORMATION

Three classes of estrogens are used for hormone therapy: natural estrogens, conjugated equine estrogens, and synthetic estrogens. Wyeth-Ayerst's Premarin, the most commonly prescribed estrogen product, is a conjugated estrogen derived from the urine of pregnant horses; in 1990 it was the fourth most prescribed drug in the United States (13). Premarin was approved by the FDA in 1942 for the treatment of menopausal symptoms. Because it was approved before the 1962 amendments to the Food, Drug, and Cosmetic Act, Wyeth-Ayerst was required to prove only safety and not efficacy. The product was later evaluated under the Drug Efficacy Study Implementation (DESI) program and judged effective in 1972 (3).

Since the introduction of Premarin the FDA has approved other estrogens, both natural and synthetic, for the treatment of menopausal symptoms, and, in the United States, there are currently 11 manufacturers of estrogen products and 5 manufacturers of progestin products used in hormone therapy (see table 4-l). CIBA's Estraderm transdermal estrogen patch, an alternative to daily oral administration, approved by the FDA in 1986, is the newest estrogen product available. According to senior managers at Wyeth-Ayerst, total sales of estrogen products were close to $460 million in 1990, and Premarin held a 68 percent market share.

Three different progestins are used in CHT: medroxyprogesterone acetate, norethindrone, and norethindrone acetate. Upjohn's Provera, amedroxyprogesterone acetate, is the most commonly prescribed progestin for CHT. Provera has been on the market since 1959, although its use in CHT began much later.

Labeling

Title 21 of the U.S. Code governs drug labeling and defines a label as any display of written, printed, or graphic material on or accompanying a drug, including the actual label, the package insert, and any other material that provides information about the drug (21 U.S.C. Sec. 321 [k][m]). The FDA requires that the following information appear on the package label or package insert: the name and place

Photo credit: National Institutes *of Health*

Conjugated estrogen, the most widely prescribed drug for estrogen therapy, is derived from the urine of pregnant mares.

of business of the manufacturer, packer, or distributor; a description of the drug, including, at a minimum, the proprietary name and other established names of the drug, the type of dosage form and route of administration, qualitative and quantitative ingredient information, pharmacological or therapeutic class of the drug, and chemical name and structural formula. The label or insert must also contain a concise factual summary of the clinical pharmacology and actions of the drug in humans, information on the indications and usage of the drug, contraindications to use, warnings that explain adverse reactions and potential hazards of use, precautions for use and information for patients, an expiration date, an identifying lot or control number, and information about the quantity of the container (21 CFR 201.1, 201.10, 201.17, 201.18, 201.50, 201.56,201.57,21 1.137).

Once a drug is approved by the FDA, doctors can prescribe it for uses other than those named in the labeling, providing the decision is based on sound scientific evidence or medical opinion. The FDA is responsible for ensuring that a drug manufacturer has demonstrated safety and efficacy for its product; it is not within the FDA's jurisdiction to dictate to physicians the proper practice of medicine.

Estrogens

Labeling for all estrogens approved for use in hormone therapy includes a boxed warning stating that estrogens "have been reported to increase the risk of endometrial cancer' and 'should not be used during pregnancy.' The FDA-approved indications for use of estrogen products, which are listed in the 1991 *Physician's Desk Reference* (PDR), are "moderate to severe vasomotor symptoms associated with menopause, female hypogonadism, palliative therapy for advanced prostate cancer, palliative therapy for breast cancer in select circumstances, atrophic vaginitis, kraurosis vulvae, primary ovarian failure, female castration, and atrophic urethritis." Both Premarin and Estraderm are approved for the prevention of osteoporosis, and Premarin is also approved for the treatment of this condition (8).

The PDR explicitly states that "there is no adequate evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause and they should not be used to treat these conditions." Several estrogen products, including the Premarin derivatives PMB-200 and PMB-400, and Menrium, contain tranquilizing or antianxiety agents. PMB-200 and PMB-400 are indicated for treatment of vasomotor symptoms and associated tension and anxiety but only when estrogens alone have not alleviated symptoms.

Epidemiologic data have suggested that the use of unopposed conjugated estrogens by women who have undergone hysterectomies results in cardioprotective effects and a reduction in cardiovascular mortality by as much as 50 percent (21). In 1990, the FDA's Fertility and Maternal Health Drugs Advi-

Table 4-l—Estrogens and Progestins Used for Hormone Therapy

Brand name	Generic name	Manufacturer
Estrogens		
Estinyl	Ethinyl estradiol	Schering
Estrace	Micronized estradiol	Mead Johnson Laboratories
Estraderm	Transdermal 17-estradiol	CIBA
Estratab	Esterified estrogen	Reid-Rowell
Estratest	Esterif ied estrogen with methyltestosterone	Reid-Rowell
Estratest H.S.	Half-strength Estratest	Reid- Rowell
Estrovis	Quinestrol	Parke-Davis
Menrium	Esterified estrogen plus chlordiazepoxide (anti-anxiety drug)	Hoffman-La Roche
Ogen	Estropipate	Abbott Laboratories
Premarin	Conjugated equine estrogens	Wyeth-Ayerst
Premarin with methyltestosterone..	Conjugated equine estrogens plus methyltestosterone	Wyeth-Ayerst
PMB-200, PMB-400	Premarin plus meprobomate (tranquilizing agent)	Wyeth-Ayerst
TACE	Chlororianisene	Marion Merrell Dow
Diethylstilbestrol	DES, synthetic estrogen	Eli Lilly
Menest	Esterified estrogen	Smith Kline Beecham
Feminone	Esterified estrogen	Upjohn
Progestins		
Provera	Medroxyprogesterone acetate	Upjohn
Amen	Medroxyprogesterone acetate	Carnick Laboratories, Inc.
Curretab	Norethindrone acetate	Reid-Rowell
Aygestin	Norethindrone acetate	Wyeth-Ayerst
Norlulate	Norethindrone acetate	Parke-Davis
Norlutin	Norethindrone	Parke-Davis

SOURCE: Office of Technology Assessment, 1992.

sory Committee recommended that the labeling for conjugated estrogens be changed to reflect its potential cardiovascular benefits; it also strongly suggested that more studies be conducted, including a secondary intervention trial for women who have experienced cardiovascular disease and a large cohort study to evaluate subgroups of women at particular risk for developing cardiovascular disease. The decision by the advisory committee to recommend the change in the labeling of conjugated estrogens was nearly unanimous, with one committee member abstaining from the vote. Despite several substantial gaps in knowledge (e.g., the lack of long-term data from randomized clinical trials, a lack of consensus on and knowledge about optimal dosages and regimens and which subgroups of women are most likely to benefit from its use), the medical community generally agrees that evidence of unopposed estrogen's cardioprotective effects support general recommendations for its use (20). Wyeth-Ayerst, the manufacturer of Premarin, is actively seeking this labeling change, but the FDA is still evaluating the submitted data to determine Premarin's cardioprotective effects and has yet to make changes in the labeling (7,17).

The PDR lists several absolute contraindications to estrogen use: "known or suspected breast cancer, estrogen-dependent neoplasia, pregnancy, and undiagosed abnormal genital bleeding" (16). Thromboembolitic disorders or a history of such disorders associated with estrogen use has historically been identified as contraindications, but advances in medical knowledge now allow women with these conditions to use estrogen (14). In addition, many relative contraindications and side effects are taken into consideration in the decision to prescribe estrogens.

Progestins

The labeled indications for progestins are "secondary amenorrhea, abnormal uterine bleeding related to hormonal imbalance when there is no organic pathology present (e.g., fibroids or uterine cancer), and endometriosis. " Contraindications are "thrombophlebitis, thromboembolic disorders, cerebral apoplexy (or a past history), markedly impaired liver function, liver disease, breast cancer, undiagnosed vaginal bleeding, missed abortion, and use as a diagnostic pregnancy test. ' No progestin has been approved for use in treating meno-

pausal symptoms or in conjunction with estrogen for such treatment, although it is standard practice to prescribe progestin together with estrogen for women with an intact uterus to protect the endometrium. In addition, progestin is sometimes prescribed alone for the treatment of hot flashes when estrogen cannot be used (see the later section on prescribing practices).

Combined Hormone Therapy

The PDR discusses the use of progestins to counter the increased risk of endometrial hyperplasia associated with the use of unopposed estrogen. Under a section entitled "Precautions" in the labeling for both estrogen and progestin, the PDR addresses concomitant estrogen and progestin use:

> Studies of the addition of a progestin for 7 or more days of a cycle of estrogen administration have reported a lower incidence of endometrial hyperplasia. Morphological and biochemical studies of the endometrium suggest that 12 to 13 days of progestin are needed to provide maximal maturation of the endometrium and to eliminate any hyperplastic changes. Whether this will provide protection from endometrial carcinoma has not been clearly established. There are possible additional risks that may be associated with the inclusion of progestin in estrogen replacement regimens. The potential risks include adverse effects on carbohydrate and lipid metabolism. The choice of progestin and dosage may be important in minimizing these adverse effects.

A great deal of controversy has arisen over whether to change the labeling to reflect a recommendation for the use of CHT for women with intact uteri. The use of CHT reduces the risk of endometrial hyperplasia that occurs with unopposed estrogen use, but other risk-benefit comparisons-for osteoporosis, breast cancer, and cardiovascular disease--are less conclusive and more controversial. The use of CHT was the subject of an FDA advisory committee (the Fertility and Maternal Health Drugs Advisory Committee) meeting in June 1991. The FDA sought information from the committee on several topics: the associations between the use of estrogens and progestins and the risk of endometrial cancer, breast cancer, osteoporosis, and cardiovascular disease; the effects on those risks of the use of specific estrogens and progestins when given at various dosages and in various regimens; and the risks and benefits of ET compared with CHT. The committee agreed that estrogen labeling should **be changed to more positively endorse the recommended use of CHT for the treatment of menopausal symptoms and the prevention of osteoporosis (when indicated) for women with intact uteri. The committee concluded, however, that the data were inadequate to identify the effect of added progestin on the risk of breast cancer or on cardiovascular protection, or to determine how specific estrogen and progestin compounds, in various dosages and regimens, affect the risk-benefit balance. Despite the lack of data on long-term progestin use, the committee also recommended that the FDA consider new drug applications for** CHT compounds, should they be submitted.

Generics

The FDA, in the spring of 1991, withdrew approval for generic conjugated estrogens on the basis of demonstrated bioinequivalence (5,6). The definition of bioequivalence, which is the basis for approval of generics, requires that the generic product include the same therapeutic ingredient and that its rate and extent of absorption be the same as the innovative product—in this case, Premarin. Information available only after approval of the generic conjugated estrogens showed different rates of absorption for several of them, and concern about the therapeutic significance of these differences led the FDA to reconsider its original approval decision (l). The FDA issued a revised guidance (i.e., guidelines for conducting studies to show bioequivalence) for the approval of generic conjugated estrogens in August 1991 (see box 4-A). Currently, several manufacturers are seeking approval for generic equivalents of Premarin, but the FDA has estimated that it will be several years before any products will be on the market (4).

PRESCRIBING PRACTICES

Obstetricians and gynecologists write the largest percentage of prescriptions for estrogens and progestins used in hormone therapy, but many other specialists care for midlife women and also prescribe these hormones. According to data collected by Wyeth-Ayerst, in terms of percentage of Premarin prescriptions written, obstetricians and gynecologists are followed by family practitioners, internists, general practitioners, and other specialists (see table 4-2).

Box 4-A—Bioequivalence for Generic Conjugated Estrogens

The Food and Drug Administration's (FDA) Generic Drugs Advisory Committee made recommendations in early 1991 concerning bioequivalence testing and approval of generic conjugated estrogen products. The comparison product is Premarin, and part of what makes demonstrating bioequivalence to Premarin so difficult is that Premarin itself is quite complex. Premarin is derived from the urine of pregnant mares and has 10 components: estrone sulfate, equilin sulfate, 17-a dihydroequilin, 17-ß dihydroequilin, ***17-a*** estradiol, 17-ß estradiol, delta (8,9) dehydroestrone, equilenin, ***17-a*** dihydroequilenin, and 17-ß dihydroequilenin. Nine of these components are currently commercially available, but delta (8,9) dehydroestrone is not. Premarin contains about 50 to 60 percent estrone sulfates, 22.5 to 32.5 percent sodium equilin sulfate, and 7.5 to 20 percent unspecified conjugated estrogens.

The United States Pharmacopoeia (USP), the legal standard for drugs in the United States, specifies properties, action, use, dosages, strength, and purity. Conjugated estrogens are derived, either in whole or in part, from equine urine, or they may be produced synthetically using estrone and equilin. Currently, the USP requires only two compounds to be present in a conjugated estrogen product: sodium estrone sulfate and sodium equilin sulfate. Additionally, such products "may contain other conjugated estrogenic substances of the type excreted by pregnant mares." In February 1991, the FDA Generic Drugs Committee recommended that changes be made to the USP monograph for conjugated estrogens to make the required contents more specific, which would result in generic products (when approved) that are closer in composition to Premarin.

The committee recommended that the 10 components of Premarin be divided into several categories:

- therapeutic moieties, which independently demonstrate therapeutic activity and are required components;
- . concomitant components, which are present in a substantial amount in the innovator product but for which independent therapeutic activity has not been established-these components are required to be present in quantities that fall within set upper and lower limits;
- components requiring a limit test, Which allows no more than a specific percentage, which can be zero, to be present; and
- signal impurities, which must not exceed a set upper limit but which may be zero, provided the product is adequately stable.

The committee proposed that the generic product contain two therapeutic moieties present in Premarin--estrone sulfate and equilin sulfate; three concomitant components—***17-a*** dihydroequilin, 17-ß dihydroequilin, and 17-a estradiol; two limit tests for 17-ß estradiol and delta (8,9) dihydroestrone; and signal impurities for equilenin, *17-a* dihydroequilenin, and 17-ß dihydroequilenin. The other five components of Premarin are not required in generic products. The USP is currently revising its monograph for conjugated estrogen tablets and considering a redefinition of content requirements. The FDA issued a revised guidance for bioequivalence studies in August 1991, and several companies are pursuing approval of generic products.

SOURCES: D.B. Burlington Deputy Director, Office of Drug Evaluation II, Center for Drug Evaluation and Research Food and Drug Administratiom , testimony before the Subcommittee on Aging, Committee on Labor and Human Resources, U.S. Senate, Apr. **19,** 1991; Food and Drug Administratiou Guidance, Conjugated Estrogen Tablets, August 1991; transcript of the FDA Generic Drugs Advisory Committee meeting held in February 1991.

Most of the relatively scarce research on physician prescribing practices concentrates on gynecologists and family practitioners. Several studies of the prescribing patterns and strategies of doctors and the indications they follow for use of hormone therapy reveal significant prescription by gynecologists 'of estrogens, and to a lesser extent progestins, for postmenopausal women (9,11,18). Two surveys conducted in California reveal frequent prescription of both estrogens and progestins in this geographic region (see box 4-B).

Most of the available information on the prescription of estrogens and progestins provides data on the number of prescriptions dispensed (both new and refill prescriptions) and the number of times a drug is mentioned during visits to a physician. Some product-specific information is available from pharmaceutical manufacturers, but the more comprehensive information is derived from two pharmaceutical marketing research data bases: the National Prescription Audit (NPA) and the National Disease and Therapeutic Index (NDTI), which are maintained and distributed on a limited basis by a private consulting firm, IMS America, Ltd.

The NPA tracks prescriptions dispensed by a panel of 2,500 retail pharmacies and gives national

Table 4-2—New Prescriptions (Rx) of Premarin (tablets only) by Specialty, 1990

Specialty	New Rxs (000s)	Percent share	Percent[a] change
Obstetricians/gynecologists.....	2,897	43.0	+14
Family practitioners	1,353	20.1	+17
Internal medicine	983	14.6	+19
General practitioners	492	7.3	+ 3
All others	1,010	15.0	+18
Total	6,735	100.0	+15

[a]Compared with 1989.

SOURCE: National Prescription Audit, IMS America, Plymouth Meeting, PA, 1991.

estimates of prescription volume. The data these pharmacies provide for estrogens include all dosage forms and estrogen/androgen combinations. The second data base, the NDTI, collects information from a panel of approximately 2,130 office-based physicians who report on each patient they see or have contact with in any way during a 48-hour period each quarter. All mentions of a drug are reported-whether as a prescription written or dispensed, as the administration of a drug, or as a recommendation (9). Private researchers and the FDA's Division of Epidemiology and Surveillance have also performed several analyses of prescriptions of noncontraceptive estrogen and progestin. The latest available published data from these sources are from 1986.

Estrogens

Until 1990, according to NPA data, 1975 was the peak year for prescriptions containing noncontraceptive estrogen, with 28 million dispensed from retail pharmacies. At about that time, new information became available about the increased risk of endometrial cancer associated with the use of estrogen, and estrogen prescriptions tapered off until 1980, when they began to increase, a trend that has continued. Between 1979 and 1986, the prescription of oral estrogen, the form most often used to treat menopausal symptoms, increased 117 percent (9). In 1990, retail pharmacies in the United States dispensed more than 30 million prescriptions for noncontraceptive estrogens, surpassing the previous peak in 1975 (10).

The vast majority of estrogen prescriptions are for oral preparations, which accounted for 88 percent of all prescriptions in 1986 (9). Conjugated estrogens are most often prescribed, and Premarin is the preparation most commonly used. In 1990, Premarin accounted for 61.9 percent of all prescriptions (both new and refills) for oral and transdermal estrogen (see table 4-3). According to NPA data, in 1981,11 million prescriptions for conjugated estrogens were dispensed, about 95 percent of which were for Premarin. In 1987, 16 million prescriptions were dispensed, of which 75 percent were for Premarin. (Most of this **increase in** prescriptions can be attributed to the prescription of generic conjugated estrogens; as of the spring of 1991, however, these preparations were no longer on the market(5). There is great geographical diversity in estrogen use and prescribing patterns by region within the United States (see table 4-4) (11).

The most common diagnosis mentioned in relation to the prescription of estrogen is menopausal symptoms. In 1990, according **to the** NDTI, diagnosis of menopausal or climacteric states accounted for 47 percent of the prescriptions of noncontraceptive estrogens. The next most common diagnosis was unspecified endocrine disorder, followed by primary ovarian failure/premature menopause, postoperative followup exam, vaginitis/vulvovaginitis, artificial menopause, unknown/unspecified cause of morbidity and mortality (or other), osteoporosis, and malignant neoplasm of the prostate. These diagnoses together accounted for 90 percent of those associated with the use of noncontraceptive estrogen. Although prevention of osteoporosis is an approved indication for Premarin and Estraderm, osteoporosis accounted for only 2 percent of the diagnoses mentioned (10). Other studies show that osteoporosis has rarely been given as a distinctive diagnosis for ET, although mention of this condition is increasing over time. In 1974, prevention or treatment of osteoporosis was mentioned during 1.4 million physician visits; in 1986, this figure had risen to 1.8 million (9).

Progestins and Combined Hormone Therapy

Approved indications for the use of progestins are treatment of amenorrhea, abnormal uterine bleeding, and endometriosis. As noted earlier, no progestin

Table 4-3-Premarin Prescriptions (Rx), 1990

	Number (000s)	Percent of total oral and transdermal estrogen Rx
New Rx	6,735	64.5
Refill Rx	12,105	60.6
Total Rx	18,840	61.9

SOURCE: National Prescription Audit, IMS America, Plymouth Meeting, PA, 1991.

Box 4-B—Prescribing Practices in California

Two studies have been published concerning the prescribing practices of hormone therapy among San Diego and Los Angeles gynecologists. Both studies used mailed surveys to garner responses from the doctors, one group of which was listed under gynecology in the 1985 San Diego telephone directory, while the other was composed of members of the Los Angeles County Obstetrics and Gynecology Society. It is important to remember that regional differences in prescribing practices for hormone therapy have been shown to exist, with the West Coast having a demonstrated higher incidence of use. The results of these studies follow.

A 1985 survey of 166 (108 respondents) San Diego gynecologists showed that between 79 and 83 percent (depending on the length of time as practicing physicians) prescribed estrogens for at least 75 percent of recently postmenopausal women, and that 58 percent prescribed estrogens for virtually all such patients. Seventy-three percent usually prescribed estrogen therapy for 10 years or more, and none reported prescribing estrogen for less than 1 year. The San Diego gynecologists most commonly prescribed 0.625-mg Premarin daily. None of the doctors that had been in practice for less than 10 years at the time of the survey prescribed oral estrogens without a progestin. Menopausal symptoms, followed by the prevention of osteoporosis, were the major indications and reasons cited for hormone therapy.

A 1984/1985 survey of 516 (330 respondents) Los Angeles gynecologists revealed prescribing patterns similar to those found in San Diego. Routine use of hormone therapy was indicated by 94 percent of the respondents for women with intact uteri and by 97 percent for women without uteri. Ninety-seven percent preferred using Premarin for women with and without uteri, and O.625 mg of Premarin daily was the overwhelmingly favored dose (80 percent and 76 percent, respectively). Eighty-six percent routinely prescribed a progestin for women with intact uteri. Ninety-five percent used medroxyprogesterone acetate, with 73 percent prescribing 10 mg daily and 20 percent prescribing 5 mg daily. Surprisingly, 47 percent reported prescribing progestin for women without uteri.

The Los Angeles study compared the 1985 results with data from a 1975 survey of Los Angeles gynecologists. The preferred dosage decreased from 1.25 mg of Premarin daily in 1975 to 0.625 mg in 1985. The use of progestin therapy increased from 17 percent in 1975 to 86 percent in 1985, and the dose and brand remained the same (10 mg daily of medroxyprogesterone acetate). For women without intact uteri, the percentage of doctors prescribing a progestin increased from 11 percent in 1975 to 47 percent in 1985. The use of progestins for women without a uterus was not explained in the study.

SOURCES: E. Barrett-Connor, "Postmenopausal Estrogens--Current Prescribing Patterns of San Diego Gynecologists," *Western Journal of Medicine 144:620-621, 1986;* R.K. Ross, A. Paganini-Hill, S. Roy, et al., "Past and Present Preferred Prescribing Practices of Hormone Replacement Therapy Among Los Angeles Gynecologists: Possible Implications for Public Health," *American Journal of Public Health 78(5) :516-5 19, 1988.*

has been approved for use in CHT, although doctors prescribe it for this purpose, and most progestin use related to hormone therapy is in conjunction with estrogen. Studies have shown that progestin is effective in treating hot flashes, and it is sometimes used for this indication when estrogen is contraindicated. Doctors prescribe CHT most often for women with intact uteri to counteract the increased risk for endometrial cancer associated with ET.

In parallel with estrogen use, progestin use gradually increased through 1976, **at which** point it began to decrease. Like estrogen, however, it began **to rise in** 1981 and has continued **to increase since then. Thus,** 1983 saw the dispensing of 3.2 million prescriptions for progestins, and that number continued to increase rapidly between 1984 and 1986. In 1979,79 percent of progestins were prescribed **to be** used alone, and menopausal problems represented only 18 percent of diagnoses related to progestin prescriptions. In 1986, only 37 percent of prescribed progestins were used alone, and menopausal symptoms represented 59 percent of mentioned diagnoses. Concomitant use of estrogens and progestins has increased over time and was common in 1986. The increase in progestin prescriptions evident after 1982 coincides with the trend toward the use of oral progestin with oral estrogen (9,11).

There is no official standard or protocol for administering or prescribing CHT. Furthermore, no conclusive studies have been performed that indicate which regimen is most beneficial, and there have been no studies that meet design, duration, and sample size requirements for determining conclusively the risks and benefits of long-term use of CHT (2). The current Postmenopausal Estrogen/Progestin Intervention (PEPI) trial

Table 4-4-Estrogen Therapy by Geographic Region, January-December 1991[ab]

Region	States	Percent share	Base (000s)
Total		100	10,626
South Central		34	3,656
South Atlantic	DE, DC, MD, VA WV, NC, SC, GA, FL		
West South Central	LA, AR,TX, OK		
East South Central	TN, AL, MS, KY		
West		28	2,950
Pacific	WA, CA, OR, HI, AK		
Mountain	MT, CO, WY, ID, UT, AZ, NM, NV		
North Central		24	2,503
East North Central	OH, IN, MI, IL, WI		
WestNorth Central	IA, NE, MN, SD, ND, MO, KS		
East		14	1,517
Middle Atlantic	NJ, PA, NY		
New England	MA, RI, NH,VT, ME, CT		

[a]Classes52112 (estrogens oral) and 52114 (estrogens topical) drug occurrences (physician mentions in thousands).
[b]Physician Drug and Diagnosis Audit (PDDA) geographic regions conform to standard U.S. Census regions. PDDA is a nationally projected sample and is not designed to be a subnational database.

SOURCE: Scott-Levin Associates, Physician Drug and Diagnosis Audit, January-Deoember 1991.

being conducted by the National Institutes of Health is investigating the effects on intermediate endpoints of different regimens of CHT used for 3 years each (12). No combination estrogen and progestin products are currently approved in the United States, although some have entered clinical testing; combination products are available in Europe. Many different regimens of CHT are prescribed by physicians; indeed, anecdotal information indicates that as many as 19 different regimens are prescribed in the United States and more than a hundred are prescribed in Europe (21).

One of the main drawbacks to CHT is the incidence of unwanted withdrawal bleeding related to the administration of progestin. Clinicians thus are experimenting with various regimens that will either make bleeding more predictable or eliminate it entirely. The most commonly prescribed regimens are cyclic administration of estrogen and progestin, continuous administration of estrogen plus intermittent progestin, and, increasingly, continuous/combined administration of estrogen and progestin. Cyclic administration typically prescribes estrogen for the first 25 days of the calendar month and adds progestin on days 14 through 25. Both hormones are stopped for the last several days of the month at which point withdrawal bleeding occurs. Another cyclic method involves daily use of both estrogen and progestin for 21 days, followed by 7 days of no hormone use. This regimen also results in withdrawal bleeding. Continuous use of estrogen with intermittent progestin prescribes estrogen everyday, 365 days of the year, and adds progestin for the first 12 days of each calendar month. Withdrawal bleeding typically occurs for several days after progestin use is stopped, with the length and intensity of the bleeding dependent on the dose and type of progestin used (15). Amenorrhea is often achieved after several months of use of continuous/combined therapy. Increasingly, clinicians are prescribing continuous/combined therapy in an attempt to avoid withdrawal bleeding.

PROMOTION OF HORMONE THERAPY

Pharmaceutical manufacturers market their drugs in several ways: they send sales representatives to meet with individual physicians, place advertisements in medical journals, sponsor symposia and meetings, and fund clinical research on their products. In addition, pharmaceutical companies provide public education about medical conditions and drug use. FDA regulations prohibit companies from promoting drugs for unapproved uses; thus, manufacturers of progestin products may not promote their products for use in treating menopausal symptoms. They do fired research, however, both within their companies and within the medical community, to investigate this use.

Many advertisements for estrogen products feature pictures of attractive women who appear barely old enough to be menopausal. Often the women in the pictures are exercising or vacationing. Even advertisements focusing on osteoporosis (e.g., a recent Wyeth-Ayerst advertisement) feature relatively young-looking women. Many ads focus on femininity, sex appeal, and emotional and marital issues. The captions below have been used in recent advertisements:

- "Menopause Myth No. 1: No man in his right mind would be interested in a menopausal woman,' and "Menopause Myth No. 2: You'd better leave sports to the youngsters." These were both used by CIBA in its promotion of Estraderm, along with the statement, 'Now the change of life doesn't have to change yours. "
- "Calcium every day. Aerobics every week. Bone loss every year. She needs Premarin to help prevent further bone loss," used by Wyeth-Ayerst.
- "I feel more like a woman again," used by Reid-Rowell in its promotion of Estratest, Estratab, and Curretab. This ad also includes the following: "Hormones can make an important difference in a woman's life. These hormones can affect the way a woman feels about herself and those she loves. '

The first ad was directed toward consumers in women's magazines, while the second two ads appeared in professional journals for physicians (6). The implication in these ads is that without hormones, women will experience serious loss (15). Medical information required by the FDA is also part of these ads, and some contain further explanation of the menopause and menopausal symptoms. Many of the ads focus attention on a woman's looks and emotions, however, rather than on the scientific and medical effects of the drugs, and some have been criticized as demeaning, insulting, and degrading to menopausal women (19).

In addition, pharmaceutical companies fund individual and group research teams that conduct studies of their products or perform research in relevant medical areas; they also sponsor clinical trials of their drugs, as well as symposia and conferences that promote the exchange of both scientific and product information. Companies often contribute to commercial exhibitions held at professional meetings and promote their products to the attendees. Many researchers who study the menopause and related fields receive funding from pharmaceutical companies, a not uncommon practice in clinical research.

SUMMARY

There are 11 U.S. manufacturers of estrogen and 5 U.S. manufacturers of progestins. Three classes of estrogens are used for hormone therapy: natural estrogens, conjugated equine estrogens, and synthetic estrogens. Three progestins are used as well: medroxyprogesterone acetate, norethindrone, and norethindrone acetate. In 1990, total sales of estrogen products were close to $460 million. Premarin, the top-selling estrogen and the fourth most prescribed drug in the United States, held a 68-percent market share.

Approved estrogen products have labeled indications for the treatment of the vasomotor symptoms associated with the menopause; Estraderm is approved for the prevention of osteoporosis and Premarin for both the treatment and prevention of this condition. The FDA is considering changes in labeling that would reflect the cardioprotective effect of unopposed estrogen use. None of the progestins used in CHT has been approved by the FDA for the treatment of menopausal symptoms, but this use is common medical practice. FDA is considering labeling changes that reflect a recommendation for the use of CHT for women with intact uteri. The approval of generic conjugated estrogens remains a topic of debate within industry and at the FDA.

Obstetricians and gynecologists write more than 40 percent of estrogen prescriptions and general medicine physicians another 20 percent; all of these physicians most commonly prescribe conjugated oral estrogens. In 1990, more than 30 million prescriptions for noncontraceptive estrogens were dispensed, and the most common diagnosis associated with these prescriptions was relief of menopausal symptoms. Doctors commonly prescribe progestins for use with estrogen in women with intact uteri, but there is no officially approved regimen of CHT. Research continues to explore the long-term effects of CHT and different regimens to reduce side effects, especially withdrawal bleeding.

Many in the field of menopause research and women's health believe that serious gaps exist in the menopause and hormone therapy knowledge base, particularly in the area of long-term effects (see ch.

5). In the absence of sufficient research, especially on long durations of use, doctors are beginning to use CHT for long-term preventive therapy and pharmaceutical companies are pursuing labeling changes for existing estrogen and progestin products. Identifying and then closing these gaps are important tasks that will affect the market for hormone products.

CHAPTER 4 REFERENCES

1. "Abbreviated New Drug Applications for Conjugated Estrogens; Proposal to Withdraw Approval; Opportunity for a Hearing," Federal Register 55(30): 5074-5078, 1990.
2. Barrett-Connor, E., "Postmenopausal Estrogens—Current Prescribing Patterns of San Diego Gynecologists," *Western Journal of Medicine* 144:620-621, *1986.*
3. "*Certain* Estrogen-Containing Drugs for Oral or Parenteral Use," *Federal Register* 37(143):14826, *1972.*
4. "Conjugated Estrogens' Rate of Absorption Should Be Measured-FDA Advisory Committee; New Generic Formulations Could Take at Least Two Years To Develop," *F-D-C Reports* 53(9):9-10, *1991,*
5. "Conjugated Estrogen Tablets; Withdrawal of Approval of 28 Abbreviated New Drug Applications," *Federal Register* 56(57):12376-12377, *1991.*
6. Dodd, D., Wyeth-Ayerst, Philadelphia, PA, personal communication, September 1991.
7. "Estrogen Replacement Therapy Should Include a Progestin To Reduce Risk of Endometrial Cancer Advisory Committee Says; FDA To Consider Combo NDAs," *F-D-C Reports* 53(25):11, *1991.*
8. "FDA Approves Using Estrogen To Treat Post-Menopausal Osteoporosis," Associated Press wire service, Oct. 30, 1991.
9. Hemminki, E., "The Use of Combined Estrogen-Progestin Replacement Therapy,' *International Journal of Technology Assessment in Health Care* 4:511-519, *1988.*
10. Kaufman, S., Medical Officer, FDA, Epidemiology Branch, Division of Epidemiology and Surveillance, Office of Epidemiology and Biostatistics, Rockville, MD, personal communication, July 1991.
11. Kennedy, D.L., Baum, C., and Forbes, M.B., "Noncontraceptive Estrogens and Progestins: Use Patterns Over Time," *Obstetrics and Gynecology 65(3):441-447, 1985.*
12. Mebane, I., Epidemiologist, National Institutes of Health, Bethesda, MD, personal communication at a workshop sponsored by the Office of Technology Assessment, "Menopause and Hormone Replacement Therapy: Policy and Practice," Washington, DC, Mar. 22, 1991.
13. Merz, B., "Pharmaceutical List Tracks Hit Parade of Prescriptions," *American Medical News* 34(9):4, *1991.*
14. Notelovitz, M., Women's Medical and Diagnostic Center and the Climacteric Clinic, Gainesville, FL, personal communication, 1991.
15. O'Leary Cobb, J., A Friend Indeed, Montreal, Canada, personal communication, September 1991.
16. *Physicians Desk Reference,* 45th ed. (Oradell, NJ: Medical Economics Data, 1991).
17. "Prema.rin Cardioprotective Effect To Be Reconsidered,' *F-D-C Reports 53(17)* :T&G-3-T&G-4, *1991.*
18. Ross, R.K., Paganini-Hill, A., Roy, S., et al., "Past and Present Preferred Prescribing Practices of Hormone Replacement Therapy Among Los Angeles Gynecologists: Possible Implications for Public Health," *American Journal of Public Health* 78(5): *516-519, 1988.*
19. Seaman, B., and Seaman, G., *Women and the Crisis in Sex Hormones (New* York, NY: Rawson Associates Publishers, Inc., 1977).
20. Stampfer, M., Harvard University School of Public Health, Boston, MA, personal communication, November 1991.
21. Transcript of the meeting of the FDA Fertility and Maternal Health Drugs Advisory Committee, June 20-21, 1991.