April 19, 2000

00-013169

Distribution List

RE: Guidelines for Preparation of New Drug Submissions for Products Used for Estrogen-Progestin Replacement Therapy in Menopause (HRT)

Please find attached the Guidelines for Preparation of New Drug Submissions for Products Used for Estrogen-Progestin Replacement Therapy in Menopause (HRT).

The comments received in response to my letter of March 29, 1996, have been reviewed and a number of the suggestions have been incorporated into the current guidelines. For your information, a summary of the comments received, together with our analysis of them, is attached (Appendix). I trust this information will be helpful to you.

The guidelines are effective immediately. If you have any questions or comments, please do not hesitate to contact Dr. André-Marie Leroux at (613) 941-3173.

Original signed by

Dann M. Michols
Director General

Enclosure
GUIDELINES FOR PREPARATION OF A NEW DRUG SUBMISSION FOR PRODUCTS USED FOR ESTROGEN-PROGESTIN REPLACEMENT THERAPY IN MENOPAUSE (HRT)

INTRODUCTION

The approach to the management of menopause has undergone significant changes during the last two decades. Hormone replacement therapy (HRT), and the management of menopause constitute a major area of interest for the medical profession and are the subjects of much discussion. The Therapeutic Products Programme's (TPP) Special Advisory Committee on Reproductive Physiology has developed a document entitled The Menopause (1994).

In addition, the Therapeutic Products Programme co-sponsored with the U.S. Food and Drug Administration a "Workshop on Osteoporosis" (Washington, May, 1992), which resulted in the development of guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Post Menopausal Osteoporosis. The Therapeutic Products Programme has adopted these guidelines. All HRT drugs of this classification which are considered to be in New Drug status are subject to the requirements of Division 8 of the Food and Drug Regulations, in particular in Canada should meet the requirements of Section C.08.002 of these Regulations and must be demonstrated to be safe and effective for each of the indications proposed for inclusion in the Product Monograph.

The New Drug Submission (NDS) should be structured according to current guidelines and should contain the expected data outlined in general and specific guidelines.

DATA EXPECTED IN THE NDS

Hormone replacement therapy may provide various benefits to patients undergoing menopause, including improvement of symptoms due to hypoestrogenic status (e.g. hot flushes, senile vaginitis, atrophic changes of the vulva or urethra) and prevention of osteoporosis.

1. OVERVIEW

It is expected that a New Drug Submission for HRT will contain a brief and precise description of the scientific rationale for a single or multiple ingredient product(s), the
recommended therapeutic regimen(s) for the product and precise indication(s).

2. PRECLINICAL DATA

2.1 Individual active ingredients

Full Toxicological investigations should be conducted as per current *Therapeutic Products Programme Toxicology Guidelines*. The pharmacologic profile should be available, and all appropriate documentation is required.

2.2 Toxicologic profile

Full toxicologic studies including reproductive toxicology and carcinogenicity testing are required for any new drug substance, whether estrogen or progestin.

Studies on active ingredient ratios intended for use in the final dosage form (fixed combination), or the projected combination use of single ingredient products, are required.

_Cyclic and/or Phasic Regimens:_ If cyclic and/or phasic use of the product is intended, appropriate studies should be conducted in suitable species (models).

_Non-Fixed Combinations:_ For non-fixed combinations or single ingredient products projected for combination use, full toxicology including reproductive toxicology and carcinogenicity testing are required, as well, for the combination(s) tested clinically.

_Fixed Combinations:_ For fixed combination(s) or for projected combination(s) clinically tested, results of bioavailability, pharmacokinetics, pharmacodynamics and metabolic transformation should be available in all species studied.

In certain situations (e.g. when substantial information already exists on the drug substance(s)), abridged toxicology may be considered or toxicology testing may be waived. A request for waiver or variance should be supported by a strong rationale and discussed with Therapeutic Products Programme staff prior to filing the submission. The following is an example of such a situation:

*If both estrogen and progestin were already tested in a marketed oral contraceptive (OC) combination, one may cross-refer to the preclinical studies in the NDS of the OC. Supporting data from the literature may be*
used, as plasma levels achieved from the estrogen and progestin in the HRT product should be equal to or lower than, those from the OC product, as a precondition. Refer to “Guidelines for the Toxicological Evaluation of Contraceptive Steroids”.

2.3 **Pharmacologic Drug Interaction**

Results of studies on pharmacologic interaction of the active ingredients are expected. Effects on target tissues and organs (especially breast and endometrium), changes in metabolic and hematologic parameters should be documented.

2.4 **Topical or Intravaginal Products**

Data on local irritation, allergenic potential and systemic absorption should be available.

2.5 **Metabolic Effects**

The following metabolic effects of the drug product(s) should be well investigated:

- Lipid and lipoprotein profiles.
- Glucose and insulin homeostasis.
- Hematology, blood coagulation.

2.6 **Effects on the Skeletal System**

These studies should conform to the *Guidelines for Preclinical and Clinical Evaluation of Agents used in the Prevention or Treatment of Postmenopausal Osteoporosis*.

3. **CLINICAL DATA**

Because estrogens can promote the growth of hormone sensitive tumors, the lowest effective dose of estrogen for the proposed indication will have to be documented through well designed dose ranging studies.
Women who have intact uteri should always receive a progestin treatment in association with estrogen replacement therapy, with the objective of avoiding endometrial hyperplasia. According to the document entitled “The Menopause” published by Health Canada, cyclical administration of a progestin for 12 to 14 days of every month of estrogen therapy is required to prevent the development of endometrial hyperplasia. The selected progestin regimen must be proven safe and effective. For different dosages of estrogen, the appropriate dosage of progestin for the prevention of endometrial hyperplasia must be identified on the basis of well-designed dose ranging studies.

Independently of the particular indication or the route of administration proposed for the drug, the following information must be submitted for each active ingredient and each dosage form:

! Pharmacokinetic parameters including:

" Blood levels at steady state and/or during the therapeutic cycle.
" Metabolic pathways, metabolites, routes of excretion.

It should be noted that for a second entry product which shows bioequivalence to a marketed reference product in Canada, requirements for clinical studies may be reduced. Discussion with Therapeutic Products Programme staff prior to filing is encouraged.

! Effects on: lipid, lipoprotein profile and glucose metabolism hematological profile coagulation liver function cardiovascular function renal function endometrium body weight

! Interaction of progestin administration on the above parameters.

! Methodology used to obtain above results and its validation.

All women participating in these studies should have a baseline mammography and this radiological exam should be repeated at termination of the study or on a yearly basis if the study lasts more than one year.

Women with intact uteri should have a cervical cytology and an endometrial biopsy before enrolment in these studies; both the cervical cytology and the endometrial biopsy must be obtained again at termination of the study or on an annual basis if the study lasts more than...
one year. Ultrasound evaluation of the endometrium cannot replace endometrial biopsy for adequate endometrial surveillance, but may be complementary.

If a patient elects to discontinue her participation in the study, a final mammography should be obtained and depending on the gynecological surgical history of the patient, a cervical cytology and an endometrial biopsy should also be performed.

Reasons invoked by the patient to discontinue her participation in the study or medical diagnoses that would justify interruption of participation should be well documented.

3.1 **Routes of administration**

Besides the above information that must be submitted for all oral dosage forms, drugs for topical, intramuscular, subcutaneous or intravaginal administration should also be evaluated for local irritation or allergenic potential.

If the drug is to be delivered by an adhesive device, stability of adhesiveness of this device and systemic delivery of drug must be monitored through normal daily activities such as bathing and showering.

If the drug is to be delivered by a device that should be inserted into or removed from the subcutaneous tissue, exact technique, safety measures, complication rates, nature of complications related to the procedure must all be well documented.

A specific risk/benefit analysis must be carried out and form part of the submission for any drug delivery system that would require a surgical approach such as insertion in the subcutaneous tissue.

3.2 **Proposed indications**

3.2.1. **Menopausal symptomatology**

Because several of the symptoms due to menopause can be modified by the placebo effect, placebo-controlled studies are required. In order to document adequately the uterine bleeding pattern, the efficacy of progestin administration to prevent endometrial hyperplasia, metabolic changes and the patient's tolerance and acceptability, these clinical studies should last a minimum of 12 months. If efficacy of the study drug to relieve menopausal
flushes can be demonstrated statistically, the placebo group may be discontinued as early as three months after initiating the study.

In order to take care of the variable intensity of symptoms encountered during menopause, it is expected that several dosages of the drug will be evaluated during these studies.

Comparative studies with a drug already marketed in Canada for the same indication may be required.

If a candidate was already receiving some treatment for menopausal symptomatology, an appropriate wash-out period should be planned before enrolment in these studies.

**Quality of Life:** An evaluation of quality of life (QOL) based on standardized questionnaires such as the Psychological General Well-Being (PGWB) index or the Kupperman index should be performed before and during treatment. Other QOL questionnaire(s) may be considered but should be validated for the intended purposes.

**Vasomotor symptoms:** A well designed diary should be used to record both the frequency and the severity of the various vasomotor symptoms. A numerical gradation of the severity of these symptoms should allow for a reliable biostatistical analysis.

**Vaginal Maturation Index:** An improvement of atrophic changes at the level of the vaginal mucosa should be documented with serial vaginal cytology and evaluation of the maturation index.

**Uterine bleeding pattern:** Women with intact uteri who participate in these studies should be given a diary to record any episode of uterine bleeding. The amount and the duration of uterine bleeding should be clearly documented. Episodes of bleeding following progestin withdrawal should be analyzed separately from episodes of bleeding occurring at other points of time during the treatment cycle.

**Adverse effect:** All participants should record in their diaries any adverse event or unpleasant symptom that can possibly be related to the treatment.

**Additional Proposed Indications:** If the manufacturer wishes to add specific claims about treatment of vulvar, urethral or bladder mucosal
atrophy, special studies will be required:

! **Vulvar atrophy (optional)** - Beneficial effect of therapy at the level of vulvar tissue should be confirmed by controlled vulvar biopsies.

! **Atrophy of urethra or bladder mucosa (optional)** - An improvement of atrophy of urethra or bladder mucosa following treatment must be confirmed with controlled urethrocystoscopy and other urodynamic studies.

3.2.2. **Prevention of osteoporosis**

Reference is made to the document *Guidelines for Preclinical and Clinical Evaluation of Agents used in the Prevention or Treatment of Postmenopausal Osteoporosis* published by the Division of Metabolism and Endocrine Drug Products, Food and Drug Administration, U.S.A.

3.2.3. **Treatment of osteoporosis**

Same reference as for prevention of osteoporosis.
Guidelines for Preparation of New Drug Submissions for Products Used for Estrogen-Progestin Replacement Therapy in Menopause (HRT)

Appendix - Consultation

Comments concerning the draft guidelines were solicited from the stakeholders. Nine responses were received: two from health professionals’ associations, one from a pharmaceutical manufacturer association, and six from health professionals. Three of the respondents agreed with the proposed guideline as it is or with minor editorial changes. Others, though supportive of the guidelines had specific comments which have been addressed as follows in considering the final version:

+ One respondent, although in agreement that a minimum of one year is necessary to assess the effect of a new treatment on menopausal symptoms, questioned the ethics of administrating placebo for 12 months in placebo-controlled studies. It suggested that a currently approved therapy be used as a comparator to eliminate the use of placebo.

Response:

This suggestion was well received by TPP and the draft guidelines were amended to indicate that if efficacy of the study drug to relieve menopausal flushes can be demonstrated statistically, the placebo group may be discontinued as early as 3 months after initiating the study.

It was considered by TPP that the administration of a placebo, for the management of menopausal symptoms indication, be limited to three months, a period of time that should be just long enough to rule out a placebo effect and allow statistically valid confirmation of the efficacy of the study drug at the appropriate dosage. The remaining part of the 12-month period is then used to document the safety and the tolerance parameters of the study drug without continuing the placebo arm.

As written in the guidelines and as recommended by the respondent, the sponsor of a new drug for the management of menopausal symptoms may elect to compare the study product with a drug already marketed in Canada for the same indication. On the other hand, a placebo group receiving no active treatment for a few months may be required when blinding is necessary for an objective assessment of the study drug’s efficacy and no marketed drug can be identified that will permit such blinding among patients and possibly among physicians in charge of the study.

+ Some respondents suggested including the claim for “cardiovascular risk reduction” under the section for “Data Expected in the NDS”, and specify how is this to be
evaluated.

Response:

This section indicates that hormone replacement therapy may provide various benefits to patients undergoing menopause and cites only few examples. It is not meant to be an exhaustive list and the document states that each proposed indication must be supported with respect to safety and efficacy.

+ One respondent recommended that the “Clinical Data” section identifies the “lowest dosage of progestin instead of “appropriate” dosage of progestin for the prevention of endometrial hyperplasia when different dosages of estrogen are used.

As the endogenous secretion of estrogen may vary significantly among menopausal women and can influence the risk of developing endometrial hyperplasia, it is more important to define the “appropriate” dosage of progestin to avoid completely such complication instead of aiming for the “lowest” dosage of progestin.

+ One respondent asked whether drug effects on parameters such as lipid glucose metabolism, hematological profile, and coagulation would be compared with baseline data.

Response:

Yes, this is implied in follow-up of such parameters.

+ One respondent asked whether it is necessary to specify, under the “Metabolic Effects” section, over which time frame these effects will be measured since it is not possible to keep a drug in the clinical trials for five or ten years waiting for long-term effects.

Response:

The intent is to follow-up these parameters during the length of the trials as specified in the guidelines (i.e. one year for the claim for management of menopausal symptoms and two years for osteoporosis).

+ Some respondents suggested allowing the use of other quality of life questionnaires which should be validated for the intended purpose.

Response:

This suggestion is now incorporated in the guidelines.
+ One respondent suggested using other less invasive test than biopsy to study the
drug efficacy for treating vulvar atrophy.

Response:

It is TPP’s general policy to accept alternative tests when well validated.

+ One respondent questioned the applicability of toxicity data created for approval of
an oral contraceptive (which is intended for young population) to the same product
when used for hormonal replacement therapy (which is intended for young
premenopausal and older postmenopausal women).

Response:

The guidelines state “studies used for oral contraceptive registration can be used for
hormone replacement therapy submissions provided that the ratios of the compounds
are the same as, and the doses are less than, those used for contraception in
humans.” Since there is an overlap in the age for use of oral contraceptives and
hormone replacement therapy, the same toxicity data are required.

+ One respondent questioned the need of reproductive toxicology and suggested to
specify which animal models will be used because of the “ambiguity with previous
animal models”.

Response:

TPP recently issued a draft guideline for the toxicological evaluation of
“contraceptive steroids” which may be of relevance to the HRT products. These
guidelines differ from previous requirements stipulated for pre-clinical testing in the
following:

• the elimination of the monkey 10 year carcinogenicity test

• the elimination of the dog carcinogenicity test

• the inclusion of more detailed pharmacokinetic data.

These guidelines should be used in conjunction with the Guidelines for Toxicological
Evaluation.
It should be noted that these guidelines do not constitute requirement; and TPP maintains the right to request additional data as seen fit on a case by case basis.