The College of Naturopaths of Ontario

BRIEFING NOTE
Oral Micronized Progesterone

PURPOSE: To consider possible amendments to Table 3 of the General Regulation.

OUTCOME Determination of proposed amendments to Table 3 of the General Regulation.

NATURE OF DECISION ☐ Strategic ☑ Regulatory Processes & Actions ☐ Other

PROCESS:

Activity:	Review and discussion of public consultation feedback of amendment to Table 3.		
Results:	Council determination on whether to add OMP to Table 3		
Overall Timing:	20 minutes.		
Steps/Timing:	**1.**	Review of materials from staff.	10 minutes
	2.	Questions from Council.	7 minutes
	3.	Motion and vote	3 minutes

BACKGROUND:

The College of Naturopaths of Ontario (the College) is responsible for reviewing the prescribed substances that naturopathic doctors may administer by injection or inhalation and the designated drugs that they may prescribe, dispense, compound or sell. These drugs and substances are listed on the Tables that are included in the General Regulation (Ontario Regulation 168/15) made under the *Naturopathy Act, 2007.* This responsibility includes ensuring that the drugs and substances accessible by naturopathic doctors are safe and effective when used within naturopathic practice.

To amend one or more of the Tables, the Council of the College must propose an amending regulation which, after review by the Minister of Health, must be approved by the Lieutenant Governor in Council.

In 2019, the College Council proposed amendments to the Tables set out in the General Regulation made under the *Naturopathy Act, 2007* including the addition of Oral Micronized Progesterone (OMP) to Table 3. In 2022, the Ministry concluded its review of the changes to the Tables in the General Regulation submitted on behalf of the Council. The Ministry agreed to some, but not all of the changes submitted by the Council. OMP was not among the approved changes.

In 2024, the Ontario Association of Naturopathic Doctors (OAND) submitted a new proposal to the College seeking to add OMP to Table 3 of the General Regulation. Upon receipt of the proposal, the College engaged Dr. Jamie Kellar, BScHK, PharmD, PhD, Associate Dean, Academic Associate Professor, Teaching Stream, with the Leslie Dan Faculty of Pharmacy at the University of Toronto to conduct an independent expert review of the submission. The

College also asked that Dr. Kellar obtain an independent review of her report prior to submitting the report to the College. Dr. Kellar retained the services of Dr. Tiana Tilli, BScHK, PharmD, RPh, ACPR, Lecturer and Clinical Pharmacist at the Faculty of Pharmaceutical Sciences, University of British Columbia. Both Dr. Kellar and Dr. Tilli were remunerated for their work as independent reviewers. Neither has had any prior relationship with the College of Naturopaths of Ontario, the Ontario Association of Naturopathic Doctors nor with drug manufacturers related to Oral Micronized Progesterone.

In preparing the report, Dr. Kellar was asked to consider the initial DIRC report, which was obtained during the earlier drug review in 2019, and identify what, if any, factors had changed since the initial review was conducted in 2018. A copy of the report is attached. The key highlights are:

- Indications for use – The only approved label indication for oral micronized progesterone in Canada is for the prophylaxis of endometrial hyperplasia. Other proposed indications such as vasomotor symptoms or infertility are considered off label indications.

Other key recommendations of the report also note that:

- Using OMP in combination with topical estrogen is viable and beneficial t and that oral estrogen is not required when prescribing OMP.
- Physician co-management is reserved for high-risk medications of which OMP is not one; however, referral or physician co-management is recommended for certain listed patient populations.
- Ontario NDs who have completed the Canadian Therapeutic Prescribing Course and Examination, i.e., have met the Standard of Practice for Therapeutic Prescribing can effectively and safely prescribe and use OMP.
- Combining transdermal estrogen with oral micronized progesterone is evidence-based, effective, and safe for most healthy women needing hormone therapy.
- OMP is considered the gold standard for progesterone therapy in hormone replacement treatment plans and has a favourable safety profile for most individuals when used as prescribed.

On May 28, 2025, the Council of the College received a briefing on the OAND submission, Dr. Kellar's Report, and the Working Group feedback, and was asked to consider the matter. Specifically, the Council was asked to consider adding Oral Micronized Progesterone to Table 3 with a limitation that it would only be permitted for use in accordance with the indications on the label. The Council was asked not to amend Table 4 (dispense), Table 5 (compound) or Table 6 (sell) as it relates to oral micronized progesterone for the following reasons:

- Table 4 – by not adding OMP to Table 4, patients will be required to obtain the drug from a pharmacist ensuring that patient safety is enhanced through the checks and balances inherent in the knowledge, skill, and judgment of two professions.
- Table 5 – by not adding OMP to Table 5, OMP cannot be compounded. As was noted in the report, Prometrium® is the brand name of the drug that is currently available as well as several generic manufacturers. Given the broad availability of the drug, compounding it for use is not necessary and would likely be in breach of clause 11(2)(9) of the General Regulation.
- Table 6 – by not adding OMP to Table 6, OMP cannot be sold by an ND in Ontario. This coincides with the rationale for not enabling it to be dispensed.

The Council agreed with the rationale set out and approved, in principle, the addition of OMP to Table 3 in the General Regulation and asked that a mandatory 60-day consultation be initiated.

Summary of Drugs to be Added

In summary, the Council of the College of Naturopaths of Ontario is proposing an addition to Table 3 of the General Regulation, Ontario Regulation 168/15 by adding the following:

Table 3
Drugs that may be Prescribed

Drug	Limitations, routes of administration, dosages
Progesterone (oral micronized)	For use only in accordance with label indications approved by Health Canada.

DISCUSSION POINTS:

Formal 60-day Consultation

As noted earlier, the Council approved in principle an amendment to Table 3 in the General Regulation to add Oral Micronized Progesterone and to conduct a 60-day public consultation. The purpose of this consultation was to seek feedback from registrants, system partners, and interested parties on the proposed addition to Table 3 of the General Regulation.

In line with the consultation's intent, the College included the Independent Expert Review – Oral Micronized Progesterone (Appendix 1) and the Proposed Amendments to Table 3 (Appendix 2) to the public consultation. The formal consultation opened on June 30, 2025, and closed at 5:00 pm on September 8, 2025.

Consultation Feedback

During the public consultation period, the College received feedback (Appendix 3) of support for the addition of OMP to Table 3 of the General Regulation from:

- The Association of Ontario Midwives
- The Ontario Association of Naturopathic Doctors
- The Ontario Pharmacists Association
- The Nurse Practitioners Association of Ontario
- The Canadian College of Naturopathic Doctors
- 47 Naturopathic Students
- 22 Members of the Public
- 58 Naturopathic Doctors
- 2 Pharmacists
- 3 Nurse Practitioners
- 2 Medical Doctors

The College did not receive any public consultation feedback opposing the addition of OMP to Table 3 of the General Regulation.

Limitation

Several respondents to the public consultation, although in support of the addition of Oral Micronized Progesterone to Table 3 of the General Regulation, recommended the removal of the limitation "For use only in accordance with label indications approved by Health Canada."

The removal of this limitation would allow for NDs to prescribe OMP for purposes that are not currently approved by Health Canada. The term "off-label" refers to the use of a medication in a manner that is different from what Health Canada has approved to be marketed in Canada. For example, when research shows that the benefits of using the medication in new ways outweighs the risks, prescribers may wish to provide this option to their patients. Off-label use includes prescribing a medication for a new health condition or to a different age group.

The purpose of the initial limitation approved for consultation was to ensure a narrow and controlled addition of the drug while maintaining alignment with evidence considered in previous Ministry reviews. This limitation was included as the Independent Expert Review stated: “The only approved label indication for oral micronized progesterone in Canada is for the prophylaxis of endometrial hyperplasia. Other proposed indications such as vasomotor symptoms or infertility are considered off label indications.” The consultation feedback did note that the Independent Expert Review confirmed that OMP has a favourable safety profile and is not considered a high-risk medication and that off-label prescribing is common in OMP therapy and is commonly utilized by other prescribers in Ontario.

In considering the public consultation feedback, the Council has two decisions to make:

1) Whether to approve the addition of Oral Micronized Progesterone to Table 3 of the General Regulation.

2) If the answer to question 1 is in the affirmative, whether they wish to include or remove the current proposed limitation.

To assist the Council with its decision on whether to prohibit off-label use, the College has invited the external reviewer, Dr. Jamie Kellar, BScHK, PharmD, PhD, to make a brief presentation on the matter and to answer any questions the Council may have.

It is important to note that the removal of the proposed limitation would be considered a substantial change and require that the College initiate a new 60-day public consultation on the proposed addition of OMP to Table 3 of the General Regulation.

ANALYSIS

Risk Assessment – The risk assessment is based on the document Understanding the Risk Analysis Terminology, a copy of which is included in the Reference Materials package provided to the Council. The only significant risks that have been identified relate to strategic risks.

- With any changes to regulations, the College may face a reputational risk with regards to stakeholders questioning the decision of the Council to proceed with adding additional drugs. This risk is mitigated by engaging expert review both internal and external to the profession and conducting a public consultation on the proposed amendment before making any final decision. In this instance, the external expert reviewer recommended a limitation on the use of OMP in naturopathic practice to its approved use as established by Health Canada. Removing that limitation without further expert review advice and further consultation, brings a significant risk as stakeholders who may have withheld any opposition because of this limitation would be denied the opportunity to register an objection to the boarder use by the profession. Additionally, should the Council remove the proposed limitation in the regulation, it will need to take actions to mitigate any risk of harm to patients through one or more of a Standard of Practice, Guideline or Council Policy on Off-Label Prescribing by NDs.

Privacy Considerations – There are no privacy considerations. The proposed regulation and Independent Expert Review were circulated publicly for feedback. The feedback (redacted where required) from the public consultation is also available.

Transparency – The transparency assessment is based on the document 'Understanding the College's Commitment' to Transparency, a copy of which is included in the Council package. Only those risks that have been identified will be addressed.

- The information presented on the proposed amendment was made publicly available on the College website during the public consultation.

Financial Impact – There is no direct financial impact; however, there is an indirect financial impact through the use of College resources, including the possible addition of a further consultation on OMP.

Public Interest – The public interest assessment is based on the document 'Understanding the Public Interest', a copy of which is included in the Council package. Only those relevant factors have been identified and addressed.

- Proposed amendments to the General Regulation may ensure that the most appropriate drug is available to patients and in line with the independent review.

EDIB – The Council and the College have made a commitment to equity, diversity, inclusion and belonging generally and to ensuring that its policies and programs do not include any elements of racism and promote EDIB principles.

RECOMMENDATIONS

None.

ACTION ITEMS

If Council approves the addition of OMP with the current proposed limitation, College staff will create the necessary Regulation Submission materials and submit the proposed regulation amendment to the Ministry of Health for consideration.

If the current proposed limitation is removed, College staff will initiate a new public consultation on the proposed addition of OMP to Table 3 of the General Regulation.

Jeremy Quesnelle
Deputy CEO, Regulations

Drug Name	**Oral Micronized Progesterone**
National Drug Schedule	**Schedule I**
Therapeutic Category	**Hormone**

Prepared By: **Dr. Jamie Kellar, RPh, BScHK, BScPhm, PharmD, PhD**
Associate Dean Academic,
Leslie Dan Faculty of Pharmacy, University of Toronto

Reviewed By: **Dr. Tiana Tilli, BScH, PharmD, RPh**
Clinical Pharmacist and Lecturer
Faculty of Pharmaceutical Sciences
University of British Columbia

SCOPE OF REVIEW

The College of Naturopaths of Ontario (CoNO) commissioned this drug review for oral micronized progesterone (OMP). This drug was previously reviewed by the Drug Information and Resource Centre (DIRC) of the Ontario College of Pharmacists in 2018, which has since ceased operation. Several years have passed since the initial review. Hence, new scientific literature is available. As such, CoNO has requested an updated review of OMP.

METHODOLOGY OF REVIEW

In preparing this report, the DIRC submission and several online drug information databases, clinical practice guidelines, and current scientific literature were reviewed. The focus was on updates and/or changes since the 2018 submission. Dr. Jamie Kellar completed the initial report, and then Dr. Tiana Tilli independently reviewed it. Dr. Tilli provided additional information, which Dr. Kellar incorporated to ensure a thorough and accurate review.

QUALIFICATIONS OF REVIEWERS

Dr. Jamie Kellar is the Associate Dean Academic at the Leslie Dan Faculty of Pharmacy, University of Toronto. She is a licensed (Part A) pharmacist in Ontario. She obtained an honours Bachelor of Science in Human Kinetics from the University of Guelph, followed by an honours Bachelor of Science in Pharmacy and a Doctor of Pharmacy degree both from the University of Toronto. She received her PhD in Health Professions Education from the School of Health Professions Education, Maastricht University, Netherlands. For a fulsome description of Dr. Kellar's expertise, please refer to her CV.

Dr. Tiana Tilli is a Clinical Pharmacist and Lecturer at the Faculty of Pharmaceutical Sciences, University of British Columbia. She is a licensed (Part A) pharmacist in Ontario and British Columbia. She obtained an honours Bachelor of Science in Life Sciences from Queen's University, followed by a Doctor of Pharmacy degree from the University of Toronto. She completed her Accredited Canadian Pharmacy Residency (ACPR) at St. Michael's Hospital in Toronto. For a fulsome description of Dr. Tilli's expertise, please refer to her CV.

CONFLICT OF INTEREST

Neither Dr. Kellar nor Dr. Tilli have any conflicts of interest to declare. They have no previous or ongoing relationships with the College of Naturopaths of Ontario. They have no financial, personal, or professional relationships with pharmaceutical companies/manufacturers of hormone therapies, nor are they affiliated with any advisory groups associated with the development of clinical practice guidelines that include recommendations on the use of hormone therapy.

TERMINOLOGY

Progestogens is the term used for the general category of compounds that exhibit progestational activity, which includes natural progestogen (progesterone) and synthetic progestogens (progestins). Progestogens commonly co-administered with estrogen in women with a uterus include medroxyprogesterone acetate (MPA), norethindrone acetate (NETA), and oral micronized progesterone (OMP).[1] Both MPA and NETA are synthetic progestins, whereas OMP is bioidentical, meaning it is structurally identical to the progesterone produced by the corpus luteum.[1,2]

Oral Micronized Progesterone

OVERVIEW OF PROGESTERONE

Progesterone is a naturally occurring steroid hormone crucial for menstruation and pregnancy. It also plays a role in breast development, mood regulation, and maintaining bone density.[2] Although the ovaries primarily produce progesterone, it is also produced by the adrenal glands and, during pregnancy, the placenta.[2]

Bioidentical progesterone is a lab-made hormone chemically identical to the progesterone naturally produced by the corpus luteum in the human body.[2] Health Canada, the FDA, and other regulatory authorities have commercially approved it for use. In Canada, bioidentical progesterone is available as oral micronized progesterone (OMP) in both brand-name (e.g., Prometrium®) and generic (e.g., Teva-progesterone) products.[3]

WHY PROGESTOGENS?

Conditions associated with low progesterone levels sometimes require individuals to supplement their bodies with exogenous progestogens. In this case, they may be prescribed a bioidentical form of progesterone or a synthetic progestin designed to mimic the effect of progesterone in the body.

In perimenopause and menopause, progestogens are used to prevent the increased risk of endometrial overgrowth and endometrial cancer from unopposed estrogen therapy in women with an intact uterus.[4]

MECHANISM OF ACTION

Progesterone is a natural steroid hormone that induces secretory changes in the endometrium, promotes mammary gland development, relaxes uterine smooth muscle, blocks follicular maturation and ovulation, and maintains pregnancy.[2] When used as part of an assisted reproductive technology (ART) program in the luteal phase, progesterone supports embryo implantation.[2]

OVERVIEW OF INDICATIONS FOR BIOIDENTICAL PROGESTERONE

Progesterone can be used to treat a variety of conditions. It has both approved ‘on-label’ indications and ‘off-label’ uses. Notably, ‘off-label’ uses are not formally approved by the Food and Drug Administration and/or Health Canada. However, they are evidence-informed indications, meaning there are scientific studies to support and guide the use.

APPROVED/’ON-LABEL’ INDICATIONS

- *Estrogen therapy-associated endometrial hyperplasia – prophylaxis[4-6]
- Assisted reproductive technology, luteal phase support[4,5]
- Abnormal uterine bleeding[4,5]
    - Unrelated to the menstrual cycle
- Secondary amenorrhea – diagnostic aid (“progesterone challenge”)[4,5]

*The only approved label indication for oral micronized progesterone in Canada is for the prophylaxis of endometrial hyperplasia. Specifically, the Canadian labeling states:

'Indicated for women with an intact uterus as an adjunct to postmenopausal estrogen replacement therapy to significantly reduce the risk of endometrial hyperplasia and carcinoma.'

OFF-LABEL INDICATIONS

- Menopause – vasomotor symptoms (i.e., hot flashes, night sweats)[4]
- Spontaneous preterm birth, prevention[4,5]
- Ischemic heart disease – acute, exercise-induced[4]
- Menstrual epilepsy[4]
- Primary menorrhagia[4]

PROPOSED INDICATIONS BEING SOUGHT BY THE COLLEGE OF NATUROPATHS OF ONTARIO

1. Endometrial hyperplasia prophylaxis (as adjunct to estrogen replacement therapy in women, trans men, or non-binary people registered female at birth, with an intact uterus)
2. Infertility (due to luteal phase defects)
3. Menopausal symptom relief (vasomotor symptoms)

ADMINISTRATION AND DOSAGE

Bioidentical progesterone is available in different formulations in different countries, including oral capsules, vaginal gels and inserts.[4] In Canada, the only health Canada-approved formulation is oral micronized progesterone, which is the focus of this review.

In Canada, OMP is available as a prescription product under the brand name Prometrium® and from several generic manufacturers.[3,6] Each capsule contains 100 mg of micronized progesterone.[6]

Oral micronized progesterone is typically used orally, but the tablet has been administered intravaginally; further study is needed before recommending this route routinely.[4,5,7]

According to the monograph recommendations, 200mg or less of oral micronized progesterone can be administered once daily, ideally at bedtime, as some of its metabolites are associated with somnolence.[8] Higher doses (i.e., 300 mg) should be divided; the larger amount (200 mg) should be given at bedtime, while the lower dose (100 mg) can be given in the morning, ideally two hours after breakfast.[6] Although recommended in the monograph, divided doses are not mandatory. A single 300 mg dose can be given safely at bedtime and may be desirable for some patients, particularly if being used to improve sleep.[4]

<u>Dosing for estrogen therapy-associated endometrial hyperplasia prophylaxis:</u>

- Cyclically: 200mg/day orally for 12-14 days sequentially each month, along with conjugated estrogen[4-6]
    - The Canadian label states: 200 mg daily for the last 14 days of estrogen treatment per cycle (i.e., from day 8-21 for a 28-day cycle or from day 12-25 for a 30-day cycle)[6]
    - The Canadian label recommends patients being treated with high doses of estrogen (equivalent to 1.25 mg conjugated estrogens or higher) receive 300 mg daily for the last 12-14 days of estrogen treatment.

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- Preferred in late menopause transition and early postmenopause[5]
- Continuously: 100mg/day orally continuously
  - Preferred if ≥2 to 3 years postmenopause[5]

Dosing for assisted reproductive technology (ART), luteal phase support:

Multiple regimens are available for ART. Data regarding the most effective route of administration and dose are insufficient.[4] Possible regimens include, but are not limited to:

- Vaginal administration of OMP 200 mg capsule three times daily starting the day of oocyte retrieval and continuing for up to 12 weeks' gestation.[5]

Dosing for menopause – vasomotor symptoms

- 300 mg orally every night; reevaluate periodically to determine the need for ongoing use.[1,4]

EFFICACY

Are the proposed indications for oral micronized progesterone sought by CoNO supported in the literature?

☐Yes (all), ☒Yes (some), ☐No (data not conclusive), ☐No (data not available)

Estrogen Therapy-Associated Endometrial Hyperplasia Prophylaxis

Oral micronized progesterone is approved by Health Canada and the Food and Drug Administration (FDA) for the treatment of women with an intact uterus as an adjunct to postmenopausal estrogen replacement therapy to significantly reduce the risk of endometrial hyperplasia and carcinoma.[4-6] The estrogen therapy may be for the vasomotor symptoms associated with menopause or secondary amenorrhea.

Guideline Recommendations (North American Menopause Society)[1]

- In women with a uterus and symptoms associated with menopause, estrogen plus progestogen therapy or tissue-selective estrogen complex (conjugated equine estrogens plus bazedoxifene) should be used for protection against endometrial hyperplasia and cancer; good, consistent evidence supports this recommendation (Level 1).[1,4]
- The safety of progestogen-only treatment has not been evaluated in long-term studies.[4]
- Hormone therapy should be individualized and reevaluated periodically to determine the need for ongoing use; based primarily on consensus and expert opinion[4]

Assisted Reproductive Technology (ART): Luteal Phase Support

Progesterone replacement or supplementation as part of assisted reproductive technology (ART) for infertile patients with progesterone deficiency is supported by evidence.[4] Several small studies have demonstrated encouraging conception rates with progesterone therapy for luteal phase inadequacy.[4]

Vaginal administration of oral micronized progesterone formulation can effectively support the luteal phase and provides greater bioavailability of the active component at the endometrial

level than other routes of administration (e.g., IM, oral).[9] A meta-analysis comparing 50 mg intramuscular progesterone to vaginal progesterone, as either micronized progesterone 200 mg three times a day or progesterone gel 90 mg daily, found similar rates of clinical pregnancy and ongoing pregnancy between the two routes of administration with non-statistically significant lower miscarriage rates with intravaginal use.[10,11]

Treatment of Menopause Symptoms – Vasomotor Symptoms

Hormone therapy, with estrogen-alone for symptomatic women without a uterus and estrogen-progestogen or tissue-selective estrogen complex for symptomatic women with a uterus, is the gold standard for the treatment of vasomotor symptoms of menopause (Level 1).[1] An alternative approach using oral micronized progesterone 300 mg nightly has been found to reduce average daily vasomotor symptoms scores compared to placebo.[1] A small (n=133) randomized double-blind trial found the average daily vasomotor symptoms scores were better with progesterone vs. placebo (mean reductions of 10.0 [95% CI, -12.0 to -8.1] vs. 4.4 [95% CI, -6.6 to -2.2] in progesterone vs. placebo, respectively). [12]

Guideline Recommendations (North American Menopause Society)[1]

- In symptomatic women with a uterus, estrogen plus progestogen therapy or tissue-selective estrogen complex (conjugated equine estrogens plus bazedoxifene) should be used for protection against endometrial hyperplasia and cancer; based on good and consistent evidence (Level 1).[1,4]
- Micronized progesterone 300 mg nightly significantly decreases VMS (hot flashes and night sweats) compared with placebo and improves sleep. Synthetic progestins have also shown benefit for VMS in some studies. No long-term study results are available, and use of progestogens without estrogen for either indication is off-label. (Level II).[1]
- Hormone therapy should be individualized and reevaluated periodically to determine the need for ongoing use; based primarily on consensus and expert opinion.[1,4]

Guideline Recommendations (NICE Guidelines)[13]

Gender-affirming hormone therapy: past use

- Ensure that trans men or non-binary people registered female at birth who have taken gender-affirming hormone therapy in the past and have symptoms associated with menopause can discuss these with a healthcare professional with expertise in menopause.[13]

The NICE Guideline committee noted a lack of evidence on HRT use in trans men and non-binary people registered female at birth who have taken gender-affirming hormone therapy in the past. Therefore, it is not known whether past hormone treatment could influence the choice of HRT, or whether giving HRT to someone who previously had hormone therapy would alter their health risks. The NICE Guideline committee recommends new research be conducted on the impact of HRT on health outcomes for trans men and non-binary people registered female at birth, which covers people who have never taken gender-affirming hormone therapy, or who have taken it in the past but are not currently taking it.[13]

SAFETY

The overall safety profile of progesterone is favourable for most individuals when used orally as prescribed.[2] It has been safely used in many clinical trials lasting up to 3 years.[2] Additionally, studies have found oral micronized progesterone may be safer than synthetic progestins like medroxyprogesterone acetate (MPA).[14,15] For example, a review by Jiang and colleagues illustrates that OMP does not change most lipid levels or diminish estrogen's beneficial effects on lipoprotein metabolism.[16] Another study by Panay and colleagues compared the risk of venous thromboembolism (VTE) between patients treated with the combined oral product 17β-estradiol/micronized progesterone (E2/P4) and those treated with oral conjugated equine estrogen and medroxyprogesterone acetate (CEE/MPA) regimens and found that those treated with E2/P4 had a significantly lower risk of VTE compared with oral CEE/MPA, suggesting there may be lower risk of thromboembolic events with OMP compared to synthetic progestins.[15] A French study found the risk of invasive breast cancer was lower in patients receiving estrogen/progesterone combinations compared to estrogen/progestin or estrogen alone treatments.[14]

Although OMP is relatively safe, all drugs have potential risks and adverse effects.

Adverse Effects

Oral (percentages reported when used in combination/cycled with conjugated estrogens):

>10%:[4-6]

- Abdominal pain (20%)
- Bloating (12%)
- Breast tenderness (27%)
- Mastalgia (6% to 16%)
- Urinary tract abnormality (11%)
- Viral infection (12%)
- Depression (19%)
- Dizziness (15% to 24%)
- Headache (16% to 31%)
- Musculoskeletal pain (12%)

1% to 10%:[4-6]

- Chest pain (7%)
- Acne (5%)
- Cholecystectomy (2%)
- Constipation (3%)
- Diarrhea (7% to 8%)
- Nausea and vomiting (5 - 8%)
- Breast carcinoma (2%)
- Vaginal discharge (10%)
- Anxiety (8%)
- Fatigue (8%)
- Irritability (8%)

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- Cough (8%)

Frequency not defined:[4]

- Acute myocardial infarction
- deep vein thrombosis
- pulmonary embolism
- cerebrovascular accident
- dementia

Contraindications for Progesterone Use

There are certain contraindications and box warnings associated with progesterone:

- allergy or hypersensitivity to progesterone, soya, peanuts/peanut oil or to any ingredient in the formulation[5,6] [4]
- liver dysfunction or disease[4-6]
- personal history of known or suspected estrogen-dependent or progestin-dependent malignant neoplasia (e.g., breast cancer or endometrial cancer)[4-6]
- endometrial hyperplasia[6]
- undiagnosed abnormal vaginal bleeding[4-6]
- known or suspected pregnancy[4-6]
- active or past history of arterial thromboembolic disease (e.g., stroke, myocardial infarction, coronary heart disease) or active or past history of confirmed venous thromboembolism (such as deep venous thrombosis or pulmonary embolism) or active thrombophlebitis[4,6]
- classical migraine[6]
- partial or complete loss of vision due to ophthalmic vascular disease[6]

The Women's Health Initiative Study & Warnings

The Women's Health Initiative (WHI) is the largest, randomized, controlled trial (RCT) of hormone therapy in women aged 50 to 79 years to date. It examined the health benefits and risks of combined estrogen (conjugated equine estrogen) plus progestin (medroxyprogesterone acetate) therapy (n=16 608) and estrogen-alone therapy (n=10 739) for the prevention of heart disease, breast and colorectal cancer, and osteoporosis in postmenopausal women.[6]

The estrogen plus progestin arm demonstrated an increased risk of myocardial infarction (MI), stroke, invasive breast cancer, pulmonary embolism and deep vein thrombosis in postmenopausal women receiving treatment with combined conjugated equine estrogens (CEE, 0.625 mg/day) and medroxyprogesterone acetate (MPA, 2.5 mg/day) for 5.2 years compared to those receiving placebo.[6]

The estrogen-alone arm demonstrated an increased risk of stroke and deep vein thrombosis in hysterectomized women treated with CEE-alone (0.625 mg/day) for 6.8 years compared to those receiving placebo.[6]

In addition, the Women's Health Initiative Memory Study (WHIMS) estrogen plus progestin ancillary study reported an increased risk of probable dementia in postmenopausal women 65 years of age or older.[6]

Based on the Women's Health Initiative (WHI) trial findings, the Food and Drug Administration (FDA) and Health Canada put a boxed warning on all bioidentical progesterone and synthetic progestins.

Health Canada Serious Precautions and Warnings

Based on these study findings, the following should be given serious consideration at the time of prescribing:[6]

- Estrogens with or without progestins should not be prescribed for primary or secondary prevention of cardiovascular diseases or dementia.
- Estrogens with or without progestins should be prescribed at the lowest effective dose for the approved indication.
- Estrogens with or without progestins should be prescribed for the shortest period possible for the approved indication.

Box Warning – Food and Drug Administration, United States

Similarly, the US boxed warning states:

<u>Cardiovascular Disorders and Probable Dementia</u>

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia. The Women's Health Initiative (WHI) estrogen plus progestin substudy reported increased risks of deep vein thrombosis, pulmonary embolism, stroke and myocardial infarction in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral conjugated estrogens (CEE) (0.625 mg) combined with medroxyprogesterone acetate (MPA) (2.5 mg), relative to placebo.[4]

The WHI Memory Study (WHIMS) estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CEE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.[4]

<u>Breast Cancer</u>

The WHI estrogen plus progestin sub study also demonstrated an increased risk of invasive breast cancer. In the absence of comparable data, these risks should be assumed to be similar for other doses of CEE and MPA, and other combinations and dosage forms of estrogens and progestins. Progestins with estrogens should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.[4]

Oral Micronized Progesterone

Issues with the Serious/Boxed Warnings

After the boxed warnings mentioned above were issued, there was a significant decrease in the use of hormone replacement therapy, resulting in many women suffering from menopausal symptoms.[1]

In recent years, there has been increasing criticism that the results of the WHI study were too broadly generalized, which has had a negative impact on women's health care. For example, the WHI study used medroxyprogesterone acetate (MPA), which is a synthetic progestin, not a bioidentical progesterone, yet the warning labels were applied to all progesterone. While further investigation is needed, more recent studies suggest that oral micronized progesterone may not carry the same risk as synthetic progestins, particularly as it relates to cardiovascular and breast cancer risk.[14-16]

In addition, the WHI study included postmenopausal women aged 50-79, with the risks identified as more pronounced in older postmenopausal women (65+) than in younger women. Therefore, estrogen and oral micronized progesterone may be safe in younger women with less risk than that reported in the WHI study. Further, the study was not designed to evaluate efficacy on vasomotor symptoms. Therefore, there was limited enrolment of women with bothersome vasomotor symptoms who were under age 60 or who were fewer than 10 years from menopause onset, which is the group of women for whom hormone therapy is primarily indicated.[1]

The National Institute of Health and Care Excellence (NICE) menopause guidelines include a statement in the 2024 update that "overall, life expectancy is unlikely to change with the use of combined hormone replacement therapy" in people aged 45 or over[13]. Similarly, an analysis of the effects of hormone therapy in women aged 50-59 years from the WHI found overall benefits to outweigh potential risks, including for all-cause mortality. While the WHI was not powered for age-related subset analyses, these estimates highlight the limitations to the boxed warnings.[8]

General Warnings/Precautions for Progestogen Use

Breast cancer:

- Estrogen with or without progestogen for the management of menopausal symptoms may be associated with an increased risk of breast cancer. The risk of breast cancer in patients who are postmenopausal on hormone therapy may depend upon type of estrogen and/or progestogen, dose, timing of therapy initiation, duration of therapy, route of administration, and individual patient characteristics.[4]

CNS depression:

- Oral progesterone may cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks that require mental alertness (e.g., operating machinery, driving).[4]

Endometriosis:

- Estrogens may exacerbate endometriosis. Malignant transformation of residual endometrial implants has been reported post-hysterectomy with unopposed estrogen

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therapy. Consider adding a progestogen in patients with residual endometriosis post-hysterectomy.[4]

Fluid retention:

- May cause fluid retention; use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, cardiac or renal impairment, epilepsy, and migraine.[4]

Retinal thrombosis:

- Discontinue pending examination in cases of sudden partial or complete vision loss, sudden onset of proptosis, diplopia, or migraine; discontinue permanently if papilledema or retinal vascular lesions are observed on examination.[4]

Cardiovascular disease:

- In the Women's Health Initiative studies, an increased risk of deep vein thrombosis, pulmonary embolism, stroke, and myocardial infarction was observed in patients taking conjugated estrogens combined with medroxyprogesterone. Additional risk factors include diabetes mellitus, hypercholesterolemia, hypertension, systemic lupus erythematosus, obesity, tobacco use, and/or history of venous thromboembolism (VTE). Manage risk factors appropriately; discontinue immediately if adverse cardiovascular events occur or are suspected.[4]

Dementia:

- Dementia risk might increase with progestogen plus estrogen if it is started at 65 or over.[13]

Diabetes:

- May impair glucose tolerance though generally no adverse effect on blood glucose control is report; use caution in patients with diabetes. Prior to therapy, consider age, cardiovascular, and metabolic risk factors in patients previously diagnosed with diabetes.[4]
- Risk of developing type 2 diabetes does not increase with progestogen plus estrogen.[13]

Surgery:

- Whenever possible, discontinue progestogens in combination with estrogens at least 4 to 6 weeks prior to elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.[4]

DRUG RECALLS

None currently (as per Health Canada’s Recalls and Safety Alert Database)

PLACE IN THERAPY: CLINICAL PRACTICE GUIDELINES

North American Menopause Society (NAMS) Position Statement (2022 Update)[1]

- Hormone therapy (i.e., estrogen-alone in women without a uterus, estrogen-progestogen or tissue-selective estrogen complex (TSEC) in women with a uterus) is the most effective treatment for the vasomotor symptoms (VMS) and the genitourinary syndrome of menopause and has been shown to prevent bone loss and fracture. For symptomatic women with a uterus, estrogen-progestogen or TSEC protects against endometrial neoplasia.
    - The risks of hormone therapy differ depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used, hence treatment should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic re-evaluation to assess need for continued use. HRT should be individualized based on a woman's age, health risks, and personal goals. Shared decision-making should be used when considering formulation, route of administration, and dose of hormone therapy with adjustment tailored to symptom relief, adverse events, and patient preferences.
- For women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-to-risk ratio is favourable for the treatment of bothersome VMS and the prevention of bone loss.
- For women who initiate hormone therapy more than 10 years from menopause onset or who are older than 60 years, the benefit-risk ratio appears less favourable because of the greater absolute risks of coronary heart disease, stroke, venous thromboembolism, and dementia.
- Transdermal estradiol + oral micronized progesterone is preferred for reducing clot and stroke risk.
- Hormone therapy is safe for women under 60 or within 10 years of menopause if they have no contraindications.
- Micronized progesterone significantly decreases VMS (hot flashes and night sweats) and improves sleep. No long-term study results are available, and use of progestogens without estrogen for either indication is off-label.

Monitoring Requirements

Assisted Reproductive Technology (ART): Luteal Phase Support

- Infertility (assisted reproductive technology): Serum progesterone, particularly with intravaginal administration, to ensure proper endometrial preparation and support during the luteal phase.[8] Measuring urinary progesterone can be a marker of luteal activity.

Menopause (endometrial hyperplasia prophylaxis and vasomotor symptoms):

At Baseline (prior to combination hormonal therapy)[8]

Assess baseline risk for breast cancer and cardiovascular disease (CVD). Potential approaches:

- Breast cancer: IBIS Breast Cancer Risk Assessment
    - Low Risk (<1.67%): hormone therapy ok
    - Intermediate Risk (1.67 – 5%): caution
    - High Risk (>5%): avoid hormone therapy

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- Cardiovascular disease: ACC/AHA Cardiovascular Risk Calculator
    - Low Risk (<5%): hormone therapy ok
    - Intermediate Risk (5-10%): hormone therapy ok (choose transdermal estrogen)
    - High Risk (>10%): avoid hormone therapy

Safety Parameters

Physical Examination

- blood pressure
- breast exam
- pap smear
- pelvic exam
- endometrial biopsy (if appropriate)

Laboratory Tests

- mammography
- blood glucose
- calcium
- triglycerides
- cholesterol
- liver function tests

First Follow Up (3-6 months after initiation of treatment)

Efficacy Parameters

- response to treatment

Safety Parameters

- age-appropriate breast and pelvic exams
- blood pressure
- heart rate
- unscheduled bleeding lasting >6 months for endometrial pathology
    - sooner in patients who are obese, diabetic, or have a history of endometrial cancer
- serum triglycerides (2 weeks after starting therapy in patients with baseline level >200 mg/dL)
- TSH (6 to 12 weeks after starting oral therapy in patients taking thyroid replacement).
- Duration of treatment should be evaluated at least annually

Annual Monitoring

Efficacy Parameters

- Response to treatment and ongoing need/appropriateness of use

Safety Parameters

- Ongoing need and appropriateness of therapy (e.g., beyond 5-10 years, > 60 years old)
- Blood pressure

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- Heart rate
- Lipid levels
- Triglycerides
- Glucose
- Liver function tests
- Patients are encouraged to practice frequent breast self-exams

PRESCRIBING RESTRICTIONS

None

WHO CAN PRESCRIBE IN CANADA?

- Medical doctors and nurse practitioners across Canada can prescribe oral micronized progesterone.
- In British Columbia, naturopaths can also prescribe oral micronized progesterone
- In Alberta, pharmacists with prescriptive authority can also prescribe progesterone

TRAINING NEEDED FOR NATUROPATHS TO PRESCRIBE

- Additional training in therapeutics and prescribing (i.e., beyond the standard 4-year naturopathic degree)

CO-MANAGEMENT WITH A PHYSICIAN

Co-management with a physician is generally reserved for high-risk medications, controlled substances, biologics, or specialty drugs, and/or patients with complex medical needs that exceed the scope of practice of the healthcare professional involved.

Progesterone, including oral micronized progesterone, is not classified as a high-risk medication, nor is it a controlled substance, specialty, or biologic drug. As outlined above, prescribing OMP requires baseline physical and laboratory assessments, a 3–6-month follow-up, and annual assessments for efficacy and safety thereafter. The assessment requirements for oral, topical, and vaginal progesterone are similar, however OMP undergoes first pass metabolism which topical/vaginal formulations do not, which increases the potential impact on lipid levels. The effect on lipids with OMP is generally considered less than with synthetic progestins but more than with topical/vaginal formulations. As such, baseline lipid levels, liver function tests, and ongoing monitoring are recommended with OMP.

These monitoring requirements are within the current scope of practice of Naturopaths in Ontario.

<u>Referral or Co-management with a Physician is recommended for patients with the following:</u>

- Liver dysfunction or disease
- Undiagnosed abnormal vaginal bleeding
- History or presence of hormone-sensitive cancers (especially breast & uterine)
- History or presence of venous thromboembolism (DVT, PE) or active thrombophlebitis
- History of presence of arterial thromboembolic disease (stroke, MI, coronary heart disease)
- Allergy to peanuts/peanut oil, soya

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- Suspected or Actual Pregnancy
- Abnormal labs (i.e., elevated LFTs, hyperlipidemia)

Can Oral Micronized Progesterone Be Taken With Topical Estrogen?

Currently, naturopaths in Ontario who have completed the Canadian Therapeutics Prescribing Course can prescribe bioidentical estrogen and progesterone in topical and suppository form. If oral micronized progesterone were added to the prescribing list, it could be effectively and safely used in combination with topical bioidentical estrogen.

Topical bioidentical estrogen is often preferred over oral formulations because it bypasses the liver and does not undergo first-pass metabolism. This results in a lower risk of blood clots and less effect on triglycerides. In addition, it may also have a lower stroke risk.

Several studies have shown oral micronized progesterone to be safe and effective. The French E3N Cohort Study, a large observational study, showed that transdermal estrogen plus micronized progesterone was associated with a lower breast cancer risk than combinations involving synthetic progestins.[14] The North American Menopause Society (NAMS) position statement recommends transdermal estrogen as a safer option for women at risk for venous thromboembolism or with metabolic syndrome and oral micronized progesterone as a first-line option for endometrial protection due to its favourable side effects and safety profile.[1] The International Menopause Society also endorses this combination as clinically appropriate.

Therefore, combining transdermal estrogen with oral micronized progesterone is evidence-based, effective, and considered safe for most healthy women needing hormone therapy. It may even have advantages over the traditional oral estrogen + synthetic progestin combinations, particularly in terms of clotting risk, breast cancer risk, and metabolic effects.

Additional Comments

OMP is the gold standard for progesterone therapy in hormone replacement treatment plans. It is effective and safe when prescribed and monitored as per the guidelines and monograph recommendations.

The Ontario healthcare system is currently facing significant resource challenges; hence, many residents do not have regular access to a family physician or nurse practitioner. Relying on a referral or physician co-management system for menopause hormone therapy could reduce access to treatment, lead to delays, added costs, and fragmented care, which negatively impact patient outcomes.

Regulated health professionals with the appropriate scope of practice and knowledge, skill, and judgment can independently assess, prescribe, and monitor menopause hormone therapy for patients without contraindications. For high-risk or complex patients, co-management with a physician is warranted.

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TABLE 3
DRUGS THAT MAY BE PRESCRIBED

Drug	Limitations, routes of administration, dosages
Adenosine triphosphate	Only if prescribed for intravenous injection to be administered by the member in his or her office to the patient.
Calcium Chloride	Only if prescribed in injectable form for intravenous injection to be administered by the member to the patient.
Calcium Gluconate	Only if prescribed in injectable form for intravenous injection to be administered by the member to the patient.
Colchicine	Must not be prescribed unless the drug is botanical colchicine, compounded from the corm of colchicum autumnale.
Dextrose Injection	May only be prescribed when in concentrated solutions for intravenous injection to be administered by the member to the patient.
Digitalis Purpurea and its glycosides	Only if prescribed in conjunction with monitoring of patient's serum levels by member.
Estrogen (bioidentical)	Only if prescribed in topical or suppository form.
Folic Acid	Only if prescribed in oral dosage containing more than 1.0 mg of folic acid per dosage or, where the largest recommended daily dosage would, if consumed by a patient, result in the daily intake by that patient of more than 1.0 mg of folic acid.
L-Tryptophan	Only if prescribed for patient's use in oral dosage form at a concentration of more than 220 mg per dosage unit or per daily dose. Recommended daily dose must not exceed 12g and must be provided. May be prescribed as a single ingredient intended for intravenous injection.
Levocarnitine and its Salts	Only if prescribed for the treatment of primary or secondary levocarnitine deficiency.
Nitroglycerin	Administered to a patient by the member in his or her office only in emergency circumstances and only for angina pectoris. Dosage: 1 to 2 metered doses (0.4 or 0.8 mg nitroglycerin) administered on or under the tongue, without inhaling. The mouth must be closed immediately after each dose (up to 3 doses in total, at least 5 minutes apart). A sublingual tablet may be used (0.3 or 0.6 mg for initial dose). Maximum dose of 1.8 mg.
Pancreatin	Only if prescribed in a dosage form that provides more than 20,000 USP units of lipase activity per dosage unit or for the treatment of pancreatic exocrine insufficiency.

Pancrelipase	Only if prescribed in a dosage form that provides more than 20,000 USP units of lipase activity per dosage unit or for the treatment of pancreatic exocrine insufficiency.
Pilocarpine and its salts	Must not be prescribed unless, 1. the drug is botanical pilocarpus, compounded from the leaves of pilocarpus microphyllus, 2. the member monitors his or her patient's drug levels during treatment with the drug and, 3. the drug is never prescribed to treat a patient with glaucoma.
Podophyllotoxin	Must not be prescribed unless, 1. the drug is botanical podophyllotoxin compounded from podophyllum peltatum and, 2. the drug is never prescribed to treat a patient with rheumatoid arthritis.
Progesterone (bioidentical form)	Only if prescribed in a topical or suppository form.
Progesterone (oral micronized)	For use only in accordance with label indications approved by Health Canada.
Rauwolfia	No limitation, etc., specified.
Thyroid	No limitation, etc., specified.
Vitamin A	Only if prescribed in oral dosage form containing more than 10,000 International Units of Vitamin A per dosage or, where the largest daily dosage would, if consumed by a patient, result in the daily intake by that patient of more than 10,000 International Units of Vitamin A.
Vitamin D	Only if prescribed in oral dosage form containing more than 2,500 International Units of Vitamin D per dosage form or where the largest recommended daily dosage shown on the label would result in the daily intake by that patient of more than 2,500 International Units of Vitamin D.
Vitamin K1	Only if prescribed in oral dosage when the maximum daily dose is more than 0.120 mg.
Vitamin K2	Only if prescribed in oral dosage when the maximum daily dose is more than 0.120 mg.
Yohimbine and its salts	Must not be prescribed unless the drug is botanical yohimbine, compounded from the bark of pausinystalia yohimbine.

O. Reg. 168/15, Table 3; O. Reg. 94/23, s. 2