M EXPERT MONOGRAPH ISSUE 10

Overcoming Barriers to Menopausal Hormone Therapy

PROF BRONWYN STUCKEY BA MBBS FRACP

Professor Bronwyn Stuckey is a clinical endocrinologist specialising in reproductive endocrinology. Professor Stuckey is a consultant physician in Endocrinology and Diabetes at the Sir Charles Gairdner Hospital in Perth, Western Australia, Medical Director of the Keogh Institute for Medical Research and Clinical Professor in the School of Medicine and Pharmacology, University of Western Australia. Her clinical and research interests, and that of the Keogh Institute, lie within the interface between reproductive hormones and metabolism.

This article is an update about the risks and benefits of menopausal hormone therapy.

Introduction

Today, the life expectancy of the average Australian woman is eighty-seven years. Although this has increased over time with better healthcare, the average age of menopause is fifty-one years and this has not changed. The majority of women will spend over thirty years of their lives in the postmenopausal state. At menopause, most women will experience symptoms ranging from hot flushes, arthralgia, insomnia, cognitive dysfunction, genito-urinary symptoms and reduced libido. Some of these symptoms may or may not resolve with time. Importantly, menopause and the fall in oestrogen leads to bone loss, an unfavourable change in lipids and a rising cardiovascular and stroke risk, which do not resolve with time.[1-3]

Menopausal Hormone Therapy: Changing Opinions and Practice

The use of oestrogen to treat menopausal symptoms goes back to the 1940s. Oestrogen is certainly the most effective treatment for most menopausal symptoms.[4] However, over the years, perceptions of the wisdom of menopausal hormone therapy (MHT) containing

Take Home Messages

- Re-analysis of randomised controlled trials and observational studies suggest that MHT started within ten years of menopause does no cardiovascular harm.
- A re-analysis of the Nurses' Health Study showed that no significant increase in breast cancer was identified until after twenty years of oestrogen-only use.
- Not all MHT preparations have the same risk and side-effect profile; treatment should be individualised to each patient.
- A recent position statement by the Endocrine Society states that 'bio-identical' compounded hormone preparations are untested, unregulated and potentially harmful and should not be prescribed.
- The menopause consultation should include a full history and physical examination, preventative healthcare and requires time to effectively communicate information.

oestrogen, with or without progestogen, in terms of long-term health and chronic disease have swung back and forth. This is mostly due to large observational studies and several randomised controlled trials that have examined the long-term risks and benefits, as opposed to efficacy in symptom relief. The Nurses' Health Study was the first influential study in this regard. It documented a marked reduction in all-cause mortality, cardiovascular deaths and cancer deaths in women using oestrogen compared with non-users.[5] Although an increase in breast cancer diagnosis was identified, an increase in breast cancer deaths was not. As cardiovascular disease is the greatest threat to health in postmenopausal women, the trade-off seemed to be in favour of hormone use.

This 'trade off' perception changed with the publication of the Women's Health Initiative (WHI) Study in 2002.[6,7] The WHI Study stated that MHT was associated with an increased, rather than decreased, number of cardiovascular events. This received widespread and alarmist media coverage. The prescribing of MHT around the world dropped dramatically.[8] Women stopped taking their MHT, doctors stopped prescribing it, and there emerged a whole generation of younger medical graduates who were, and remain, uncomfortable with the provision of MHT to menopausal patients. This has become the watershed and the greatest barrier to provision of effective MHT for women with menopausal symptoms.

However, whilst there is apprehension on the part of younger medical graduates about prescribing MHT, there is also often a lack of understanding of the impact of moderate to severe menopausal symptoms on a woman's life and her consequent ability to cope. Hot flushes, insomnia and cognitive impairment can affect functioning in the workplace and lead to early resignation from employment.[9] Genito-urinary symptoms and sexual dysfunction can have an adverse impact on relationships.

Since 2002, however, re-analysis of the WHI Study results has brought some clarity as to when MHT is beneficial for long-term health and when it is not.[10] The concept of a 'timing hypothesis' has originated, whereby MHT started within ten years of menopause does no cardiovascular harm.[11] This is distinct from commencing MHT in the older woman, as trialled in the WHI Study. More recently, and somewhat ironically, WHI Study authors have complained that their results are being interpreted inappropriately to deny menopausal women effective therapy for their symptoms.[12] They want to 'get clinical care back on track'.

Why is clinical care of the menopausal patient so off track? What are the continuing barriers to providing good, evidence-based and effective treatment of menopausal symptoms?

Understanding Individual Risk and Benefit

There is no doubt that oestrogen-containing MHT is the most effective treatment for most menopausal symptoms.[4] However, not every woman will be comfortable with, or want to take, postmenopausal oestrogen therapy despite, at times, quite disabling symptoms. Sometimes this is an informed choice, but sometimes the decision is based upon a distorted interpretation of the data surrounding risk and benefit. One of the reasons for this is that the patient will come to the consultation with information from magazine articles or newspapers, from the Internet or from friends. This information may be about the risks of MHT, the benefits of 'natural therapies', and the 'safety' of complementary medications. Some of this may be partly true and some of it completely erroneous.

At the heart of the anxiety about MHT is the lack of understanding of risk. All epidemiological studies and randomised controlled trials express risks and benefits of treatment in terms of 'relative risk'. The WHI Study expressed the risk of breast cancer in participants taking continuous, combined MHT as a relative risk of 1.26.[2] Most patients, and some doctors, do not understand what this means. 'Relative risk' is the probability of a risk or benefit with treatment, divided by the probability of that risk or benefit with placebo. Certainly, the media infrequently understands it. One daily paper[13] published after the WHI Study reported that a woman taking MHT has a 26% chance of developing breast cancer! The fact that many risks and benefits of treatment, not only in menopause medicine, continue to be expressed as relative risk is a failure of communication. It is a failure to translate what is an epidemiologist's term of reference into clinically meaningful information for the clinician and the patient.

RISKS AND BENEFITS CHANGE WITH DIFFERENT MHT TYPES

- There is a distinct difference between the risk/benefit ratio of oestrogen-only treatment versus oestrogen plus progestin treatment
- There is a reduced concern about the risk of breast cancer in women who use oestrogen only and who have had hysterectomies
- A re-analysis of the Nurses' Health Study showed that no significant increase in breast cancer was identified until after twenty years of oestrogen-only use
- Oral oestrogen therapy has greater risk of thrombosis compared to transdermal oestrogen therapy
- Obese women and those with a family history of thromboembolic disease may be offered transdermal oestrogen therapy
- The risk of cardiovascular disease is not increased by either oestrogen only, or combined MHT, for women who are within ten years of cessation of menstruation

The most informative way to express risk and benefit for an individual woman is in terms of absolute risk, that is, the number of patients affected by the treatment minus the number affected without treatment. As an example, if a treatment reduces the number of people who die from a disease from six to four per thousand, that is a relative risk reduction of 33.3%, but an absolute risk reduction of two in one thousand, or 0.2%. For instance, in the WHI Study, the translation of the relative risk of breast cancer of 1.26 into absolute risk is an increase of nine breast cancers per ten thousand women per year, from thirty-four per ten thousand per year in the placebo group.[14] For an individual, this constitutes an increase in absolute risk over seven years of 0.5%. An alternative is to express risk and benefit as a comparison to other modifiers. For example, the increase in risk of breast cancer for women using combined MHT is less than that associated with consuming two standard drinks per day.[15] The risk of venous thrombosis with oral MHT is equivalent to that of having a body mass index (BMI) of over 30 kg/m^2.[16] The benefit of MHT in preventing osteoporotic fractures is equivalent to that of bisphosphonate therapy.[17,18] There are other ways for conveying absolute risk for breast cancer and other risks and benefits to the patient, for example, icon array diagrams and bar charts. A visual representation can lead to a greater understanding and a more informed choice.

Not All Hormone Therapy is the Same

The continuous combined arm of the WHI Study used conjugated equine oestrogens and medroxyprogesterone acetate. There is a widespread perception that the risks and benefits of all MHT types are equivalent to this arm of the study, however, this is not the case.

First, there is a distinct difference between the risk/benefit ratio of oestrogen-only treatment versus oestrogen plus progestin treatment. The risk/benefit discussion with a woman who has had a hysterectomy is much simpler, because there is a reduced concern about the risk of breast cancer. In the WHI Study, the absolute risk of breast cancer with oestrogen-only MHT was a reduction of seven breast cancers per ten thousand women per year, from thirty-four per ten thousand per year in the placebo group.[14] The change in individual breast cancer risk was a reduction of 0.53%.[11] This surprising finding has been upheld by a re-analysis of the Nurses' Health Study, in which no significant increase in breast cancer was identified until after twenty years of oestrogen-only use.[19]

Secondly, oral oestrogen therapy has a very different risk of thrombosis compared to transdermal oestrogen therapy. Women with a personal history, or even family history, of thromboembolic disease need not be denied MHT for menopausal symptoms, but should preferentially use transdermal therapy, since transdermal therapy avoids the first-pass effect on the hepatic coagulation cascade.[20, 21] This recommendation should also be considered in those with a BMI of over 30 kg/m^2, in whom the baseline risk of thromboembolic disease is already raised.[16]

Expert Interviews

HRT Contraindications
by Prof Bronwyn Stuckey

For more interviews visit www.healthed.com.au/video

Thirdly, re-analysis of data from both randomised controlled trials and observational studies has identified that the benefit to risk ratio of MHT, in terms of long-term health, is greatest when MHT is started in the early menopausal years.[11] This is an important concept that is one of the positive legacies of the WHI Study and that has been confirmed by meta-analysis of randomised trials.[22] For the woman who is within ten years of cessation of menstruation, the risk of cardiovascular disease is not increased by either oestrogen only or combined MHT.[13] Moreover, the meta-analysis upholds the reduction in cardiovascular disease in oestrogen-only MHT when this is commenced early (within ten years of cessation of menstruation).[22]

Therefore, not all MHT preparations have the same risk profile and the same side-effect profile. Although there are a number of preparations with different dosages, different delivery systems, and different formulations available for use, the range of options has not expanded, and in fact has contracted, since the publication of the WHI Study. This situation has improved recently as some new formulations have become available, but there is still room for the development of new MHT formulations that have been tested in clinical trials. The importance of this is that not one product is suitable for, or tolerated by, all women. It is useful for clinicians to be aware of the different formulations, their appropriateness in different situations, and for them to have an understanding of how to manage side-effects and complications. The 'Australasian Menopause Society Guide to Equivalent HRT/MHT Doses' is very helpful when there is a need to change MHT formulations from one to another. Go to http://www.menopause.org.au/for-women/information-sheets.

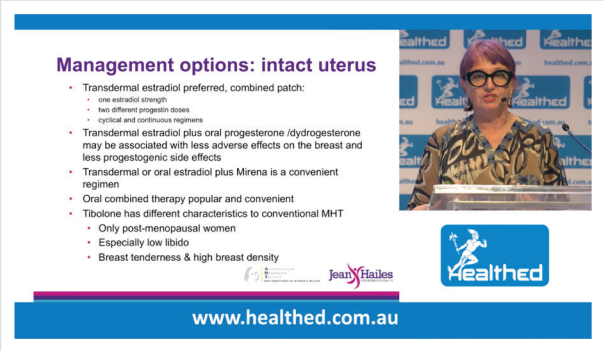
The Rocky Road of the Menopausal Transition

The most difficult part of menopause to treat is the menopausal transition, defined as the perimenopause and the very early postmenopausal years.

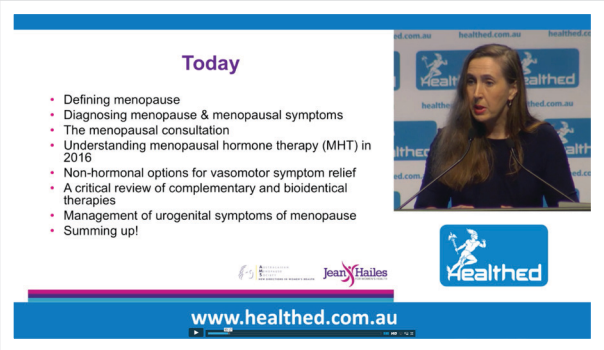
The perimenopause can be a time of hormonal chaos.[23] Rising

Video Resources

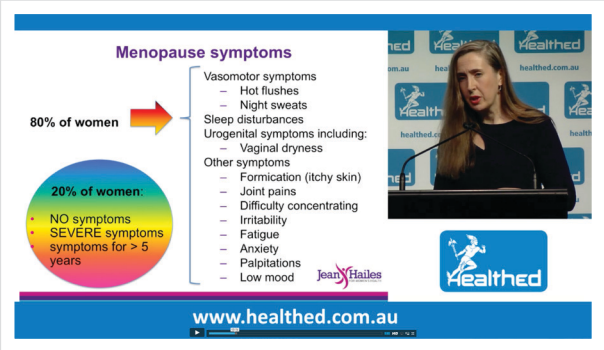
Menopause Management Update
Prof Bronwyn Stuckey



Menopause Management Update
Dr Elizabeth Farrell AM



Menopause Management Update
Dr Sonia Davison



A Practical Guide and Update on Using HRT in Practice – Dr Sonia Davison

Watch full lectures on the Healthed website. Visit www.healthed.com.au/video

FSH levels are associated with wide swings of oestradiol, often shortened menstrual cycles and even 'double ovulation' within one cycle.[14] Menopausal symptoms such as hot flushes alternate with symptoms due to high oestrogen, such as mastalgia, coupled also with the continued need to consider contraception in an unpredictable cycle. MHT introduced at this time needs to have, or be combined with contraceptive efficacy, either, for example, the newer oestradiol-containing (rather than ethinyl-oestradiol-containing) OCPs, or MHT with a progestin-containing IUD.

Just about the only element of menopause that most women appreciate is amenorrhoea. A woman whose periods have just ceased may want relief from other menopausal symptoms, but may also not want a return of cyclical vaginal bleeding. An attempt to accommodate this too early by commencing continuous combined MHT is likely to be accompanied by irregular and unscheduled break-through bleeding and the consequent abandonment of what would have been effective therapy.[24] Cyclical hormone replacement is preferable in the early year or years after the last menstrual period. If both the patient and the doctor understand this, it will lead to more effective and better tolerated early treatment. Progression to continuous combined MHT and the consequent elimination of cyclical bleeding can come later.

Patients with Specific Problems

There are some specific premenopausal conditions which need a special approach.

Migraine, either with or without aura, is not a contraindication to MHT for menopausal symptoms. Many women who have migraine with aura believe that MHT is contraindicated because they were told they should not take the oral contraceptive pill. Although migraine is not a contraindication, there are some management adjustments to be made. Premenopausal migraine, especially migraine without aura, is often triggered by falling oestrogen (such as the migraine headaches occurring just before and during menstruation). This can make the perimenopause, with its chaotic rises and falls of oestrogen, particularly troublesome. The transdermal patch delivers a more even dose of oestrogen, avoiding fluctuating serum oestradiol levels, and so is preferable as a form of MHT. In addition to this, the lack of prothrombotic effect due to transdermal delivery compared to oral delivery is preferable in the setting of migraine with aura.[25]

It is not uncommon for women to report mood disturbance in the progestin-containing phase of MHT. Women with a history of premenstrual dysphoric symptoms or mood disturbance on the oral contraceptive pill may present a challenge if they have an

intact uterus, and progestogen is therefore required. Apart from micronised progesterone, which is identical to natural progesterone, the progestins used in MHT are structurally related to either progesterone or to testosterone. They have varying interactions, positive and negative, with androgen receptors, glucocorticoid receptors and mineralocorticoid receptors. Intolerance to progestins may present a barrier to delivering effective oestrogen therapy. It would be easy to say that a more androgenic progestin is more likely to be associated with mood disturbance, but this is not always the case. A resolution to this problem requires testing the patient's response to different progestogens, or changing to an alternate progestogen delivery (such as intrauterine therapy), to less frequent progestogen exposure than every month. Or possibly changing to the newly developed combination of conjugated oestrogens and bazedoxifene (a selective oestrogen receptor modulator).

Women with a history of hormone-dependent cancer and menopausal symptoms are best managed by non-hormonal treatment of their symptoms. Usually, such a history is a genuine contraindication to the use of oestrogen and/or progestin-containing medication. Occasionally, there may not be an absolute contraindication (e.g. following hysterectomy for low grade endometrial metaplasia). Liaising with the treating surgeon, oncologist or pathologist will help to clarify the risk. There are a number of non-hormonal medications, such as serotonin-noradrenaline reuptake inhibitors, selective serotonin re-uptake inhibitors, gabapentin or pregabalin, which have been found to significantly reduce menopausal symptoms.[26] However, a woman who has tried these without satisfactory effect may still decide upon the use of oestrogen for quality of life. After a discussion with her treating oncologist, a fully informed and documented decision such as this should be supported.

It is clear from the preceding discussion that neither one form of MHT will suit every woman, nor will one form or one dose of MHT suit an individual woman in every phase of her postmenopausal life. A recognition of this, and an appreciation of when and how to change treatment formulation, is one of the challenges of menopausal medicine. This is the art of knowing how to individualise treatment within the framework of evidence-based MHT. It is also knowing that MHT will not be appropriate for every postmenopausal woman, particularly those with a history of hormone-dependent cancer. A good knowledge of non-hormonal treatment is therefore also required.

The Menopause Consultation

One of the main barriers to effective menopausal management is consultation time. There is hardly any other area in medicine which requires such a detailed initial discussion of risk and benefits, as well as reassessment of individuals over time. The consultation is not something that can be covered in ten minutes. To attempt to address this in a standard consultation is impossible and will lead to an incomplete understanding by the patient and often an unsatisfactory outcome.

THE MENOPAUSE CONSULTATION

- Address immediate concerns first and schedule a longer meeting about menopause
- Direct patients to evidence-based information about menopause at the first consultation
- Take the opportunity to address long-term health goals and institute beneficial lifestyle changes
- Discuss preventative medicine issues such as alcohol intake, smoking, Pap tests and mammograms
- Follow-up consultations are important as therapy requirements or the choice of therapy is unlikely to remain constant over the years
- Adjust and fit the therapy to the needs of the patient.

It is best to address immediate concerns first and to schedule a longer meeting about what to expect from menopause and from MHT, if that treatment is indeed what the patient is interested in. It is useful to direct patients to evidence-based information about menopause at the first consultation. The Australasian Menopause Society website at http://www.menopause.org.au/ has evidence-based information sheets on many aspects of menopause and MHT.

The consultation at the menopause transition is an ideal time to conduct a 'health audit'. Since many risk factors pertaining to health appear or worsen at menopause, this consultation is an excellent time to address long-term health goals, discuss preventative medicine and institute beneficial lifestyle changes, whether or not MHT is prescribed. It is important to assess BMI, lipid profiles, blood glucose levels and bone density, but there is also a need to discuss smoking, alcohol intake, mammograms and Pap tests. The resulting information often influences the management or the formulation of MHT, if that is what is decided upon.

Follow-up consultations are equally important, because it is unlikely that the requirement for therapy or the choice of therapy will remain constant over the years. Clinicians must be prepared to adjust and fit the therapy to the needs of the patient.

Compounding Caution

The anxiety surrounding MHT has opened the door to an industry promoting 'bioidentical' compounded hormones in the form of creams and troches, as more 'natural' and therefore safer. These custom compounded preparations may seem attractive to the patient. They may contain a variety of oestrogens, progestogens

and androgens and their steroid precursors. However, a recent position statement by the Endocrine Society has sounded a note of warning.[27] These preparations are untested, unregulated and potentially harmful. They should not be prescribed.

Conclusion

In Australia, 32% of women today are over fifty years old. The majority will experience menopausal symptoms of some form or another and these typically persist for four to eight years. Some women will find the symptoms persist much longer and even into their eighth decade. Barriers to effective menopause therapy have arisen because menopausal symptoms are perceived to be just a nuisance, that they will inevitably resolve in a few years and that the interventions are too risky. Alarmist articles in the popular press about research (such as the WHI Study), involving pharmaceutical preparations have opened the door to unregulated promotion of alternative hormones and hormone delivery systems, such as 'bio-identical' troches and cream therapies. Women who do not receive an educated and informative discussion about the appropriateness of evidence-based therapy and the true risks and benefits may be diverted to these alternative therapies, which have no safety data.

The answer is, of course, education of clinicians and education of women. The clinician must be able to explain to a woman, in a manner that she understands, the impact her choice will have on her as an individual, and not in a manner that is couched in terms of an epidemiological relative risk equation. To this end, the Australasian Menopause Society has declared as its mission to educate, to provide referenced information sheets, for both clinicians and consumers, on every aspect of menopause and to assist the general practitioner to practise medicine relating to this stage of a woman's life.

Further Reading

The Australasian Menopause Society website at http://www.menopause.org.au/

Baber RJ, Panay N, Fenton A. *2016 IMS Recommendations on women's midlife health and menopause hormone therapy.* Climacteric. 2016; 19:2, 109-150

Declaration

Prof Bronwyn Stuckey was commissioned by Healthed for this article. The ideas, opinions and information presented are solely those of the author. The advertiser does not necessarily endorse or support the views expressed in this article. Prof Bronwyn Stuckey declares no significant competing financial, professional or personal interests that might influence this article.

References

A list of references is included in the website version of this article.
Go to www.healthed.com.au/monograph

Cyklokapron® (tranexamic acid, 500 mg tablets)

PBS Information: This product is listed as an antifibrinolytic agent.

BEFORE PRESCRIBING, PLEASE REVIEW PRODUCT INFORMATION AVAILABLE AT WWW.PFIZER.COM

Indications: Menorrhagia. See full PI for complete list. Contraindications: History or risk of thrombosis, active thromboembolic disease (cerebral embolism, DVT, pulmonary embolism), colour vision disturbances, subarachnoid haemorrhage, hypersensitivity to tranexamic acid or other ingredients in the tablet. **Precautions:** Not for use in haematuria, do not use concomitantly with Factor IX Complex Concentrates or Anti-Inhibitor Coagulant Concentrates, irregular menstrual bleeding, disseminated intravascular coagulation, convulsions*. **Pregnancy Category B1**, use cautiously in nursing mothers. See full PI for details. **Adverse Effects: Common side effects:** Nausea, vomiting, diarrhoea. **Serious but rare side effects:** Thromboembolism, visual impairment, convulsions*. See full PI for details. **Dosage and Administration:** 1 g orally four times daily, increase to 1.5 g four times daily, for four days if needed. Initiate treatment at onset of bleeding continue for first 4 days of cycle. Assess patients after three months of treatment. Dosage adjustment in renal impairment. See full PI for dosage for other indications. Before prescribing, please review full Product Information available from Pfizer Australia Pty Ltd. V10313.

**Please note change to Product Information.*

LOETTE® (levonorgestrel 100µg and ethinyloestradiol 20µg) Tablets

PBS Information: This product is not listed on the PBS.

BEFORE PRESCRIBING, PLEASE REVIEW PRODUCT INFORMATION AVAILABLE AT WWW.PFIZER.COM

Indications: Prevention of pregnancy, treatment of moderate acne not responding to topical preparations in women. **Contraindications:** Presence or risks of venous / arterial thromboembolism (VTE / ATE) arising from a history or current VTE or ATE (MI or stroke), hereditary or acquired predisposition for VTE/ATE such as in cases of APC-resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia, antiphospholipid-antibodies, major surgery with prolonged immobilisation, existing higher or multiple risk factors for VTE/ATE, headaches with focal neurological symptoms, diabetes, severe hypertension, disorders of lipid metabolism and sickle cell anaemia; presence or history of pancreatitis, hepatic tumours or dysfunction, jaundice (including that related to pregnancy or previous use of combined oral contraceptives); steroid-influenced malignancy of genital organs or breasts; undiagnosed vaginal bleeding; pregnancy; hypersensitivity to any of the ingredients in LOETTE. **Precautions:** Ascertain full medical history prior to prescribing. Possible increased risk of circulatory disorders such as VTE, ATE; cardiovascular diseases especially with pre-existing risk factors such as hypertension, hyperlipidemia, obesity, diabetes, smoking (especially in women over 35) and in peri- and post-operative patients; headaches may increase risk of stroke; increased risk of blood clots in legs; ocular lesions; liver and gallbladder disease; carcinoma of the reproductive organs and liver; exacerbation of some conditions e.g. angioedema, sickle cell anaemia, multiple sclerosis, epilepsy, renal dysfunction; interference with lactation; genital bleeding; uncontrolled dyslipidaemias; interference with laboratory test results; risk of depression See PI for details. **Interactions with other Medicines:** rifampicin; phenytoin; carbamazepine; primidone; rifabutin; dexamethasone; griseofulvin; topiramate; some protease inhibitors; modafinil; ritonavir; barbiturates; St. John's wort; antibiotics such as ampicillin, penicillins and tetracyclines; atorvastatin; competitive inhibitors for sulfation in the gastrointestinal wall such as ascorbic acid and paracetamol; cytochrome P450 3A4 inhibitors such as itraconazole, fluconazole, and indinavir; cyclosporine; theophylline; corticosteroids; lamotrigine. See PI for details. **Adverse Effects:** ***Major***, see Precautions above. ***Most common***, headache (including exacerbation of migraine), vaginitis, nausea, vomiting, changes in appetite, mood or libido, nervousness, dizziness, acne, dysmenorrhoea, intermenstrual bleeding, metrorrhagia, amenorrhoea, abdominal pain, breast pain, tenderness, enlargement or secretion, change in cervical ectropion and secretion, fluid retention/oedema, changes in weight. See PI for details. **Dosage and Administration:** One tablet daily. Start with a pink tablet on first day of menstrual bleeding (new starters) or after last tablet of previous pack. Take all pink tablets before taking white tablets. Start new pack day after last tablet of previous pack. Before prescribing, please review Product Information available from Pfizer Australia Pty Ltd. ® Registered trademark V11216

MACRODANTIN® (nitrofurantoin) 50 and 100 mg capsules

PBS Information: This product is listed as an antiinfective for systemic use.

BEFORE PRESCRIBING, PLEASE REVIEW PRODUCT INFORMATION AVAILABLE AT WWW.PFIZER.COM

Indications: Urinary tract infections e.g. cystitis and pyelitis when due to susceptible pathogens. Not for cortical or perinephric abscesses or prostatitis. **Contraindications:** Anuria, oliguria or extensive renal impairment; hypersensitivity to furan derivatives; pregnant women during labour and delivery or imminent onset of labour; infants under one month of age. **Precautions:** Peripheral neuropathy (risk increases with renal impairment, anaemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency, and debilitating disease), hepatic reactions, pulmonary reactions, haemolytic anaemia, pseudomembranous colitis, renal impairment, acidosis, nursing mothers. Monitor liver, renal and pulmonary function. Acidifying, alkalinising or uricosuric medicines, phenobarbitone and antacids. See full PI for details. **Adverse Effects:** Very common/common: Nausea with associated anorexia and emesis. Uncommon/Rare: Abdominal pain, diarrhoea, hepatitis, polyneuropathy, dizziness, vertigo, depression, euphoria, confusion, psychotic reactions and benign intracranial hypertension, pulmonary hypersensitivity, dermatological reactions, sensitivity reactions, haematological reactions, urinary tract superinfections. Others, See full PI for details. **Dosage:** Take with food or milk. Adults: 50-100 mg four times a day. DO NOT EXCEED 400 mg DAILY. Prophylactic therapy: 50 mg or 100 mg at night. Children: Dose at 5-7 mg/kg body weight per 24 hours in divided doses 4 times a day. Please review full Product Information before prescribing. Product Information is available from www.Pfizer.com.au. ® Registered Trademark V10113

DUAVIVE® 0.45/20 0.45 mg Conjugated Estrogens/20 mg Bazedoxifene Modified-release Tablets.

PBS Information: This product is not listed on the PBS.

The risk associated with DUAVIVE is unknown due to the lack of long term safety data (see CONTRAINDICATIONS, PRECAUTIONS and ADVERSE EFFECTS, Description of Selected Adverse Reactions). The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women aged 50 to 79 years (mean age 63.6 years) during 7.1 years of treatment with conjugated estrogens (0.625 mg/day) alone therapy relative to placebo. Estrogen-alone therapy is also associated with an increase risk of ovarian cancer.