



This fact sheet has been developed to provide current general information about selective estrogen receptor modulators (SERMs) in the United States. As with all medical treatment, you should discuss any possible side effects with your clinician.

Q: Lately I've been hearing and reading about SERMs. What are they, and what do they do?

A: SERMs stands for “selective estrogen receptor modulators,” also called estrogen agonists/antagonists, which describes what these drugs do. They activate or block the estrogen receptors only in certain areas of the body and not others. That can make them safer than estrogen alone or result in fewer side effects. For example, a SERM that acts like estrogen mainly in the vagina and not the uterus helps avoid the risk of uterine cancer because it doesn't stimulate the uterine lining (called the *endometrium*) the way estrogen does. Because SERMs vary in their activating (agonist) or blocking (antagonist) properties, they can be used to selectively target, prevent, and/or treat several diseases, including breast cancer, osteoporosis, and the genitourinary syndrome of menopause, also known as vulvovaginal atrophy.

Q: Back to basics. What are estrogens?

A: Estrogens are the primary female sex hormones naturally produced by the ovaries. Estrogens, especially the most potent one known as *estradiol* or sometimes just estrogen, play a major role in women's cycles and reproduction. They also act on many other tissues in the body, including the brain and breast. Estrogen levels begin to decline naturally as women go through menopause. It is this lack of estrogen that may lead to hot flashes, sleep disturbances, night sweats, vaginal dryness, and other symptoms of menopause you commonly hear about. Over the past 60 years, estrogens have been used to treat hot flashes at menopause. But for women after menopause (called *postmenopause*) who still have a uterus, taking estrogens alone increases the chance that the uterine lining will thicken, which can lead to cancer of the uterus. Adding progestogen or a progestogen-like drug (called a *progestin*) can help lower this risk. That's why estrogens have been combined with progestin for women who have not had a hysterectomy.

Q: How do SERMs differ from estrogen?

A: Estrogen activates estrogen receptors, which produce actions such as growth of vaginal, endometrium, or breast tissue. SERMs may activate or block estrogen receptors and the resulting actions. See, “Lately I've been hearing and reading about SERMs. What are they, and what do they do?” for more details.

Q: Are there SERM-containing drugs that help with hot flashes?

A: To date, there are no SERMs that relieve hot flashes, although there is one in phase 2 testing. There is a SERM combination being used for hot flashes in a pill form that combines conjugated estrogens with the SERM *bazedoxifene* (marketed as Duavee). Together, they form what's called a *tissue-selective estrogen complex*, or TSEC. This drug has been approved to treat hot flashes and to prevent osteoporosis in women with a uterus. Bazedoxifene acts both as an estrogen receptor agonist and antagonist, depending on the tissue. In the uterus, for example, it blocks estrogen receptors, so it

reduces the risk of uterine cancer. Therefore, prescribing a progestin is *not* needed for women with this TSEC.

Q: Is there a hormone therapy for women with a uterus that does not cause bleeding?

A: Yes, the combination of bazedoxifene and conjugated estrogen (marketed as Duavee) provides relief of hot flashes and prevention of bone loss, with a bleeding pattern similar to taking a placebo. This is very different than the increase in bleeding patterns seen with traditional estrogen and progestogen combinations.

Q: My breasts are dense. Is there a SERM that treats hot flashes but doesn't increase breast density?

A: Yes, the combination of bazedoxifene and conjugated estrogen (marketed as Duavee) provides relief of hot flashes and prevention of bone loss without causing bleeding and does not increase breast density, similar to placebo.

Q: My mother had breast cancer. Is there a SERM that can prevent breast cancer?

A: Yes, two of them are FDA approved to prevent breast cancer. Raloxifene (marketed as Evista) is a SERM that is approved to prevent invasive breast cancer in women at risk for breast cancer. Tamoxifen (marketed as Nolvadex) is a SERM used to treat breast cancer but has also been shown to prevent breast cancer.

Q: I've had breast cancer. Can a SERM help me?

A: Yes. There are two SERMs approved and used in breast cancer. Tamoxifen was the first clinically significant SERM ever developed and is a strong estrogen blocker (antagonist). It is used as an add-on to other cancer drugs to treat breast cancer, to treat metastatic breast cancer, and to reduce the risk of invasive breast cancer in women who have ductal carcinoma in situ, the most common type of breast cancer (sometimes called a *precancer*), or at high risk of developing breast cancer based on risk factors such as family history. Toremifene (marketed as Fareston) is a mixed activator (agonist)/blocker (antagonist). It has been approved to treat metastatic breast cancer after menopause in women who have either estrogen receptor-positive cancer or unknown tumors.

Q: I have low bone mineral density. Is there a SERM that can help?

A: Raloxifene (marketed as Evista), a mixed estrogen activator (agonist) and blocker (antagonist), acts as an activator in bone and as a blocker in the uterus and breast. It is FDA approved to prevent and treat osteoporosis and to reduce the risk of invasive breast cancer in women who have osteoporosis or who are at high risk of breast cancer. Its benefits include slowing the process of bone loss and rebuilding (called bone turnover), increasing bone density, and reducing the risk of vertebral fractures caused by osteoporosis. Raloxifene may be a good option for women in the years not long after menopause because these women may be more prone to vertebral fractures than hip fractures (unlike older women). In addition, raloxifene has been shown to reduce the risk of invasive breast cancer in women with osteoporosis and in women without osteoporosis who are at high risk of this type of cancer. When trying to improve bone density or prevent bone loss, you also need 1,200 mg of calcium (diet or supplement) and adequate amounts of vitamin D₃, as well as strength training.

Q: At my last exam, my nurse practitioner said that I have vulvar and vaginal atrophy (VVA) and that is why sex is painful for me. Has a SERM been developed to treat this?

A: Ospemifene (marketed as Osphena) is a mixed estrogen activator (agonist) and blocker (antagonist). In 2013, FDA approved ospemifene to treat moderate to severe pain with intercourse, which is a symptom of the VVA that can come with menopause. This SERM helps to rebuild the thinning and

drying lining of the vagina, which relieves painful sex. To date, no phase 3 clinical trials have evaluated its effects on breast density, breast cancer, or osteoporosis.

Q: Is there one SERM that has all of these benefits?

A: The ideal SERM would provide the effects of an estrogen activator (agonist) on the bone to prevent bone loss and on the brain to treat hot flashes while providing neutral or estrogen blocker (antagonist) effects on the breast and the lining of the uterus to reduce cancer risks. To date, the ideal SERM used by itself has not been discovered, but each one has specific benefits that may make it the right one for you. SERMs do have a slight increase in blood clot risk, similar to that seen with oral estrogen.

Q: So what is the bottom line?

A: Talk to your clinician about whether a SERM might be right for you if you are experiencing hot flashes and have a history of breast cancer, have been told you have low bone density, want to avoid bleeding or change in breast density but need relief from hot flashes, or sex is painful for you. Write your questions and all your symptoms down before your visit to discuss with your clinician. There is help out there.