A Review on Selective Estrogen Receptor Modulators
Himadri Bandolia, Waseem Khan
Siddhartha Institute of Pharmacy, Near IT Park, Dehradun- 248001, Uttarakhand, INDIA

INTRODUCTION
In postmenopausal women, selective estrogen receptor modulators drugs, which exert estrogenic as well as antiestrogenic actions in a tissue selective manner, are used for the treatment of osteoporosis, breast cancer and with effects on the uterus and vagina that depend on the interaction with the estrogen receptors in target tissues.[1] Menopause is the natural step of aging in which end of menstruation after the last menstrual period in the last 12 months take place.[2] Due to decline of estrogen levels after menopause, hot flashes and sweating occurred as the part of the menopausal vasomotor symptoms with the estrogen related urogenital atrophy and loss of bone density. Hormone Replacement Therapy is used for the treatment of these symptoms, but due to the presence of risk of using hormone replacement therapy causing breast cancer, endometrial cancer, thromboembolism, vaginal bleeding, which may reduce the use of hormone therapy.[3]

Selective Estrogen Receptor Modulators (SERMs) has three compounds Tamoxifen Citrate, Raloxifene, Bazedoxifene. These three compounds are used for clinical use. Tamoxifen Citrate is a first line hormonal treatment drug. It was made in 1962 by chemist Dora Richardson. It acts as selective estrogen receptor modulator or as a partial agonist of the estrogen receptors. It has mixed estrogenic and antiestrogenic activity with its profile of effects deficiency by tissue. Currently prescribed for estrogen receptor positive breast cancer. Tamoxifen Citrate has predominantly antiestrogenic effects in breasts but predominantly estrogenic effects in the uterus and liver. It also considered as for the treatment of osteoporosis. [1]

Raloxifene is second line hormonal treatment drug. It is used for the treatment of osteoporosis in postmenopausal women and reduces breast density. It is also an estrogen receptor antagonist and act as anti-estrogen on the uterus approved by the Food and Drug administration to treat osteoporosis. Bazedoxifene has been also developed for the treatment of osteoporosis.

Keywords: SERMs, Osteoporosis, Menopause
Re-evaluation of Medical Use on The Basis of Clinical Data

Arthritis Use (agonist activity of tamoxifen)
Arthritis is categorized as persistent synovitis and systemic inflammation which is more affected in women than men, especially during the menopause phase in which there is reduction of sex hormones, mainly estrogen. It is also known as that estrogen receptor alpha is expressed in synovial tissues which is regulated upwards in the presence of inflammation.[6] Tamoxifen represented agonist effects in inhibiting neutralized migration and preventing arthritis progression in ovariectomized mice.[7] IL-17- producing CD4 T- helper cells (Th 17 cells) are present in the inflamed joint cavity and contribute to the progression of an early inflammation to persistent chronic arthritis.[8]

Comparison between tamoxifen and clomiphene citrate
Clomiphene citrate and tamoxifen commonly used SERMs for the induction of ovulation.[9] Ovulatory dysfunction is one of the common causes of reproduction failure in sub fertile and infertile couples.[10] In 1956, clomiphene citrate has been used as the first line method of ovulation induction in couples with an ovulatory infertility. Many studies shown that approximately 80% of women ovulate using clomiphene citrate but only 40% of women achieve pregnancy.[11] Tamoxifen has also been used for the induction of ovulation. It is firstly used as an adjuvant therapy in the treatment of breast cancer but its use as an ovulatory agent was first reported in 1973.[12] It was conducted by many previous trials that the lack of conception despite evidence of ovulation may be due to anti-estrogenic effects of clomiphene citrate on the endometrium which many manifest as thin endometrium and thus tamoxifen estrogenic effects on the endometrium and cervical mucus result in higher pregnancy rates.[13]

CNS Remyelination
In multiple sclerosis, an inflammatory autoimmune disorder of the CNS, an adaptive immune response to unknown CNS antigens results in oligodendrocyte damage, loss of myelin and neurologic dysfunction.[14] A compelling remyelinating agent, bazedoxifen- EMA approved (European Medicine Agency), found that Bazedoxifen enhances OPCs into functional oligodendrocytes which enhanced OPC differentiation and remyelination.[15]

For Breast Cancer Cells
Estrogen receptor alpha play a vital roles in the etiology, treatment and prevention of the majority breast cancer.[16] Somatic mutations to ESR1 (gene for ER alpha) ligand binding domain (LBD) were identified in 25-30% of patients who previously received endocrine treatment.[17] Bazedoxifene possesses improved inhibitory potential against the Y537S and D538G ER-alpha mutants as compared to tamoxifen and has inhibitory activity in combination with CDK4/6 inhibitor palbociclib.[18]

For Osteoporosis
Several SERMs are being utilized clinically. The SERMs raloxifene and bazedoxifen also both reportedly inhibit bone resorptive activity in postmenopausal osteoporosis patients and have been used to prevent bone fragility fractures. Under sex hormone depleted conditions, Hif1-alpha was demonstrated to be a therapeutic target in conditions of postmenopausal and male osteoporosis. Since in postmenopausal, estrogen deficient conditions promote osteoclast activation leading to bone loss, estrogen administration is considered a means to reverse these conditions, although treatment can have adverse effects.

However, SERMs have been found to be less effective in inhibiting osteoclastic bone resorption than bisphosphonates. Testing inhibitory effects on Hif1-alpha protein in osteoclasts in vitro is useful to screen candidate anti-bone resorptive agents before animal models.[19]

Adverse effects of SERMs
Clinical usage of SERMs medication can have several side effects. Hot flashes, vomiting, vaginal bleeding, vaginal discharge, menstrual irregularities are the side effects. Increased risk of venous thromboembolism is due to estrogenic action on clotting mechanism, by consuming tamoxifen. Raloxifene consumption causes hot flushes, and leg cramps which are quite mild. The only serious concern is 3-fold increase in risk of deep vein thrombosis and pulmonary embolism. Use of tamoxifene has also been linked to higher occurrence of cataract.[5]

Conclusions
With the advanced version of SERMs, they have become suitable for treatment of osteoporosis in postmenopausal women. SERMs also used in arthritis inflammation but require caution in their use. SERMs also have their effect pregnancy rates. After 80 years of usage, side effects are more likely to be absorbed. Based on large epidemiological studies which have shown 45% reduction in the incidence of ER- positive breast cancer, tamoxifen has been approved for primary prophylaxis of breast cancer in high –risk women. Improvement in bone mass due to anti-resorptive effect, and in lipid profile are the other benefits of tamoxifen therapy. Several long-term multicentric studies have shown that raloxifene prevents bone in postmenopausal women. Mainly SERMs are used for the treatment and prevention of breast cancer and osteoporosis in postmenopausal women and expected to be a good choice of treatment.

References
8. Paulissen SMJ. The role and modulation of CCR6-1 Th17 cell population in rheumatoid arthritis. Cytokins.2015;45-53.