Nestorone® Gel - A Novel Contraceptive Gel

Antares Pharma and the Population Council are collaborating to develop a novel hormonal contraceptive gel product, comprising Nestorone® and estradiol (E2). This proprietary product recently completed a Phase II clinical trial and is based on Antares' Advanced Transdermal Delivery (ATD™) gel system and incorporates the Population Council's Nestorone®, a novel progestin. Although not active orally, clinical studies have shown that when delivered to the skin Nestorone® is highly effective at stopping ovulation at low doses and has a good safety profile, with no androgenic hormonal side effects.

The novel combination of Nestorone® and estradiol is being developed to offer a better safety profile compared to commonly-used hormonal contraceptives and also to provide an effective, easy-to-use method of contraception requiring once-daily application of gel to the skin from a metered-dose pump or sachet.

Contraception – The Background

Approximately 80 million women in the top seven pharmaceutical markets use hormonal contraception during their reproductive stages of life, which is typically between the ages of 15-49 years. According to a recent Datamonitor report the global market for systemic hormonal contraceptives is US$9 billion.

The majority of marketed hormonal contraceptives contain different combinations of estrogen and progestin. These prevent pregnancy in a number of ways: they inhibit ovulation, thicken the cervical mucus to make sperm entry difficult, thin the endometrium so that it cannot support implantation of a fertilised egg, and alter the fallopian tubes so that eggs cannot be moved effectively towards the uterus.

Monophasic contraceptives (those containing a fixed dose of both estrogen and progestin during the entire menstrual cycle) dominate the hormonal contraceptives market and, although oral dosage forms have been the most popular, they are increasingly facing competition from other routes of delivery, e.g. implants, injections, and vaginal and transdermal delivery.

Despite the widespread use of hormonal contraceptives, many women stop using this form of birth control because of associated side effects, which include menstrual irregularities, weight gain, and mood changes. Indeed data from the US National Survey of Family Growth reveals that 31% of women discontinue use of reversible contraceptives within six months of starting for method-related reasons, and 44% discontinue within 12 months.

Competition in the hormonal contraceptive market is based in large part on the side effect profile of different combinations and dosages of hormones administered. As the side-effect profile plays a role in both the compliance rate and discontinuation rate of competing products, this is a key differentiating factor for newer products and will ultimately influence their market success.

Novel Contraceptive Gel

Antares Pharma and the Population Council (an international, nonprofit research organization) are collaborating to develop a novel hormonal contraceptive that combines the progestin Nestorone® and a form of estrogen, called 17β-estradiol (known as E2), which is chemically identical to the naturally occurring estrogen. This combination was chosen because of the potential for superior safety profiles of the two hormones when compared to other commonly used hormones in contraceptives.

Nestorone® is a progestin that is not active when orally administered, however the hormone is active when it is applied to the skin. Shown to be highly effective at stopping ovulation at a low dose,

Nestorone® has no androgenic hormonal activity and therefore its use results in fewer side effects (e.g. acne, weight gain, and altered cholesterol levels) compared to other common progestins. Nestorone® is also particularly applicable for use in women who are breastfeeding. Indeed, previous studies of breastfeeding women using Nestorone® delivered via implants did not show any health impact on the infants.

When delivered by the transdermal route, estradiol has the advantage of being a much less potent estrogen than the commonly used contraceptive ethinyl estradiol (EE) and therefore potentially has a lower risk of causing venous thromboembolism.

The new contraceptive gel is based on Antares' proprietary Advanced Transdermal Delivery gel system, a delivery system used with the FDA-approved product, Elestrin™. Delivered using a metered-dose pump bottle to ensure accurate dosing, ATD™ gel formulations are easy to use, unscented, clear and cosmetically acceptable. They are designed for once-daily application on the upper arms, shoulders, abdomen or internal parts of the thighs. The gel dries rapidly leaving no residues, allowing the two hormones to be slowly absorbed across the skin into the systemic circulation. A key benefit of ATD™ gels is their excellent local skin tolerance offering a particular advantage over transdermal patch systems, which frequently cause local skin irritation at the application site.

Clinical Development Status

A Phase II clinical trial demonstrated that the transdermal gel is able to suppress ovulation at all doses tested. The trial also determined the dose that gives the most stable levels of hormones. The trial, involved both US and international study sites, and evaluated three active strengths of the combination gel in eighteen healthy, ovulating women. At different times during the course of the study, each woman received different dosages, with appropriate washout periods between doses. The acceptability study revealed that participants found the gel easy to use, to remember, and that it had few side effects.

The previous Phase I study identified a dose of the two hormones that consistently resulted in blood levels that would be expected to provide effective contraception and to maintain a woman's normal estrogen levels and bleeding patterns. Additionally, the gel was well tolerated, with no serious adverse events reported.

Intellectual Property Rights and Commercial Strategy

The contraceptive gel is protected by a series of patents and patent applications owned by Antares and the Population Council. These patents cover Nestorone®, the combination of Nestorone® with estradiol and the ATD™ technology.

Antares and the Population Council share the exclusive rights to the contraceptive gel and are seeking a licensing partner(s) to develop and market the product in the major markets worldwide.

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