CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-683

PHARMACOLOGY REVIEW(S)

N20-283.000

5-6-1996

NDA 20-683

Wyeth-Ayerst laboratories
Philadelphia, PA

Submission dated: 3-27-1996 Received at CDER: 3-28-1996

Pharmacology Review of the Original NDA Submission

Drug Product established name: levonorgestrel/ethinyl estradiol

Proposed proprietary name: Alesse

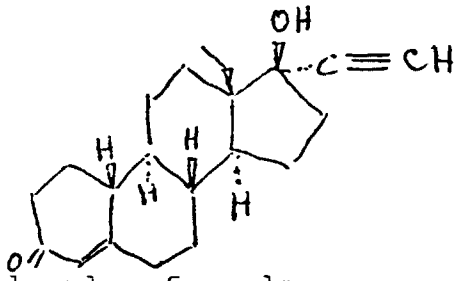
Alesse 28 version and Alesse- 21 version

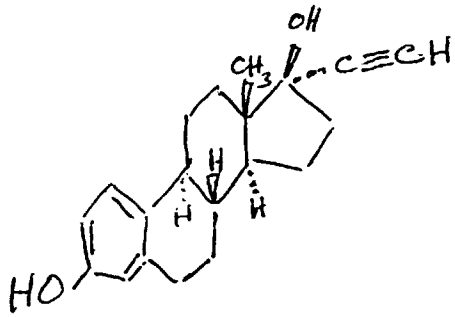
Chemical name:

levonorgestrel: (-)-13-ethyl-17-hydroxy-18,19-dinor-17-alpha-pregn-4-en-20-yn-3-one.

Ethinyl estradiol: 19 norpregna-1,3,5 (10)-trien-20-yne-3,17-diol, (17alpha).

Chemical structure:





Molecular formulas:

Levonorgestrel: C21 H28 O2
Ethinyl estradiol: C20 H24 O2

Molecular weight:

levonorgestrel: 312.45

Ethinyl estradiol: 296.41

Dosage form: Tablet

Route of administration: Oral

Strength(s): levonorgestrel (WY-5104)0.100 mg; ethinyl estradiol (AY-3877) 0.020 mg

Alesse 21 contains 21 pink tablet each containing 0.10 mg LNG and 0.02 mg EE. The inactive ingredients include cellulose, hydroxypropyl methylcellulose, iron oxide, lactose, magnesium stearate, polacrillin potassium, polyethylene glycol, titanium dioxide, and wax E.

Alesse-28 regimen has 7 light green inert tablets, which have the same inactive ingredients as for Alesse-21 plus FD&C blue no.1.

Theoretical coated tablet weight for the LNG/EE and placebo tablet is mg.

Proposed indication: Contraception

Mechanism of action: Combination oral contraceptives act by suppression of gonadotropins. Primary mechanism of action is inhibition of ovulation. They also cause alterations in the cervical mucus making sperm entry into the uterus difficult and cause changes in endometrium which reduce the likelihood of implantation.

Related INDs, NDAs and DMFs:

IN IN
NDA 19-934
DMFs

Nonclinical pharmacology and toxicology: The sponsor has stated that nonclinical pharmacology, toxicology and drug metabolism information for levonorgestrel and ethinyl estradiol submitted in this NDA consists of a historical summary of studies that were conducted to investigate the effects of these contraceptive steroids in animals. The summary encompasses Wyeth-Ayerst internal research reports (GTRs) as well as published literature.

Wyeth-Ayrest GTRs for studies involving LNG and EE administered alone or in combination were stated to have been submitted with IN) and IN Reports for studies comparing LNG with gestodene and other progestational steroids were submitted in NDA 19-934 (triphasic gestodene plus EE) on May 18,1989.

Preclinical toxicologic profiles have been evaluated in rats, dogs, and monkeys following single, subchronic and chronic multiple oral dose administration.

General technical reports by Wyeth-Ayerst comprise of acute oral toxicity studies in mice and rats with various combinations of LNG with EE; one month and 12 month oral toxicity in rats; 6 month and 7 year toxicity studies in dogs; and 3 month, one year and 10 year toxicity studies in monkeys. Reproductive toxicity studies consisted of segments 1, 2 and 3 in rats and segment 2 in rabbits.

It is further stated that inn light of the large body of existing preclinical data as well as the long history of safe and effective use of LNG/EE in humans, no new preclinical studies were conducted to support the approval of present low-dose LNG/EE oral contraceptive in accordance with an agreement made with Dr. Alex Jordan, Supervisory Pharmacologist, during a 17 Nov 1993 telephone discussion.

Clinical studies: The sponsor has stated that this NDA is submitted in accordance with the Division's 1987 oral contraceptive clinical data requirements i.e. at least 600 women who had completed 6 months of use, for products containing reduced amounts of approved steroids in the same ratio as a marketed product.
To this end sponsor has cited one ongoing multicenter Phase III clinical trial (Protocol 858-A-301-US,CA) which provides the primary evidence for the efficacy and safety of Alesse. The clinical database derived from this study includes data for 1,477 women with a total of cycles of experience; 792 of these women have completed 6 cycles of use. Five pregnancies occurred during the cycles evaluable for efficacy, for Pearl Index of 0.84, establishing this low-dose contractive's effectiveness.

Levlen-21 is the marketed oral contraceptive which has higher amounts of levonorgestrel and ethinyl estradiol mg/tablet) but has same ratio of the 2 components as in the proposed low dose OC which

has mg LNG and mg EE.

Wyeth-Ayerst Triphasil oral contraceptive tablets also have levonorgestrel and ethinyl estradiol in higher though not in 5:1 ratio. Three different phases Triphasil tablets contain mg LNG + mg EE; LNG + mg EE and mg LNG + mg EE. Wyeth-Ayerst Laboratories OC Nordett-28 also contain mg LNG + mg EE/tablet.

Labeling: The draft labeling is said to be based on the June 17,1994 package insert for Nordett-28; instructions for use of the MINI-PACK were derived from those for Triphasil-21 dated April 19, 1994 and for the use of the Clinic PILPAK, from Triphasil-28 dated September 14, 1995.

Recommendations: In light of the fact that there is a large body of available published preclinical database along with long history of safe and effective use of LNG/EE in humans with approved marketed products having similar LNG/EE ratio and containing higher doses, Pharmacology has no objection to the approval of the proposed low-dose LNG/EE oral contraceptive.

Krishan L. Raheja 5/6/96

Krishan L. Raheja, D.V.M., Ph.D.

A Jordan 5/6

Original NDA 20-683
HFD-345
HFD-510
HFD-510/A.Jordan
HFD-510/K.Raheja, 5-6-1996, N20-683.000