CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
016131Orig1s028

Trade Name:	CLOMID tablets
Generic or Proper Name:	clomiphene citrate
Sponsor:	Sanofi-Aventis U.S., LLC
Approval Date:	December 18, 2017
Indication:	For the treatment of ovulatory dysfunction in women desiring pregnancy.

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 016131/S-028

SUPPLEMENT APPROVAL

sanofi-aventis U.S., LLC
Attention: John Cook
Senior Director, Global Regulatory Affairs
North America and Global Regulatory Affairs
55 Corporate Drive
Bridgewater, NJ 08807

Dear Mr. Cook:

Please refer to your Supplemental New Drug Application (sNDA) dated and July 16, 2013, received, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Clomid (clomiphene citrate tablets, USP) 50mg.

We acknowledge receipt of your amendment(s) dated August 22, 2013, November 24, 2015, June 22, 2017, and August 4, 2017.

This "Changes Being Effected" supplemental new drug application provides for a revision to the ADVERSE REACTIONS section, subsection Postmarketing Adverse Events, for the addition of pancreatitis and endometrial thickness.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Nikia Morris, Regulatory Project Manager, at (240) 402-6625.

Sincerely,

{See appended electronic signature page}

Christine P. Nguyen, M.D.
Acting Director
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINE P NGUYEN
12/18/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

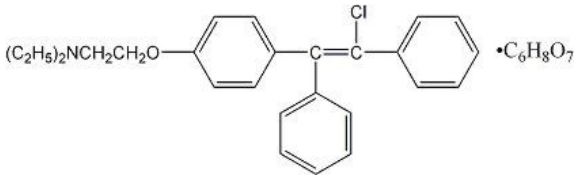
016131Orig1s028

LABELING

CLOMID®
(clomiphene citrate tablets USP)

DESCRIPTION

CLOMID (clomiphene citrate tablets USP) is an orally administered, nonsteroidal, ovulatory stimulant designated chemically as 2-[p-(2-chloro-1,2-diphenylvinyl)phenoxy] triethylamine citrate (1:1). It has the molecular formula of $C_{26}H_{28}ClNO \cdot C_6H_8O_7$ and a molecular weight of 598.09. It is represented structurally as:



Clomiphene citrate is a white to pale yellow, essentially odorless, crystalline powder. It is freely soluble in methanol; soluble in ethanol; slightly soluble in acetone, water, and chloroform; and insoluble in ether.

CLOMID is a mixture of two geometric isomers [cis (zuclomiphene) and trans (enclomiphene)] containing between 30% and 50% of the cis-isomer.

Each white scored tablet contains 50 mg clomiphene citrate USP. The tablet also contains the following inactive ingredients: corn starch, lactose, magnesium stearate, pregelatinized cornstarch, and sucrose.

CLINICAL PHARMACOLOGY

Action

CLOMID is a drug of considerable pharmacologic potency. With careful selection and proper management of the patient, CLOMID has been demonstrated to be a useful therapy for the anovulatory patient desiring pregnancy.

Clomiphene citrate is capable of interacting with estrogen-receptor-containing tissues, including the hypothalamus, pituitary, ovary, endometrium, vagina, and cervix. It may compete with estrogen for estrogen-receptor-binding sites and may delay replenishment of intracellular estrogen receptors. Clomiphene citrate initiates a series of endocrine events culminating in a preovulatory gonadotropin surge and subsequent follicular rupture. The first endocrine event in response to a course of clomiphene therapy is an increase in the release of pituitary gonadotropins. This initiates steroidogenesis and folliculogenesis, resulting in growth of the ovarian follicle and an increase in the circulating level of estradiol. Following ovulation, plasma progesterone and estradiol rise and fall as they would in a normal ovulatory cycle.

Available data suggest that both the estrogenic and antiestrogenic properties of clomiphene may participate in the initiation of ovulation. The two clomiphene isomers have been found to have mixed estrogenic and antiestrogenic effects, which may vary from one species to another. Some data suggest that zuclomiphene has greater estrogenic activity than enclomiphene.

Clomiphene citrate has no apparent progestational, androgenic, or antiandrogenic effects and does not appear to interfere with pituitary-adrenal or pituitary-thyroid function.
Although there is no evidence of a "carryover effect" of CLOMID, spontaneous ovulatory menses have been noted in some patients after CLOMID therapy.

Pharmacokinetics

Based on early studies with ^{14}C-labeled clomiphene citrate, the drug was shown to be readily absorbed orally in humans and excreted principally in the feces. Cumulative urinary and fecal excretion of the ^{14}C averaged about 50% of the oral dose and 37% of an intravenous dose after 5 days. Mean urinary excretion was approximately 8% with fecal excretion of about 42%.

Some ^{14}C label was still present in the feces 6 weeks after administration. Subsequent single-dose studies in normal volunteers showed that zuclomiphene (cis) has a longer half-life than enclomiphene (trans). Detectable levels of zuclomiphene persisted for longer than a month in these subjects. This may be suggestive of stereo-specific enterohepatic recycling or sequestering of the zuclomiphene. Thus, it is possible that some active drug may remain in the body during early pregnancy in women who conceive in the menstrual cycle during CLOMID therapy.

CLINICAL STUDIES

During clinical investigations, 7578 patients received CLOMID, some of whom had impediments to ovulation other than ovulatory dysfunction (see INDICATIONS AND USAGE). In those clinical trials, successful therapy characterized by pregnancy occurred in approximately 30% of these patients.

There were a total of 2635 pregnancies reported during the clinical trial period. Of those pregnancies, information on outcome was only available for 2369 of the cases. Table 1 summarizes the outcome of these cases.

Of the reported pregnancies, the incidence of multiple pregnancies was 7.98%: 6.9% twin, 0.5% triplet, 0.3% quadruplet, and 0.1% quintuplet. Of the 165 twin pregnancies for which sufficient information was available, the ratio of monozygotic to dizygotic twins was about 1:5. Table 1 reports the survival rate of the live multiple births.

A sextuplet birth was reported after completion of original clinical studies; none of the sextuplets survived (each weighed less than 400 g), although each appeared grossly normal.

Table 1. Outcome of Reported Pregnancies in Clinical Trials (n = 2369)

Outcome	Total Number of Pregnancies	Survival Rate
Pregnancy Wastage		
Spontaneous Abortions	483*	
Stillbirths	24	
Live Births		

Single Births	1697	98.16%†
Multiple Births	165	83.25%†

*Includes 28 ectopic pregnancies, 4 hydatiform moles, and 1 fetus papyraceous.
†Indicates percentage of surviving infants from these pregnancies.

The overall survival of infants from multiple pregnancies including spontaneous abortions, stillbirths, and neonatal deaths is 73%.

Fetal/Neonatal Anomalies and Mortality. The following fetal abnormalities have been reported subsequent to pregnancies following ovulation induction therapy with CLOMID during clinical trials. Each of the following fetal abnormalities were reported at a rate of <1% (experiences are listed in order of decreasing frequency): Congenital heart lesions, Down syndrome, club foot, congenital gut lesions, hypospadias, microcephaly, harelip and cleft palate, congenital hip, hemangioma, undescended testicles, polydactyly, conjoined twins and teratomatous malformation, patent ductus arteriosus, amaurosis, arteriovenous fistula, inguinal hernia, umbilical hernia, syndactyly, pectus excavatum, myopathy, dermoid cyst of scalp, omphalocele, spina bifida occulta, ichthyosis, and persistent lingual frenulum. Neonatal death and fetal death/stillbirth in infants with birth defects have also been reported at a rate of <1%. The overall incidence of reported congenital anomalies from pregnancies associated with maternal CLOMID ingestion during clinical studies was within the range of that reported for the general population.

In addition, reports of congenital anomalies have been received during postmarketing surveillance of CLOMID (see ADVERSE REACTIONS).

INDICATIONS AND USAGE

CLOMID is indicated for the treatment of ovulatory dysfunction in women desiring pregnancy. Impediments to achieving pregnancy must be excluded or adequately treated before beginning CLOMID therapy. Those patients most likely to achieve success with clomiphene therapy include patients with polycystic ovary syndrome (see WARNINGS: Ovarian Hyperstimulation Syndrome), amenorrhea-galactorrhea syndrome, psychogenic amenorrhea, post-oral-contraceptive amenorrhea, and certain cases of secondary amenorrhea of undetermined etiology.

Properly timed coitus in relationship to ovulation is important. A basal body temperature graph or other appropriate tests may help the patient and her physician determine if ovulation occurred. Once ovulation has been established, each course of CLOMID should be started on or about the 5th day of the cycle. Long-term cyclic therapy is not recommended beyond a total of about six cycles (including three ovulatory cycles). (See DOSAGE AND ADMINISTRATION and PRECAUTIONS.)

CLOMID is indicated only in patients with demonstrated ovulatory dysfunction who meet the conditions described below:

1. Patients who are not pregnant.
2. Patients without ovarian cysts. CLOMID should not be used in patients with ovarian enlargement except those with polycystic ovary syndrome. Pelvic

examination is necessary prior to the first and each subsequent course of CLOMID treatment.

3. Patients without abnormal vaginal bleeding. If abnormal vaginal bleeding is present, the patient should be carefully evaluated to ensure that neoplastic lesions are not present.
4. Patients with normal liver function.

In addition, patients selected for CLOMID therapy should be evaluated in regard to the following:

1. **Estrogen Levels.** Patients should have adequate levels of endogenous estrogen (as estimated from vaginal smears, endometrial biopsy, assay of urinary estrogen, or from bleeding in response to progesterone). Reduced estrogen levels, while less favorable, do not preclude successful therapy.
2. **Primary Pituitary or Ovarian Failure.** CLOMID therapy cannot be expected to substitute for specific treatment of other causes of ovulatory failure.
3. **Endometriosis and Endometrial Carcinoma.** The incidence of endometriosis and endometrial carcinoma increases with age as does the incidence of ovulatory disorders. Endometrial biopsy should always be performed prior to CLOMID therapy in this population.
4. **Other Impediments to Pregnancy.** Impediments to pregnancy can include thyroid disorders, adrenal disorders, hyperprolactinemia, and male factor infertility.
5. **Uterine Fibroids.** Caution should be exercised when using CLOMID in patients with uterine fibroids due to the potential for further enlargement of the fibroids.

There are no adequate or well-controlled studies that demonstrate the effectiveness of CLOMID in the treatment of male infertility. In addition, testicular tumors and gynecomastia have been reported in males using clomiphene. The cause and effect relationship between reports of testicular tumors and the administration of CLOMID is not known.

Although the medical literature suggests various methods, there is no universally accepted standard regimen for combined therapy (ie, CLOMID in conjunction with other ovulation-inducing drugs). Similarly, there is no standard CLOMID regimen for ovulation induction in *in vitro* fertilization programs to produce ova for fertilization and reintroduction. Therefore, CLOMID is not recommended for these uses.

CONTRAINDICATIONS

Hypersensitivity

CLOMID is contraindicated in patients with a known hypersensitivity or allergy to clomiphene citrate or to any of its ingredients.

Pregnancy

CLOMID use in pregnant women is contraindicated, as CLOMID does not offer benefit in this population.

Available human data do not suggest an increased risk for congenital anomalies above the background population risk when used as indicated. However, animal reproductive toxicology studies showed increased embryo-fetal loss and structural malformations in offspring. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risks to the fetus. (See PRECAUTIONS: Pregnancy.)

Liver Disease. CLOMID therapy is contraindicated in patients with liver disease or a history of liver dysfunction (see also INDICATIONS AND USAGE and ADVERSE REACTIONS).
Abnormal Uterine Bleeding. CLOMID is contraindicated in patients with abnormal uterine bleeding of undetermined origin (see INDICATIONS AND USAGE).
Ovarian Cysts. CLOMID is contraindicated in patients with ovarian cysts or enlargement not due to polycystic ovarian syndrome (see INDICATIONS AND USAGE and WARNINGS).
Other. CLOMID is contraindicated in patients with uncontrolled thyroid or adrenal dysfunction or in the presence of an organic intracranial lesion such as pituitary tumor (see INDICATIONS AND USAGE).

WARNINGS

Visual Symptoms

Patients should be advised that blurring or other visual symptoms such as spots or flashes (scintillating scotomata) may occasionally occur during therapy with CLOMID. These visual symptoms increase in incidence with increasing total dose or therapy duration. These visual disturbances are usually reversible; however, cases of prolonged visual disturbance have been reported with some occurring after CLOMID discontinuation. The visual disturbances may be irreversible, especially with increased dosage or duration of therapy. Patients should be warned that these visual symptoms may render such activities as driving a car or operating machinery more hazardous than usual, particularly under conditions of variable lighting.

These visual symptoms appear to be due to intensification and prolongation of afterimages. Symptoms often first appear or are accentuated with exposure to a brightly lit environment. While measured visual acuity usually has not been affected, a study patient taking 200 mg CLOMID daily developed visual blurring on the 7th day of treatment, which progressed to severe diminution of visual acuity by the 10th day. No other abnormality was found, and the visual acuity returned to normal on the 3rd day after treatment was stopped.

Ophthalmologically definable scotomata and retinal cell function (electroretinographic) changes have also been reported. A patient treated during clinical studies developed phosphenes and scotomata during prolonged CLOMID administration, which disappeared by the 32nd day after stopping therapy.

Postmarketing surveillance of adverse events has also revealed other visual signs and symptoms during CLOMID therapy (see ADVERSE REACTIONS).

While the etiology of these visual symptoms is not yet understood, patients with any visual symptoms should discontinue treatment and have a complete ophthalmological evaluation carried out promptly.

Ovarian Hyperstimulation Syndrome

The ovarian hyperstimulation syndrome (OHSS) has been reported to occur in patients receiving clomiphene citrate therapy for ovulation induction. OHSS may progress rapidly (within 24 hours to several days) and become a serious medical disorder. In some cases, OHSS occurred following cyclic use of clomiphene citrate therapy or when clomiphene citrate was used in combination with gonadotropins. Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with OHSS.

OHSS is a medical event distinct from uncomplicated ovarian enlargement. The clinical signs of this syndrome in severe cases can include gross ovarian enlargement, gastrointestinal symptoms, ascites, dyspnea, oliguria, and pleural effusion. In addition, the following symptoms have been reported in association with this syndrome: pericardial effusion, anasarca, hydrothorax, acute abdomen, hypotension, renal failure, pulmonary edema, intraperitoneal and ovarian hemorrhage, deep venous thrombosis, torsion of the ovary, and acute respiratory distress. The early warning signs of OHSS are abdominal pain and distention, nausea, vomiting, diarrhea, and weight gain. Elevated urinary steroid levels, varying degrees of electrolyte imbalance, hypovolemia, hemoconcentration, and hypoproteinemia may occur. Death due to hypovolemic shock, hemoconcentration, or thromboembolism has occurred. Due to fragility of enlarged ovaries in severe cases, abdominal and pelvic examination should be performed very cautiously. If conception results, rapid progression to the severe form of the syndrome may occur.

To minimize the hazard associated with occasional abnormal ovarian enlargement associated with CLOMID therapy, the lowest dose consistent with expected clinical results should be used. Maximal enlargement of the ovary, whether physiologic or abnormal, may not occur until several days after discontinuation of the recommended dose of CLOMID. Some patients with polycystic ovary syndrome who are unusually sensitive to gonadotropin may have an exaggerated response to usual doses of CLOMID. Therefore, patients with polycystic ovary syndrome should be started on the lowest recommended dose and shortest treatment duration for the first course of therapy (see DOSAGE AND ADMINISTRATION).

If enlargement of the ovary occurs, additional CLOMID therapy should not be given until the ovaries have returned to pretreatment size, and the dosage or duration of the next course should be reduced. Ovarian enlargement and cyst formation associated with CLOMID therapy usually regresses spontaneously within a few days or weeks after discontinuing treatment. The potential benefit of subsequent CLOMID therapy in these cases should exceed the risk. Unless surgical indication for laparotomy exists, such cystic enlargement should always be managed conservatively.

A causal relationship between ovarian hyperstimulation and ovarian cancer has not been determined. However, because a correlation between ovarian cancer and nulliparity, infertility, and age has been suggested, if ovarian cysts do not regress spontaneously, a thorough evaluation should be performed to rule out the presence of ovarian neoplasia.

PRECAUTIONS

General

Careful attention should be given to the selection of candidates for CLOMID therapy. Pelvic examination is necessary prior to CLOMID treatment and before each subsequent course (see CONTRAINDICATIONS and WARNINGS).

Information for Patients

The purpose and risks of CLOMID therapy should be presented to the patient before starting treatment. It should be emphasized that the goal of CLOMID therapy is ovulation for subsequent pregnancy. The physician should counsel the patient with special regard to the following potential risks:

Visual Symptoms: Advise that blurring or other visual symptoms occasionally may occur during or shortly after CLOMID therapy. It should be made clear to the patient that, in some instances, visual disturbances may be prolonged, and possibly irreversible, especially with increased dosage or duration of therapy. Warn that visual symptoms may render such activities as driving a car or operating machinery more hazardous than usual, particularly under conditions of variable lighting (see WARNINGS).

The patient should be instructed to inform the physician whenever any unusual visual symptoms occur. If the patient has any visual symptoms, treatment should be discontinued and complete ophthalmologic evaluation performed.

Abdominal/Pelvic Pain or Distention: Ovarian enlargement may occur during or shortly after therapy with CLOMID. To minimize the risks associated with ovarian enlargement, the patient should be instructed to inform the physician of any abdominal or pelvic pain, weight gain, discomfort, or distention after taking CLOMID (see WARNINGS).

Metabolism Disorders: Cases of hypertriglyceridemia have been reported. Preexisting or family history of hyperlipidemia and use of higher than recommended dose and/or longer duration of treatment with CLOMID are associated with a risk of hypertriglyceridemia. Periodic monitoring of plasma triglycerides is recommended in patients with preexisting or family history of hyperlipidemia (see ADVERSE REACTIONS). Pretreatment screening of triglyceride levels is recommended in patients initiating Clomid therapy.

Gastrointestinal Disorders: Cases of pancreatitis have been reported.

Multiple Pregnancy: Inform the patient that there is an increased chance of multiple pregnancy, including bilateral tubal pregnancy and coexisting tubal and intrauterine pregnancy, when conception occurs in relation to CLOMID therapy. The potential complications and hazards of multiple pregnancy should be explained.

Spontaneous Abortion and Congenital Anomalies: Inform the patient that the available data suggest no increase in the rates of spontaneous abortion (miscarriage) or congenital anomalies with maternal CLOMID use compared to rates in the general population.

During clinical investigation, the experience from patients with known pregnancy outcome (Table 1) shows a spontaneous abortion rate of 20.4% and stillbirth rate of 1.0%. (See CLINICAL STUDIES). Among the birth anomalies spontaneously reported as individual cases since commercial availability of Clomid, the proportion of neural tube defects has been high among pregnancies associated with ovulation induced by Clomid, but this has not been supported by data from population-based studies.

Drug Interactions

Drug interactions with CLOMID have not been documented.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term toxicity studies in animals have not been performed to evaluate the carcinogenic or mutagenic potential of clomiphene citrate.

Oral administration of CLOMID to male rats at doses of 0.3 or 1 mg/kg/day caused decreased fertility, while higher doses caused temporary infertility. Oral doses of 0.1 mg/kg/day in female rats temporarily interrupted the normal cyclic vaginal smear pattern and prevented conception. Doses of 0.3 mg/kg/day slightly reduced the number of ovulated ova and corpora lutea, while 3 mg/kg/day inhibited ovulation.

Pregnancy

Fetal Risk Summary

CLOMID use in pregnant women is contraindicated, as CLOMID treatment does not offer benefit in this population.

Available human data do not suggest an increased risk for congenital anomalies above the background population risk. However, animal reproductive toxicology studies showed increased embryo-fetal loss and structural malformations in offspring. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risks to the fetus.

Clinical Considerations

To avoid inadvertent CLOMID administration during early pregnancy, appropriate tests should be utilized during each treatment cycle to determine whether ovulation and/or pregnancy occurs. Patients should be evaluated carefully to exclude ovarian enlargement or ovarian cyst formation between each treatment cycle. The next course of CLOMID therapy should be delayed until these conditions have been excluded.

Human data
The available human data from epidemiologic studies do not show any apparent cause and effect relationship between clomiphene citrate periconceptual exposure and an increased risk of overall birth defects, or any specific anomaly. However, due to the small number of cases of congenital anomalies occurring in clomiphene citrate treated women, these epidemiologic studies were only able to rule out large differences in risk. The studies did not consider factors associated with female subfertility and were unable to adjust for other important confounders. In addition, available data do not support an increased rate of spontaneous abortion among subfertile women treated with clomiphene citrate for ovulation induction.

Animal data
Oral administration of clomiphene citrate to pregnant rats during organogenesis at doses of 1 to 2 mg/kg/day resulted in hydramnion and weak, edematous fetuses with wavy ribs and other temporary bone changes. Doses of 8 mg/kg/day or more also caused increased resorptions and dead fetuses, dystocia, and delayed parturition, and 40 mg/kg/day resulted in increased maternal mortality. Single doses of 50 mg/kg caused fetal cataracts, while 200 mg/kg caused cleft palate. Following injection of clomiphene citrate 2 mg/kg to mice and rats during pregnancy, the offspring exhibited metaplastic changes of the reproductive tract. Newborn mice and rats injected during the first few days of life also developed metaplastic changes in uterine and vaginal mucosa, as well as premature vaginal opening and anovulatory ovaries. These findings are similar to the abnormal reproductive behavior and sterility described with other estrogens and antiestrogens.

In rabbits, some temporary bone alterations were seen in fetuses from dams given oral doses of 20 or 40 mg/kg/day during pregnancy, but not following 8 mg/kg/day. No permanent malformations were observed in those studies. Also, rhesus monkeys given oral doses of 1.5 to 4.5 mg/kg/day for various periods during pregnancy did not have any abnormal offspring.

Nursing Mothers
It is not known whether CLOMID is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if CLOMID is administered to a nursing woman. In some patients, CLOMID may reduce lactation.

Ovarian Cancer
Prolonged use of clomiphene citrate tablets USP may increase the risk of a borderline or invasive ovarian tumor (see ADVERSE REACTIONS).

ADVERSE REACTIONS
Clinical Trial Adverse Events. CLOMID, at recommended dosages, is generally well tolerated. Adverse reactions usually have been mild and transient and most have disappeared promptly after treatment has been discontinued. Adverse experiences reported in patients treated with clomiphene citrate during clinical studies are shown in Table 2.

Table 2. Incidence of Adverse Events in Clinical Studies (Events Greater than 1%) (n = 8029*)

Adverse Event	%
Ovarian Enlargement	13.6
Vasomotor Flushes	10.4
Abdominal-Pelvic Discomfort/Distention/Bloating	5.5
Nausea and Vomiting	2.2
Breast Discomfort	2.1
Visual Symptoms	1.5
Blurred vision, lights, floaters, waves, unspecified visual complaints, photophobia, diplopia, scotomata, phosphenes	
Headache	1.3
Abnormal Uterine Bleeding	1.3
Intermenstrual spotting, menorrhagia	

*Includes 498 patients whose reports may have been duplicated in the event totals and could not be distinguished as such. Also, excludes 47 patients who did not report symptom data.

The following adverse events have been reported in fewer than 1% of patients in clinical trials: Acute abdomen, appetite increase, constipation, dermatitis or rash, depression, diarrhea, dizziness, fatigue, hair loss/dry hair, increased urinary frequency/volume, insomnia, light-headedness, nervous tension, vaginal dryness, vertigo, weight gain/loss.

Patients on prolonged CLOMID therapy may show elevated serum levels of desmosterol. This is most likely due to a direct interference with cholesterol synthesis. However, the serum sterols in patients receiving the recommended dose of CLOMID are not significantly altered. Ovarian cancer has been infrequently reported in patients who have received fertility drugs. Infertility is a primary risk factor for ovarian cancer; however, epidemiology data suggest that prolonged use of clomiphene may increase the risk of a borderline or invasive ovarian tumor.

Postmarketing Adverse Events

The following adverse reactions have been identified during post approval use of Clomid. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: Fever, tinnitus, weakness

Cardiovascular: Arrhythmia, chest pain, edema, hypertension, palpitation, phlebitis, pulmonary embolism, shortness of breath, tachycardia, thrombophlebitis

Central Nervous System: Migraine headache, paresthesia, seizure, stroke, syncope

Dermatologic: Acne, allergic reaction, erythema, erythema multiforme, erythema nodosum, hypertrichosis, pruritus, urticaria

Fetal/Neonatal Anomalies:

- Abnormal bone development: skeletal malformations of the skull, face, nasal passages, jaw, hand, limb (ectromelia including amelia, hemimelia, and phocomelia), foot (clubfoot), spine, and joints
- Cardiac abnormalities: septal heart defects, muscular ventricular septal defect, patent ductus arteriosus, tetralogy of Fallot, and coarctation of the aorta
- Chromosomal disorders: Downs syndrome
- Ear abnormalities and deafness
- Gastrointestinal tract abnormalities: cleft lip and palate, imperforate anus, tracheoesophageal fistula, diaphragmatic hernia, omphalocele
- Genitalia abnormalities: hypospadias, cloacal exstrophy
- Lung tissue malformations
- Malformations of the eye and lens (cataract)
- Neoplasms: neuroectodermal tumor, thyroid tumor, hepatoblastoma, lymphocytic leukemia
- Nervous system abnormalities: neural tube defects (anencephaly, meningomyelocele), microcephaly, and hydrocephalus
- Renal abnormalities: renal agenesis and renal dysgenesis
- Others: dwarfism, mental retardation

Gastrointestinal: Pancreatitis

Genitourinary: Endometriosis, ovarian cyst (ovarian enlargement or cysts could, as such, be complicated by adnexal torsion), ovarian hemorrhage, tubal pregnancy, uterine hemorrhage, reduced endometrial thickness

Hepatic: Transaminases increased, hepatitis

Metabolism Disorders: Hypertriglyceridemia, in some cases with pancreatitis

Musculoskeletal: Arthralgia, back pain, myalgia

Neoplasms: Liver (hepatic hemangiosarcoma, liver cell adenoma, hepatocellular carcinoma); breast (fibrocystic disease, breast carcinoma); endometrium (endometrial carcinoma); nervous system (astrocytoma, pituitary tumor, prolactinoma, neurofibromatosis, glioblastoma multiforme, brain abcess); ovary (luteoma of pregnancy, dermoid cyst of the ovary, ovarian carcinoma); trophoblastic (hydatiform mole, choriocarcinoma); miscellaneous (melanoma, myeloma, perianal cysts, renal cell carcinoma, Hodgkin's lymphoma, tongue carcinoma, bladder carcinoma)

Psychiatric: Anxiety, irritability, mood changes, psychosis

Visual Disorders: Abnormal accommodation, cataract, eye pain, macular edema, optic neuritis, photopsia, posterior vitreous detachment, retinal hemorrhage, retinal thrombosis, retinal vascular spasm, temporary or prolonged loss of vision, possibly irreversible.

Other: Leukocytosis, thyroid disorder

DRUG ABUSE AND DEPENDENCE

Tolerance, abuse, or dependence with CLOMID has not been reported.

OVERDOSAGE

Signs and Symptoms

Toxic effects accompanying acute overdosage of CLOMID have not been reported. Signs and symptoms of overdosage as a result of the use of more than the recommended dose during CLOMID therapy include nausea, vomiting, vasomotor flushes, visual blurring, spots or flashes, scotomata, ovarian enlargement with pelvic or abdominal pain. (See CONTRAINDICATIONS: Ovarian Cyst.)

Oral LD_{50}. The acute oral LD_{50} of CLOMID is 1700 mg/kg in mice and 5750 mg/kg in rats. The toxic dose in humans is not known.
Dialysis. It is not known if CLOMID is dialyzable.

Treatment

In the event of overdose, appropriate supportive measures should be employed in addition to gastrointestinal decontamination.

DOSAGE AND ADMINISTRATION

General Considerations

The workup and treatment of candidates for CLOMID therapy should be supervised by physicians experienced in management of gynecologic or endocrine disorders. Patients should be chosen for therapy with CLOMID only after careful diagnostic evaluation (see INDICATIONS AND USAGE). The plan of therapy should be outlined in advance. Impediments to achieving the goal of therapy must be excluded or adequately treated before beginning CLOMID. The therapeutic objective should be balanced with potential risks and discussed with the patient and others involved in the achievement of a pregnancy.

Ovulation most often occurs from 5 to 10 days after a course of CLOMID. Coitus should be timed to coincide with the expected time of ovulation. Appropriate tests to determine ovulation may be useful during this time.

Recommended Dosage

Treatment of the selected patient should begin with a low dose, 50 mg daily (1 tablet) for 5 days. The dose should be increased only in those patients who do not ovulate in response to cyclic 50 mg CLOMID. A low dosage or duration of treatment course is particularly recommended if unusual sensitivity to pituitary gonadotropin is suspected, such as in patients with polycystic ovary syndrome (see WARNINGS; Ovarian Hyperstimulation Syndrome).

The patient should be evaluated carefully to exclude pregnancy, ovarian enlargement, or ovarian cyst formation between each treatment cycle.

If progestin-induced bleeding is planned, or if spontaneous uterine bleeding occurs prior to therapy, the regimen of 50 mg daily for 5 days should be started on or about the 5th day of the cycle. Therapy may be started at any time in the patient who has had no recent uterine bleeding. When ovulation occurs at this dosage, there is no advantage to increasing the dose in subsequent cycles of treatment.

If ovulation does not appear to occur after the first course of therapy, a second course of 100 mg daily (two 50 mg tablets given as a single daily dose) for 5 days should be given. This course may be started as early as 30 days after the previous one after precautions are taken to exclude the presence of pregnancy. Increasing the dosage or duration of therapy beyond 100 mg/day for 5 days is not recommended.

The majority of patients who are going to ovulate will do so after the first course of therapy. If ovulation does not occur after three courses of therapy, further treatment with CLOMID is not recommended and the patient should be reevaluated. If three ovulatory responses occur, but pregnancy has not been achieved, further treatment is not recommended. If menses does not occur after an ovulatory response, the patient should be reevaluated. Long-term cyclic therapy is not recommended beyond a total of about six cycles (see PRECAUTIONS).

HOW SUPPLIED

NDC 0068-0226-30: 50 mg tablets in cartons of 30
Tablets are round, white, scored, and debossed CLOMID 50.
Store tablets at controlled room temperature 59-86°F (15-30°C). Protect from heat, light, and excessive humidity, and store in closed containers.

Rx only

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
A SANOFI COMPANY

Revised July 2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

016131Orig1s028

CLINICAL REVIEW(S)

Medical Officer's Review of NDA 016131/SLR Labeling

TO: NDA 016131/SLR (b) (4) and -028

THROUGH: Shelley R. Slaughter, MD, Ph.D.

Medical Team Leader

Division of Bone, Reproductive and Urologic Products

FROM: Rhonda M. Hearns-Stewart, MD

Medical Officer

Division of Bone, Reproductive, and Urologic Products (DBRUP)

SUBJECT: Change Being Effected – Revised Physician Information

Date: July 24, 2017

Background:

Clomid® was approved on February 1, 1967. It is indicated for the treatment of ovulatory dysfunction in women desiring pregnancy. Recommended dosing is 50 mg (1 tablet) for 5 days. If ovulation does not occur, the dose may be increased up to 100 mg (2 tablets) for 5 days. Although clomid® is not currently approved for the indication of male infertility or hypogonadotropic hypogonadism in the U.S., off-label use for this indication is not uncommon.

On January 23, 2009, the applicant submitted a changes being effected (CBE) labeling supplement (SLR-026). SLR-026 was approved as amended on October 22, 2012 with the following changes to the Physician Insert (PI):

- Visual disorders, ovarian hyperstimulation syndrome, and urticaria in the WARNINGS, PRECAUTIONS and ADVERSE REACTIONS sections
- Specific congenital abnormality terms in the ADVERSE REACTIONS section under the Postmarketing Adverse Events subsection
- Re-organization of information related to pregnancy and fetal abnormalities in labeling to better effectively communicate this information to prescribers.

Prior to approval of SLR-026, the applicant submitted a changes being effected (CBE) labeling (b) (4) proposed addition of hypertriglyceridemia to the precautions section of the labeling and hypertriglyceridemia with pancreatitis to the Postmarketing

Adverse Events section. However, this supplement did not include re-organization of pregnancy and fetal abnormalities, which was previously submitted in SLR-026 and delineated above. Upon receipt of the CBE, DBRUP consulted the Division of Pharmacovigilance I (DPVI) to perform a review of postmarketing data for clomid® (clomiphene citrate) and pancreatitis and hypertriglyceridemia. No case reports were identified in the literature; but review of the FAERS database identified 21 cases of pancreatitis and/or hypertriglyceridemia.

Ten patients developed pancreatitis, two developed hypertriglyceridemia, and nine developed both, pancreatitis and hypertriglyceridemia after treatment with clomid®. Six patients experienced a positive rechallenge after restarting clomid®. Many patients experienced pancreatitis after only a short duration of clomid® treatment or after an increase in dose. Thus, DPV recommended the addition of pancreatitis and hypertriglyceridemia to the Precautions or Warnings section of the labeling. DPV also recommended that DBRUP add pretreatment screening of triglyceride levels in patients initiating clomiphene citrate therapy to the labeling. DBRUP concurred with this recommendation. However, DBRUP did not concur with omitting the re-organization of information related to pregnancy and fetal abnormalities in labeling to better effectively communicate this information to prescribers.

On July 16, 2013, the applicant submitted SLR-028 proposing addition of pancreatitis and reduced endometrial thickness in the Postmarketing subsection of the Adverse Events section. However, the applicant submitted the wrong document. The correct document was submitted on August 22, 2013; but the red-lined tracked version was omitted. The Division requested the red-lined track version, which was subsequently submitted on November 24, 2015. SLR-028 also included re-organization of information related to pregnancy and fetal abnormalities, which is consistent with that of the most recently approved labeling (October 22, 2012).

DBRUP concurs with the addition of pancreatitis to the Postmarketing subsection of labeling along with the aforementioned DPV recommendations, which include the addition of pancreatitis in the Warnings or Precautions section of the labeling. DBRUP also concurs with addition of reduced endometrial thickness to the Postmarketing subsection. Reduced endometrial thickness is a documented adverse effect of Clomid therapy in patients with ovulatory disorders. However, on March 9, 2017, DBRUP recommended additional edits to the following sections of the supplement 028 label: Pregnancy, Metabolism Disorders, and Gastrointestinal Disorders. On June 22, 2017, the applicant submitted a revised Clomid label for supplement 028, which incorporated DBRUP recommendations.

Recommended Regulatory Action:

The labeling (b) (4) should not be approved as it does not include revisions previously approved in supplement 026.

The labeling for NDA 016131/SLR – 028, which includes the above noted revisions should be approved. The applicant accepted DBRUP recommendations.

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/s/

RHONDA M HEARNS-STEWART
07/24/2017

SHELLEY R SLAUGHTER
07/24/2017
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

016131Orig1s028

OTHER REVIEW(S)

Division of Bone, Reproductive, and Urologic Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 16131/S-028

Name of Drug: Clomid® (clomiphene citrate tablets USP) 50mg

Applicant: Sanofi-aventis US, LLC

Labeling Reviewed

Submission Date: July 16, 2013

Receipt Date: July 16, 2013

Background and Summary Description:

Clomid® (clomiphene citrate tablets USP) was approved on February 1, 1967. The sponsor submitted this supplemental new drug application – changes being effected on July 16, 2013, to provide for revisions to the ADVERSE REACTIONS section, subsection Postmarketing Adverse Events, for the addition of pancreatitis and endometrial thickness.

Subsequently, revised labeling was submitted on August 22, 2013, November 24, 2015, June 22, 2017, and August 4, 2017.

The final draft proposed labeling submitted on August 4, 2017 was compared to the last approved labeling dated October 22, 2012, in supplement 026.

Review

The following changes were made:

- CONTRAINDICATIONS, **Pregnancy** sub-section: removed 'Pregnancy Category X.'
- PRECAUTIONS, **Metabolism Disorders** sub-section: removed (b) (4) [redacted]
- PRECAUTIONS, **Metabolism Disorders** sub-section: added 'Pretreatment screening of triglyceride levels is recommended in patients initiating Clomid therapy.'
- PRECAUTIONS, added new sub-section and text: '**Gastrointestinal Disorders:** Cases of pancreatitis have been reported.'
- PRECAUTIONS, **Pregnancy** sub-section: removed 'Pregnancy Category X. (See

CONTRAINDICATIONS.)'

- ADVERSE EVENTS, **Postmarketing Adverse Events**, added new sub-section and text: '**Gastrointestinal:** Pancreatitis'
- ADVERSE EVENTS, **Postmarketing Adverse Events, Genitourinary** sub-section: added '…,reduced endometrial thickness'

- Changed 'Revised July 2013' to 'Revised July 2017'
- Changed '©2013 sanofi-adventis U.S. LLC' to '©2017 sanofi-adventis U.S. LLC'

The information supporting the revised labeling was reviewed by the Medical Officer, Rhonda Hearns-Stewart, who recommended approval on July 24, 2017.

The labeling received on August 4, 2017, is considered the final agreed upon labeling. The labeling changes submitted in this draft were administrative – a legible chemical structure on pg. 1 and revised version date, as requested by Shelley Slaughter, the clinical team leader.

Recommendations

The proposed labeling changes for NDA 016131/S-028 are consistent with labeling changes recommended by DBRUP. An Approval letter should be issued.

/s/ Nikia D. Morris	11/27/2017
Regulatory Project Manager	Date
Chief, Project Management Staff	Date

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/s/

NIKIA D MORRIS
12/18/2017

MARGARET M KOBER
12/18/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

016131Orig1s028

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Morris, Nikia

From: Morris, Nikia
Sent: Thursday, March 09, 2017 2:05 PM
To: 'John.Cook@sanofi.com'
Subject: NDA 16131 S-028 Label
Attachments: NDA 16131 S 28 Submission 8-22-13 DBRUP edits.doc

Dear Mr. Cook,

We have additional edits to the labeling for NDA 016131 S-028. Let us know if you agree with the changes and return revised labeling within one week. Return via formal submission, both tracked and clean copy versions.

Feel free to contact me should you have questions.

Thanks,

Nikia Morris, MSHA, MBA
Regulatory Health Project Manager
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993
Bldg 22, Room 5134
office: 240-402-6625
fax: 301-796-9897
Nikia.Morris@fda.hhs.gov

13 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

NIKIA D MORRIS
03/09/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE**			FROM: Nikia Morris, RPM, DBRUP, 2404026625	
DATE 11/6/2015	IND NO.	NDA NO. 16131/S-028	TYPE OF DOCUMENT Labeling Supplement	DATE OF DOCUMENT 8/22/13
NAME OF DRUG Clomid (clomiphene citrate)	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG Gonadotropin	DESIRED COMPLETION DATE January 5, 2016

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

In a CBE (SLR-28) submitted on 8/22/13, the Sponsor proposes the addition of Gastrointestinal Pancreatitis and endometrial thickness in the Postmarking subsection of the ADVERSE EVENTS SECTION. Let us know if you want to review and comment on the proposed labeling changes. The Sponsor's supportive evidence is provided in the submission. Find link to submission below.

EDR Link: Application 016131 - Sequence 0019 - 0019 (127) 08/22/2013 SUPPL-28 (Labeling) /Labeling/Package Insert Draft

Sharepoint Link: NDA 16131 S-28

Please note this supplement came in on 7-16-2013 but the sponsor sent in the wrong document. They submitted the correct one on 8-22-2013. We are asking the sponsor to submit a red lined tracked changes version to us. As soon as they do, we will place this in sharepoint and let you know.

SIGNATURE OF REQUESTER /s/Nikia Morris	METHOD OF DELIVERY (Check all that apply) ☐ MAIL ☐ DARRTS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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/s/

NIKIA D MORRIS
11/09/2015