CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 016131/S-026

Trade Name: **CLOMID**

Generic Name: **Clomiphene Citrate Tablets USP**

Sponsor: **Sanofi-Aventis U.S. LLC**

Approval Date: 10/22/2012

Indications: CLOMID is indicated for the treatment of ovulatory dysfunction in women desiring pregnancy.

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 016131/S-026

SUPPLEMENT APPROVAL

sanofi-aventis U.S. LLC
Attention: Nancy Dougherty
U.S. Regulatory Affairs
55 Corporate Drive
Bridgewater, NJ 08807

Dear Ms. Dougherty:

Please refer to your Supplemental New Drug Application (sNDA) dated January 22, 2009, and received January 23, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Clomid® (clomiphene citrate) Tablets, 50 mg.

We acknowledge receipt of your amendments dated December 10, 2009 and October 5, 2012.

This "Prior Approval" supplemental new drug application provides for 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.

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 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.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

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 Meredith Alpert, Acting Safety Regulatory Project Manager, at (301) 796-1218.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Acting Deputy Director
Division of 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/

AUDREY L GASSMAN
10/22/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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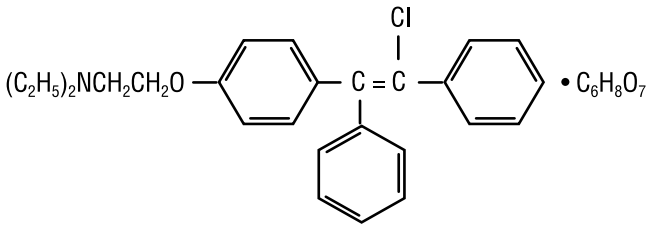
LABELING

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

Pregnancy Category X. 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).

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

Pregnancy Category X. (See CONTRAINDICATIONS.) 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

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

Hepatic: Transaminases increased, hepatitis

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

Revised October 2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 016131/S-026

MEDICAL REVIEW(S)

Clinical Review of Supplemental Labeling Request

NDA:	16-131/S-026
Sponsor:	Sanofi-Aventis US LLC
Tradename/established name:	CLOMID/clomiphene citrate
Cross-Reference ANDA:	18-361 SEROPHENE (clomiphene citrate)
Reviewers:	Audrey Gassman, M.D. Martin Kaufman, D.P.M. Christine Nguyen, M.D.
Secondary Reviewer:	Shelley S. Slaughter, M.D., Ph.D.
Date of Review:	October 11, 2012

RE: Clinical review and recommendations on revised labeling for CLOMID (clomiphene citrate) to address issues related to visual disorders and fetal abnormalities.

EXECUTIVE SUMMARY:

This review discusses issues related to visual disorders and fetal abnormalities reported with the use of Clomid (clomiphene citrate). The discussion on the visual disorders includes an assessment from the Division of Reproductive and Urologic Products (DRUP) and consultative input from the Division of Ophthalmology. The discussion on congenital abnormalities summarizes pertinent findings and recommendations provided in consults from the Office of Surveillance and Epidemiology (OSE) dated in 2000 and 2008, in response to a Citizen Petition filed in 2007, and dated in 2011, in response to a Petition to Reconsider filed in 2009. Consultative input from the Maternal Health Team, in response to the same Citizen Petition filed in 2007, was also reviewed.

Language describing visual disorders observed in postmarketing case reports will be added to the Warnings and Precautions and Adverse Reactions (Postmarketing Adverse Events) sections. Labeling will be also updated to include specific congenital abnormality terms recommended by OSE in the Adverse Reactions (Postmarketing Adverse Events) section. The presentation of information in labeling concerning pregnancy and fetal abnormalities will be revised to comply with the spirit of new labeling guidelines to better effectively communicate to prescribers.

VISUAL DISORDERS

BACKGROUND:

In a letter dated September 21, 2008, DRUP requested that the Sponsor submit a labeling supplement that included the following safety information:

1. In the Visual Symptoms subsection of the WARNINGS section, insert the following sentence after the second sentence of the first paragraph: “However, prolonged visual disturbances have been reported after clomiphene citrate therapy has been discontinued and these disturbances may be irreversible.”

2. In the Ovarian Hyperstimulation Syndrome subsection of the WARNINGS section, insert the following sentence after the first sentence of the second paragraph: “OHSS may progress rapidly (within 24 hours to several days) and become a serious medical disorder.”

3. In the Information for Patients subsection of the PRECAUTIONS section, under the heading Visual Symptoms, insert the following sentence after the first sentence of the first paragraph: “It should be made clear to the patient that, in some instances, visual disturbances may be prolonged, and possibly, irreversible.”

4. In the Postmarketing Adverse Events subsection of the ADVERSE EVENTS section, add “urticaria” to the list of adverse event terms listed under the heading Dermatologic.

Comment*: The above labeling request was initially requested in an Information Request letter dated October 16, 2002. The sponsor, however, never responded prior to DRUP’s September 2008 labeling re-request.*

DRUP consulted OSE/Division of Postmarketing Surveillance II (DPV II) to search the Adverse Event Reporting System (AERS) database for cases of irreversible visual disturbances associated with clomiphene use. In the December 3, 2008 consult, DPV II identified 8 cases that may meet the criteria of “irreversible,” but DPV II did not have any specific labeling recommendations based on these reports.

On January 22, 2009, the sponsor submitted Labeling Supplement 026 (SLR-026) in response to the Division’s September 21, 2008, request, which contains the following labeling changes (underlined text represents addition and strikethroughs deletions):

1. In the WARNING section under the Visual Symptoms sub-section:

   “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 ~~and generally disappear within a few days or weeks after CLOMID is discontinued.~~ These visual disturbances are usually reversible; however, cases of prolonged visual disturbance have been reported including 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.”

2. In the PRECAUTIONS section, under the Visual Symptoms sub-section:

   “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.”

3. In the ADVERSE REACTIONS section under the Postmarketing Adverse Events sub-section:

   “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.”

The supplement also contained a clinical overview of the Sponsor's pharmacovigilance database and a review of the available literature on visual disorders associated with clomiphene use.

OPHTHALMOLOGY CONSULT:

In the consult dated April 27, 2009, the Ophthalmology consultant evaluated the 8 AERS reports identified by DPV II that may suggest irreversible visual disturbances and concluded that "The majority of reports are unconfirmed by formal testing and several of the cases are more consistent with ocular migraine.....No changes to the labeling are recommended."

CLINICAL REVIEW:

The following section contains the clinical evaluation of the Sponsor's clinical overview submitted in SLR 026.

A. Pharmacovigilance reports: The Sponsor provided a clinical overview of the pharmacovigilance database and available literature on visual disorders associated with clomiphene use. Of the 43 reports of visual disturbances identified in the safety database, 3 reported sequelae: one case involved medication use beyond the 5-day approved dosing regime, one case reported sequelae without additional information, and one case reported stable campimetric discomfort.

Comment*: The reviewers agree with the Sponsor that the majority of cases identified in the pharmacovigilance database lack adequate information to allow a definitive causal assessment. However, discussed below are several clinically relevant cases that report prolonged visual disturbances associated with clomiphene use:*

- *Case 199814832DDC: A 25 year old female was taking clomiphene citrate as an ovulatory agent. Her past history reveals that she experienced blurred vision 2 years ago when she took clomiphene citrate (Serophene) for two courses of treatment, the first one of 5 days and the second one of 7 days. The patient was not taking any concomitant medications. She developed the events on 26-Aug-1998. She was reported to have recovered for all events except for the visual disturbance, which was reported as recovered with sequelae. The patient was noted to have double vision when looking straight ahead, however, her peripheral vision was reported as fine. She saw an ophthalmologist who recommended that she wear an eye patch on her stronger eye to help the weaker one. The reporter's assessment of a causal relationship is highly probable.*
- *Case 199920080RGB: This initial report, received from an ophthalmologist, concerns a female patient (age unknown) who was treated with Clomid (clomiphene) for one year. Treatment started three years prior to the report but the dose and the indication for Clomid usewere reported as unknown. The Clomid was discontinued after one year because the patient experienced visual disturbance in the form of photopsia: this was not resolved as of the time of the report.*
- *Case 200413430US: Initial report 04-May-2004: This spontaneous post-marketing case was reported by a physician and involves a 38 year old female patient who received clomiphene (Clomid) 50mg daily from 04-Apr-2004 to 08-Apr-2004 to become pregnant. This was her third month of taking clomiphene citrate. The patient developed symptoms of headache and abnormal vision. The patient was diagnosed with optic neuritis by a neurologist via CAT scan. She was treated with steroids. Multiple sclerosis was not ruled out. The patient's past medical history was significant for irritable bowel syndrome and migraine headaches. She was not receiving any concomitant medications. Her event was*

reported as ongoing..The reporter's assessment of the causal relationship was: possible. An addendum was received 20-May-2004: The physician returned a transcribed Medwatch with no new information. He states the event is ongoing.

- *Case 200422164GDDC: This case involves a 24-year-old female patient who initiated therapy with Clomid (clomiphene citrate) 50 mg orally, sometime in Feb-04 for the treatment of infertility. Relevant medical history and concomitant medication information were not reported. Sometime in Aug-04, the patient experienced blurred vision and a visual field defect (nos). It is unknown what treatments, if any, were provided, but Clomid therapy was discontinued sometime in Aug-04 due to this event. The event was ongoing at the time of the report. The patient had undergone more than the recommended number of cycles of Clomid.*
- *Case 200619563GDDC: This case involves a female patient (age nos) who had used Clomid (clomiphene citrate) therapy and developed visual disturbances. The patient had undergone her last treatment cycle six months prior to the report and the visual disturbances had not stopped. An addendum for follow-up information was received on 27-Oct-06: The physician reporter upgraded the event as serious due to ongoing blurred vision. The patient was identified as a 43-year-old female patient who initiated therapy with oral clomiphene citrate sometime in Nov-05 for infertility. In the same month (Nov-05), the patient experienced visual disturbances and blurred vision, which were not corrected by glasses. The prescription for the lenses in her glasses was changed by her Optician. Her treatment with clomiphene citrate was stopped five days after starting in Nov-05 (exact date nos) and the patient received corrective therapy with tamoxifen. Concomitant medications included folic acid and oral iron (neither were suspected). The physician reported that the event was probably related to therapy with clomiphene citrate. No further details were provided.*

B. Literature review of visual disorders (from clinical overview): The Sponsor conducted a literature search starting in the mid-1990s for reports of visual disorders associated with clomiphene citrate use. The search identified a total of 3 published references describing 5 cases of prolonged visual disturbances including the aforementioned 3 case reports in the Sponsor's safety database. These publications included:

1. (Lawton, et al. 1994) - Case report of a 31-year-old woman who developed acute visual loss in her right eye immediately after a 5-day course of clomiphene citrate for primary infertility. The final diagnosis after an extensive neuro-ophthalmologic evaluation was anterior ischemic neuropathy.
2. (Vincent, et al. 2008) - Case report of a 36-year old woman who developed central retinal vein occlusion during her 8th cycle of clomiphene citrate therapy. The woman had experienced visual loss in a previous cycle which had spontaneously resolved. The authors noted that thrombogenic complications of clomiphene citrate, including deep vein thrombosis, pulmonary embolism and central retinal artery occlusion have been reported.
3. (Purvin, et al. 1995) - A case series study of three patients who had prolonged visual disturbances after three to six cycles of clomiphene citrate use. This publication reported that these patients remained symptomatic 4 to 7 years after discontinuing clomiphene citrate. The authors commented that the patient's symptoms were consistent with retinal toxic dysfunction, but provided no specific diagnosis.

According to the Sponsor: "Based upon this review of the serious and non-serious spontaneous cases retrieved from global pharmacovigilance database and current

available literature, an association between treatment with clomiphene citrate and the possibility of development of irreversible and/or prolonged visual disturbances, especially when clomiphene is not used as prescribed in the current approved label, cannot be excluded."

***Comment**: The Ophthalmology consult dated April 27, 2009, did not evaluate the published literature submitted by the sponsor. In the Purvin, et al. article (1995),[1] it was reported that from 1983 to 1989, a total of 149 visual disturbance case reports related to clomiphene citrate use were identified through post-marketing reports. Of note, only 2 of the 149 cases included details on persistent (prolonged) visual changes. The Purvin article concluded that, "Women who develop visual disturbances while undergoing treatment with clomiphene should be advised that these symptoms may be irreversible if treatment is continued." It is difficult to determine from these published cases whether the visual disturbances represent emergence of preexisting conditions that predisposed these patients to the visual changes, or if these visual changes were a result of ocular migraines.*

A more recent publication (Racette, 2009)[2] evaluated 8 patients who had visual disturbances associated with clomiphene use. An extensive evaluation of these patients with comprehensive visual evaluations was performed during a wash out period and during active clomiphene treatment. This publication reported that the effect of clomiphene was minimal on the clinical examination or the psychophysical parameters of color vision, visual acuity, contrast sensitivity or visual fields. All visual disturbances reported by patients in this study were reversible and this information is very reassuring. The conclusion of the Racette publication was that "Women who experience visual symptoms with clomiphene citrate should be monitored, but therapy can be maintained."

Of note, a publication in 2009 reported a case of central retinal vein thrombosis secondary to clomiphene treatment in a male infertility patient who was a carrier of factor V (Leiden) mutation.[3]

On October 6, 2009, DRUP discussed the additional published case reports with the Ophthalmology consultant. After review of the cases, the reviewers agreed that the majority of the visual changes documented in the literature were short term or prolonged, but little documentation existed to support a WARNING or PRECAUTION of "irreversible visual disorders" associated with clomiphene citrate.

Based on the published information, the clinical reviewers concluded that discontinuation of clomiphene when visual disorders occur should be a clinical decision. Although the etiology of the majority of these visual changes is unclear, thrombotic and other visual disorders can result in prolonged visual changes that are documented in patients on clomiphene citrate treatment. The literature is unclear on whether dose or duration of therapy is critical to these visual changes and on the nature of the "irreversible changes."

CONGENITAL ANOMALIES

On December 7, 2007, the Office of Regulatory Policy (ORP) received a Citizen Petition regarding potential teratogenic effects of clomiphene citrate. In formulating its response to the Citizen Petition, ORP consulted the Maternal Health Team (MHT) and the Division of Epidemiology (DEPI). The FDA denied the petition in September 2009, which prompted the submission of a Petition to Reconsider in 2009. DEPI was consulted again in the

[1] Purvin V. Visual disturbances secondary to clomiphene citrate. Arch Ophthal l995: 113:483-4.
[2] Racette L, Casson P, et al. An investigation of the visual disturbances experienced by patients with clomiphene citrate. Fertil Steril 2009: Article in press.
[3] Politou M, Gialeraki A, et al. Central retinal vein occlusion secondary to clomiphene treatment in a male.

review of the new information submitted in the Petition to Reconsider. Pertinent recommendations from DEPI and MHT are summarized below. For more details, refer to DEPI consults dated August 5, 2008 (in response to the 2007 Citizen Petition) and October 15, 2011 (in response to the 2009 Petition to Reconsider) and MHT consult dated March 27, 2009.

DEPI CONSULTS:
On July 25, 2008 DEPI completed an assessment of the citizen petition claims and comments on the Division of Reproductive and Urologic Products' (DRUP) planned responses to the CP. The DEPI reviewer concluded the following:

- DRUP's approach and response to ORP was thorough and in harmony with ICH and FDA review standards,
- It was difficult to assess feasibility and potential benefits of conducting further epidemiological studies to explore the association between clomiphene citrate and birth defects without first completing a thorough literature review,
- The drug labeling did not accurately reflect findings from an AERS review conducted on the year 2000. Recommendations were made for labeling changes but have not been implemented.

On November 3, 2008, DEPI completed a comprehensive literature review of prenatal clomiphene exposure and congenital anomalies. The reviewers concluded "the available scientific evidence did not demonstrate an increased risk of congenital abnormalities due to clomiphene citrate periconceptional exposure." DEPI concluded:

- "The available scientific evidence does not demonstrate an increased risk of congenital abnormalities due to clomiphene citrate periconceptional exposure. Due to the rare exposure and small number of cases, these studies were powered to detect only large differences. In addition, the small number of cases did not allow for simultaneous adjustment for important confounders.
- Any additional epidemiological studies should take into account the multiple factors associated with subfertility and clomiphene's use in clinical practice.
- The evidence evaluated does not suggest that the use of clomiphene increases the rate of spontaneous abortion among subfertile women treated for ovulation induction.
- The data reviewed does not suggest the presence of an increased risk of cancer among pediatric patients exposed to clomiphene in-utero."

Comment*: In 2000, DEPI conducted an AERS review of fetal anomalies and recommended additional terms to be added to the Adverse Reaction (Postmarketing Adverse Events) section of the label. These changes will be implemented in labeling. DEPI did not have additional labeling recommendations in their 2008 consult.*

FDA denied the Citizen Petition in 2009. In response, in a Petition to Reconsider, the petitioner cited a published study from the Centers for Disease Control and Prevention that "found that clomiphene citrate was associated with a statistically significant increased risk for 9 different types of birth defects." DEPI reviewed the published study and concluded that, although the results of this well-conceived study suggest an increased risk of certain congenital malformations in offspring of mothers who were exposed to clomiphene citrate around the time of conception, a causal association was not demonstrated due to the limitations in assessing the effects of underlying subfertility. Nonetheless, some of the findings were consistent with previous findings, some of which are already included in the label directly or indirectly (under more generalized diagnoses). The DEPI recommended the following:

- The labeling could be revised to include the following more specific diagnoses in the Postmarketing Adverse Events section given that other studies have found associations, particularly for craniosynostosis.
    - Craniosynostosis
    - Septal heart defects
    - Muscular VSD
    - Coarctation of the aorta
    - Cloacal exstrophy
    - Omphalocele

Comment: DEPI's 2011 labeling recommendations will be included in this labeling supplement, with some minor formatting revisions.

MATERNAL HEALTH TEAM CONSULT:

As part of a review of and response to the 2007 Citizen Petition, ORP consulted the Maternal Health Team (MHT). In the consult dated 2009, MHT provided labeling recommendations, which considered reviews from OSE/DEPI and DRUP. The MHT consult stated the following:

"The Office of Surveillance and Epidemiology (OSE) did thorough searches of both the Adverse Event Reporting System (AERS - safety database) and of the epidemiologic literature base for clomiphene citrate exposure and teratogenicity. OSE concluded that 1) the available scientific evidence does not demonstrate an increased risk above the background population risk of congenital anomalies due to clomiphene citrate periconceptual exposure; and, 2) clomiphene citrate labeling Adverse Reactions, Postmarketing Adverse Events, Fetal/Neonatal Anomalies subsection should be updated to reflect the 2000 AERS database review and add additional fetal abnormalities reported during postmarketing surveillance.

The Division of Reproductive and Urologic Products (DRUP) reviewed the studies submitted by the petitioner and concluded that the information presented did not provide substantial evidence that clomiphene citrate inhibits cholesterol synthesis or is teratogenic in humans (responses were provided to questions formulated by the Office of Regulatory Policy regarding this Citizen's Petition). With regard to labeling, DRUP concluded that the current clomiphene citrate labeling contains adequate information with regard to teratogenicity and risks for individual birth defects. DRUP also concluded that the clinical study information regarding the overall incidence of reported fetal abnormalities from maternal clomiphene use accurately reflects the postmarketing experience and is consistent with the background population risk of congenital anomalies. DRUP recommended: 1) adopting the OSE labeling recommendations outlined below; and, 2) to develop FDA-approved patient labeling in the form of a Patient Package Insert (PPI) to adequately inform patients of the risks associated with clomiphene citrate including the risks of birth defects with maternal exposure. DRUP did not plan to convert clomiphene citrate labeling into the new Physician Labeling Rule (PLR) format at the time of the review."

The goal of the Maternal Health Team's input was to provide guidance for a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach incorporated "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The currently approved Clomid labeling, last approved in 2005, was in the old labeling format with information related to pregnancy placed in multiple sections, and no one section containing complete pregnancy use information for optimum accessibility for healthcare practitioners. The MHT consult included suggested revisions to Clomid pregnancy labeling to better inform the labeling for healthcare providers by, 1) including a complete, comprehensive pregnancy use subsection

by organizing and presenting the pregnancy information in a logical, clear, and useful manner; 2) updating outdated pregnancy language; and, 3) adding relevant information derived from the DRUP and OSE reviews. The main sections of the labeling affected by the proposed changes were Contraindications, General Precautions (Information to Patients, Pregnancy), and Adverse Reactions (Postmarketing Adverse Events).

Comment: *The labeling changes recommended by MHT regarding congenital anomalies will be included in the supplement, with some minor modifications.* (b) (4) [redacted]

CONCLUSIONS:

Visual Disorders

After review of the cases of visual disturbance and literature submitted by the Sponsor, DRUP concludes that the evidence regarding irreversible visual disturbances, although limited, is sufficient to support the labeling changes. Therefore, DRUP concurs (with slight modification to the proposed WARNING) to the following labeling changes proposed by the Sponsor in their December 10, 2009, amendment to SLR 026 (added text is underlined, deleted text indicated by strikethrough)

1. In the WARNING section under the Visual Symptoms subsection:

   "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 ~~and generally disappear within a few days or weeks after CLOMID is discontinued.~~ 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."

2. In the PRECAUTIONS section, under the Visual Symptoms sub-section:

   "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."

3. In the ADVERSE REACTIONS section under the Postmarketing Adverse Events sub-section:

   "Visual Disorders: Abnormal accommodation, cataract, eye pain, macular edema, optic neuritis, photopsia, posterior vitreous detachment, retinal hemorrhage, retinal thrombosis, retinal vascular spasm, temporary loss of vision, and visual disturbances which may be prolonged and possibly irreversible."

Congenital Anomalies and Updating of Pregnancy related sections

DEPI: The following DEPI recommendations will be implemented (2000 DEPI consult):

- The addition of the following terms to the Postmarketing Adverse Events subsection: clubfoot, spine, meningomyelocele, microcephaly, hydrocephalus, patent ductus arteriosus, cleft lip and palate, hypospadias, and Down's syndrome

- Revisions to include the following occurrence of specific diagnoses in the Postmarketing Adverse Events subsection will be implemented (2011 DEPI consult): craniosynostosis, septal heart defects, muscular VSD, coarctation of the aorta, cloacal exstrophy, omphalocele

MHT: Recommended revisions affecting the Contraindications, Precautions (Information to Patients, Pregnancy), and Adverse Reactions (Postmarketing Adverse Events) sections of labeling to update the label to more current standards will be incorporated. See the attached labeling for proposed revisions.

Other Labeling Changes

This supplement also provides for the following labeling changes requested by the DRUP in the September 2009 SLR request. DRUP accepts these changes.

1. In the WARNING section under the Ovarian Hyperstimulation Syndrome sub-section the following underlined text was added: "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."
2. In the ADVERSE REACTIONS section under the Postmarketing Adverse Events sub-section, urticaria was added as an adverse event to the list of Dermatologic adverse experiences reported spontaneously.

On July 20, 2012, the aforementioned labeling changes were conveyed to the Sponsor in an electronic communication. The sponsor responded via email on August 20 and September 18, 2012, accepting all changes.

On October 5, 2012, the sponsor submitted the final agreed upon labeling as an amendment to SLR 026. A side-to-side comparison of the labeling was conducted; all agreed upon changes have been incorporated.

Recommended regulatory action: The labeling for Clomid (NDA 16-131) submitted on October 5, 2012, as an amendment to SLR 026 should be approved.

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
10/11/2012

SHELLEY R SLAUGHTER
10/11/2012
I concur with the recommended regulatory action.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 016131/S-026

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

Maternal Health Team Review

Date: March 27, 2009

From: Jeanine Best, MSN, RN, PNP
Regulatory/Labeling Reviewer, Pediatric and Maternal Health Staff

Through: Karen B. Feibus, M.D.
Medical Team Leader, Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

To: Division of Reproductive and Urologic Products

Drug: Clomiphene citrate (Clomid, NDA 16-131 and Serephene, NDA 18-361), ANDAs 75-528 and 72-196

Subject: MHT proposed clomiphene citrate labeling revisions for Clomid pregnancy labeling in response to Citizen's Petition from Clarence J. Mix dated November 26, 2007 (received December 7, 2007).

Materials Reviewed:

- Citizen's Petition from Clarence J. Mix dated November 26, 2007 (received December 7, 2007)
- OSE Safety Review: Citizen Petition; Clomiphene citrate exposure and the risk of teratogenicity, July 25, 2008
- OSE Literature review: Clomiphene citrate exposure and the risk of teratogenicity (in support of Citizen Petition Response); Office of Surveillance and Epidemiology; November 3, 2008
- DRUP Response to Citizen's Petition from Clarence J. Mix, Esq.; February 27, 2009

INTRODUCTION

As part of a review of and response to a submitted Citizen Petition, the CDER Office of Regulatory Policy (ORP) consulted the Maternal Health Team (MHT) to review and address the petitioner's claim that clomiphene citrate is a teratogen and that FDA should require safety based labeling changes and risk management strategies for the product. In this review, the MHT makes labeling recommendations based on the thorough data reviews performed by reviewers in the Division of Reproductive and Urologic Products (DRUP) and the Office of Surveillance and Epidemiology (OSE).

BACKGROUND

Clomiphene citrate is a selective estrogen-receptor modulator (SERM) that was approved in the U.S. on February 1, 1967, for the treatment of ovulatory dysfunction in women desiring pregnancy. Clomiphene citrate is a mixture of two geometric isomers [cis (zuclomiphene) and trans (enclomiphene)] and has both estrogenic and anti-estrogenic properties. The cis isomer (zuclomiphene) has a longer half-life than the trans isomer (enclomaphene) and may be present in a woman's body for up to six weeks after administration; thereby, potentially exposing an early pregnancy.

Terrence J. Mix, Esq. submitted a Citizen's Petition[1] dated November 26, 2007, received December 7, 2007, alleging that clomiphene citrate products inhibit cholesterol synthesis, and therefore, induces teratogenicity, and requested FDA to:

1) Order postmarketing labeling changes to warn of (alleged) teratogenicity;

2) Order risk evaluation and mitigation strategies (REMS) in order to "determine"[2] if benefits of the clomiphene citrate outweigh the risks;

3) Order postmarketing studies to determine if diet and/or dietary supplements can mitigate the (alleged) risk of teratogenicity due to inhibition of cholesterol synthesis.

The Division of Reproductive and Urologic Products (DRUP) reviewed the studies submitted by the petitioner and concluded that the information presented did not provide substantial evidence that clomiphene citrate inhibits cholesterol synthesis or is teratogenic in humans (responses were provided to questions formulated by the Office of Regulatory Policy regarding this Citizen's Petition).[3] With regard to labeling, DRUP concluded that the current clomiphene citrate labeling contains adequate information with regard to teratogenicity and risks for individual birth defects. DRUP also concluded that the clinical study information regarding the overall incidence of reported fetal abnormalities from maternal clomiphene use accurately reflects the postmarketing experience and is consistent with the background population risk of congenital anomalies. DRUP recommends: 1) adopting the OSE labeling recommendations outlined below; and, 2) to develop FDA-approved patient labeling in the form of a Patient Package Insert (PPI) to

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[1] Mix T. Citizen Petition regarding Clomid (clomiphene citrate). November 26, 2007

[2] Note: Mr. Mix incorrectly interprets risk evaluation and mitigation strategies. See FD&C Act, SEC. 505-1 [21 USC 355-1] Risk Evaluation and Mitigation Strategies, "a risk evaluation and mitigation strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug"

[3] DRUP Response to Citizen's Petition from Clarence J. Mix, Esq.; February 27, 2009

adequately inform patients of the risks associated with clomiphene citrate including the risks of birth defects with maternal exposure. DRUP does not plan to convert clomiphene citrate labeling into the new Physician Labeling Rule (PLR) format at this time.

The Office of Surveillance and Epidemiology (OSE) did thorough searches of both the Adverse Event Reporting System (AERS - safety database) and of the epidemiologic literature base for clomiphene citrate exposure and teratogenicity. OSE concluded that 1) the available scientific evidence does not demonstrate an increased risk above the background population risk of congenital anomalies due to clomiphene citrate periconceptual exposure[4]; and, 2) clomiphene citrate labeling Adverse Reactions, Postmarketing Adverse Events, Fetal/Neonatal Anomalies subsection should be updated to reflect the 2000 AERS database review and add additional fetal abnormalities reported during postmarketing surveillance.[5]

OSE Suggested Label Text Changes (in blue)

ADVERSE REACTIONS

Fetal/Neonatal Anomalies

The following fetal abnormalities have also been reported during postmarketing surveillance: delayed development; abnormal bone development including skeletal malformations of the skull, face, nasal passages, jaw, hand, limb (ectromelia including amelia, hemimelia, and phocomelia), **foot (clubfoot), spine**, and joints; **nervous system abnormalities including** neural tube defects (anencephaly**, meningomyelocele), microcephaly,** and **hydrocephalus; cardiac abnormalities including** ventricular septal defects, **patent ductus arteriosus, and** tetralogy of Fallot; **gastrointestinal tract abnormalities including cleft lip and palate,** imperforate anus, tracheoesophageal fistula, and diaphragmatic hernia; **abnormalities of the** genitalia **including hypospadias;** chromosomal disorders **including Down's syndrome; renal abnormalities including** renal agenesis and renal dysgenesis; malformations of the eye and lens (cataract); ear **abnormalities and** deafness; diaphragmatic hernia; dwarfism; **and** mental retardation and delayed development.

PREGNANCY AND NURSING MOTHERS LABELING

Background

The Maternal Health Team has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The MHT reviewer ensures that the appropriate regulatory language is present and that available information is organized and presented in a clear and useful manner for healthcare practitioners. Animal data in the pregnancy subsection is presented in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human exposure or dose equivalents (with the basis for calculation), and outcomes for dams and offspring. (For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.)

The Physicians Labeling Rule (PLR) or *Final Rule: Requirements on Content and Format of Labeling for Human Prescription Drugs and Biological Products*, published January 24, 2006,

[4] OSE Literature review: Clomiphene citrate exposure and the risk of teratogenicity (in support of Citizen Petition Response); Office of Surveillance and Epidemiology; November 3, 2008

[5] OSE Safety Review: Citizen Petition; Clomiphene citrate exposure and the risk of teratogenicity, July 25, 2008

effective June 30, 2006, revised labeling regulations for labeling to include highlights of prescribing information and a table of contents, reordered certain sections, required minor content changes, and set minimum graphical requirements. The labeling revisions were done to make it easier for healthcare practitioners to access, read, and use information in prescription drug labeling.[6] An implementation timetable was established at which time conforming labeling must be submitted to the Agency for Approval. Because Clomid was approved in 1967 (approved more than 5 years before June 30, 2006), the requirement to submit conforming PLR labeling is voluntary at any time.

The current approved Clomid (clomiphene citrate) labeling is in the old labeling format with information related to pregnancy placed in multiple sections, and no one section containing complete pregnancy use information for optimum accessibility for healthcare practitioners.

This review provides MHT's suggested revisions to Clomid (clomiphene citrate) pregnancy labeling to better inform the labeling for healthcare providers by, 1) including a complete, comprehensive pregnancy use subsection by organizing and presenting the pregnancy information in a logical, clear, and useful manner; 2) updating outdated pregnancy language; and, 3) adding relevant information derived from the DRUP and OSE reviews.

A tracked-changes copy containing recommended labeling revisions is provided in Appendix A. We have provided our tracked-changes to the revised Clomid labeling submitted by the Sponsor on January 22, 2009 (NDA 16-131/S-026).

[6] See Final Rule: Requirements on Content and Format of Labeling for Human Prescription Drugs and Biological Products, January 24, 2006

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(b) (4)

MHT Clomid Pregnancy Labeling Recommendations
Provided below are MHT's recommended revisions for pregnancy use labeling for Clomid and all clomiphene citrate products. MHT notes that the approved Nursing Mothers subsection of Clomid labeling accurately reflects the known data on the effect of clomiphene citrate on lactation and requires no revisions.

Refer to Appendix A of this review for a tracked-changes version of labeling that highlights all MHT labeling revisions.

(b) (4)

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(b) (4)

MHT Reviewer Comment: The P/T reviewer, where possible, should add the human dose multiples for animal doses to provide meaningful information for a clinician's use.

(b) (4)

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/s/

Jeanine Best
3/27/2009 12:40:45 PM
LABELING REVIEWER

Karen Feibus
3/27/2009 03:19:58 PM
MEDICAL OFFICER
I agree with the content and recommendations contained in this review.

Lisa Mathis
3/27/2009 04:27:05 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 016131/S-026

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PRIOR APPROVAL SUPPLEMENT

NDA 16-131/S-026

sanofi-aventis U.S., LLC
Attention: Debra L. Kolb
U.S. Regulatory Affairs
55 Corporate Drive
Bridgewater, NJ 08807

Dear Ms. Kolb:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Clomid® Tablets (clomiphene citrate) Tablets, 50 mg

NDA Number: 16-131

Supplement number: 026

Date of supplement: January 22, 2009

Date of receipt: January 23, 2009

This supplemental application proposes to update the Clomid® package insert to include additional safety information in the subsections of warnings, precautions, and adverse reactions.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 24, 2009 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 23, 2009.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, call me at (301) 796-4154.

Sincerely,

{See appended electronic signature page}

Celia R. Peacock, MPH, RD
Regulatory Project Manager
Division of Reproduction and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Celia R Peacock

4/1/2009 11:10:04 AM