SUMMARY OF PRODUCT CHARACTERISTICS

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Clomid 50 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Clomifene citrate ..... 50.000 mg

For one 320 mg tablet.

Excipients with known effect: lactose, sucrose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of infertility caused by normoprolactinemic functional anovulation or irregular ovulation:

- anovulatory infertility
- infertility due to irregular ovulation:
  - inadequate corpus luteum function
  - luteal phase defect (LPD)
  - polycystic ovary syndrome.

Testing for diagnostic and therapeutic purposes:

- in certain types of amenorrhea caused by disorders of the hypothalamus or pituitary gland,
- in persistent amenorrhea following use of oral contraceptives (after it has been ascertained that plasma prolactin levels are normal).

Ovulation induction in the context of medically-assisted procreation (intrauterine insemination, *in vitro* fertilization).

4.2. Posology and method of administration

Posology

Treatment of infertility caused by normoprolactinemic functional anovulation or irregular ovulation:

The initial dose is 1 tablet daily (i.e. 50 mg) for 5 days.

Treatment should be initiated 2 to 5 days after the start of withdrawal bleeding that is either spontaneous or progestin-induced or, in the absence of a menstrual cycle, on any date chosen by the primary healthcare provider.

If ovulation occurs, there is no advantage to increasing the dose in subsequent courses of treatment. If ovulation does not occur (no thermoregulatory disorders, plasma progesterone less than 3 ng/ml from days 20 to 26 of the cycle), 100 mg daily for 5 days should be prescribed during the second course of therapy (2 tablets as a single daily dose).

The daily dose should not exceed 100 mg/day, and the treatment duration, 5 days. If 3 courses of therapy at this dose have not induced ovulation, the therapy can be considered finished. When ovulation is achieved at a dose of 50 or 100 mg, without resulting in pregnancy, therapy can be continued for up to a total of 6 treatment courses.

Some patients with polycystic ovaries may be hypersensitive to **Clomid**, even at the initial dose (50 mg daily). In these patients, the dose for subsequent cycles can be decreased to ½ tablet daily (25 mg/day).

The couple must be reminded of the necessity of frequent sexual intercourse during the theoretical fertile period.

Clomid is not indicated in women who ovulate.

Testing for diagnostic and therapeutic purposes

This test is used to diagnose gonadotropin deficiency when a patient wishes to become pregnant. The dose is 2 tablets/day (i.e. 100 mg) for 5 consecutive days and for one cycle only.

Ovulation induction in the context of medically-assisted procreation (IVF, etc.)

Certain ovarian stimulation protocols use **Clomid** (2 tablets daily from day 2 to 6 of the cycle) followed by hMG for several days in order to induce maturation of several follicles.

Method of administration

Clomid is administered via the oral route and can only be used under specialized medical monitoring.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe or recent hepatic disorders.
- Gynecological bleeding of undetermined etiology.
- Hormone-dependent tumors.
- Organic ovarian cysts.
- Visual disturbances during current treatment or during past treatment.

4.4. Special warnings and precautions for use

Warnings:

Before Clomid administration:

- ensure that the patient is not pregnant before administering **Clomid**. If the patient may be pregnant, a sensitive and accurate pregnancy test should be performed (the patient should be checked before each course of treatment),
- ensure that the cause of infertility is not:
  - primary ovarian failure,
  - organic hypothalamic/pituitary insufficiency,
- evaluate, and if necessary administer appropriate treatment for other possible causes of both female and male infertility,
- couples should be warned of the increased probability of multiple pregnancy and its possible complications,
- some studies in the literature report that medicinal products used in infertility treatment may increase the risk of the occurrence of certain benign or malignant tumors, particularly hormone-dependent tumors. However, a comprehensive review of the literature does not make it possible to conclude with certainty that there is an increased risk of developing certain tumors, particularly hormone-dependent tumors, in patients treated with ovulation-inducing agents.

During treatment:

- **Clomid** used alone or concomitantly with gonadotropins can cause Ovarian Hyperstimulation Syndrome (OHSS), which is often of moderate intensity, but can be severe in very rare cases. Rare cases of severe OHSS have been reported with the following symptoms: pericardial effusion, anasarca, hydrothorax, acute abdomen, renal failure, pulmonary edema, ovarian bleeding, deep vein thrombosis, torsion of the ovary and acute respiratory distress. If pregnancy occurs in a patient with OHSS, the syndrome may rapidly progress and become severe.
- Ovarian hyperstimulation occurs a few days after the end of treatment with **Clomid**.
- Special attention must be paid to patients complaining of pelvic pain, weight gain or an overall bloated feeling during treatment. In this case, an ultrasound should be performed to check for any ovarian enlargement. A new course of treatment with **Clomid** should only be initiated after the ovaries have returned to their normal size. The dose should then be reduced.

Complications due to ovarian hyperstimulation with **Clomid** use are very rare.

Visual disturbances:

Patients should be warned of the risk of visual disturbances such as blurred vision, persistent afterimages on exposure to light, phosphenes or scintillating scotomata. These symptoms may occur during or after treatment with **Clomid** and are usually reversible; however, prolonged visual disturbances have been reported, even after discontinuation of **Clomid**. These may be irreversible, especially if the dosage or duration of treatment exceeds recommendations. If visual disturbances occur, treatment should be definitively discontinued and a full ophthalmological examination performed. Some rare cases of posterior capsular cataracts have been reported in patients using **Clomid** although a causal relationship has not been established or ruled out.

Precautions for use

- In obese patients, appropriate dietary measures are recommended throughout treatment in order to achieve significant weight loss. As with all ovulation-inducing treatments, significant obesity should delay the start of treatment, and dietary measures should be made a priority.
- **Clomid** should only be administered under specialized medical monitoring.
- Clinical monitoring should be performed (functional signs, basal body temperature), and possibly monitoring of laboratory parameters with plasma progesterone assays performed between days 20 and 26 of the menstrual cycle.
- During a menstrual cycle induced by **Clomid**, if treatment with progestins is to be prescribed, it should not be given before day 20 of the cycle so as not to affect the cervical mucus, especially if ovulation is slightly delayed. Withdrawal bleeding achieved by progestin therapy at the end of an anovulatory cycle means that a new course of treatment at a higher dose can be considered immediately.
- Special monitoring is recommended for patients with uterine fibroids due to the risk of enlargement of the fibroids.
- Although isolated cases of congenital abnormalities have been observed following treatment with **Clomid**, it has not been demonstrated that **Clomid** use affects the incidence of congenital malformations in children born to women with fertility problems. The age of the mother and multiple pregnancies are risk factors for fetal or neonatal abnormalities.
- Insufficient cervical mucus caused by the antiestrogenic effect of **Clomid** may justify use of concomitant local estrogen therapy.
- Cases of hypertriglyceridemia have been reported (see section 4.8 Undesirable effects). Familial or pre-existing hypertriglyceridemia as well as exceeding the recommended dose and/or treatment duration are associated with a risk of hypertriglyceridemia. Periodic monitoring of plasma triglyceride levels may be indicated in these patients.
- When it is administered long-term, **Clomid** can interfere with the synthesis of cholesterol. Patients receiving long-term treatment with the drug can have high desmosterol levels.
- This medicinal product contains sucrose. It is therefore not recommended in patients with fructose intolerance, glucose and galactose malabsorption syndrome or sucrase-isomaltase deficiency.
- This medicinal product contains lactose. It is therefore not recommended in patients with galactose intolerance, Lapp lactase deficiency or glucose or galactose malabsorption syndrome (rare hereditary diseases).

4.5. Interaction with other medicinal products and other forms of interaction

Interactions between clomifene and other medicinal products have not been described.

4.6. Fertility, pregnancy and lactation

Animal studies have demonstrated that the drug has teratogenic effects.

To date, the clinical data are not sufficiently relevant to evaluate the possible teratogenic or fetotoxic effects of this medicinal product when administered during pregnancy.

This medicinal product is not indicated during pregnancy. However, in the event of accidental exposure, recommending termination of the pregnancy is unwarranted.

4.7. Effects on ability to drive and use machines

Adverse visual effects have been reported (see section 4.8), particularly with exposure to light of varying intensity, which can interfere with driving.

4.8. Undesirable effects

Reproductive system and breast disorders:

- Ovarian hyperstimulation (see section 4.4),
- insufficient cervical mucus caused by the antiestrogenic effect of **Clomid**, possibly justifying use of concomitant local estrogen therapy.

Cases of endometriosis or aggravation of pre-existing endometriosis have been reported.

- Menorrhagia, metrorrhagia,
- breast tenderness,
- pelvic discomfort,
- reduced thickness of the endometrium.

Renal and urinary disorders:

- Pollakiuria.

Pregnancy, puerperium and perinatal conditions:

- Moderate risk of multiple pregnancy including simultaneous intrauterine and extrauterine pregnancies. There is an increased risk of extrauterine pregnancy following **Clomid** therapy.

Eye disorders:

- Visual disturbances: blurred vision, persistent afterimages on exposure to light, phosphenes and scintillating scotoma are observed in 2% of cases (incidence increases with total dose received).

These visual disturbances usually resolve after several days or even several weeks following treatment discontinuation. However, cases of prolonged visual disturbances have been reported even after treatment with **Clomid** has been discontinued. In this case, they can be irreversible, especially after an increase in dose and/or duration of treatment. If they occur during any course of **Clomid** therapy, the drug should be discontinued immediately and any future use is contraindicated. Some rare cases of posterior subcapsular cataracts have been reported.

Cardiac disorders:

- Tachycardia, palpitations.

Skin and subcutaneous tissue disorders:

- Urticaria or allergic dermatitis, alopecia.

Neoplasms benign, malignant and unspecified:

Isolated cases of onset or aggravation of certain tumors, most often hormone-dependent tumors, have been reported.

Nervous system disorders:

- Headache, dizzy spells, lightheadedness, giddiness and transient paresthesia.
- Cases of seizure have been reported.

Psychiatric disorders:

- Some cases of aggravation of pre-existing psychosis have been reported.
- Anxiety, depression, mood disorders (including mood changes, mood swings and irritability), nervousness and insomnia have also been reported.

Vascular disorders:

- Hot flushes.

Hepatobiliary disorders:

- Increased transaminases.

Gastrointestinal disorders:

- Nausea and vomiting,
- abdominal discomfort (distention, bloating),
- pancreatitis.

Metabolic disorders:

Hypertriglyceridemia, sometimes associated with pancreatitis, has been observed in patients with familial or pre-existing hypertriglyceridemia, and/or when the medicinal product is administered at a higher dose and for a longer treatment duration than recommended. Periodic monitoring of plasma triglyceride levels may be indicated in these patients.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse effects via the national reporting system: French National Agency for Medicines and Health Products Safety (ANSM) and the network of Regional Pharmacovigilance Centers - Website: www.ansm.sante.fr.

4.9. Overdose

No cases of acute overdose have been reported.

In the event of overdose, nausea, vomiting, hot flushes, potentially irreversible visual disturbances and ovarian enlargement with abdominal and pelvic pain can be observed.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: ovulation stimulants, ATC code: G.

By competitive inhibition, **Clomid** inhibits the negative feedback effect of estrogens in the hypothalamus causing increased levels of FSH that stimulate follicle maturation. Follicle maturation is accompanied by an increase in estradiol secretion, which promotes a marked increase in luteinizing hormone (LH) that triggers ovulation and formation of a corpus luteum capable of secretion.

In 5 413 patients with ovulation disorders, treatment with **Clomid** induced ovulation in over 70% percent of cases.

5.2. Pharmacokinetic properties

After oral administration, the medicinal product is well absorbed. Excretion is primarily fecal; the parent drug and its metabolites are slowly excreted via enterohepatic circulation.

5.3. Preclinical safety data

Reproduction toxicity

A harmful effect (inhibition of fetal development and possible fetal abnormalities) in rat and rabbit fetuses has been demonstrated during administration of high doses of clomifene in gestating animals.

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Carcinogenicity – Mutagenicity

No long-term mutagenicity and carcinogenicity studies have been performed to evaluate the carcinogenic potential of **Clomid**.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sucrose, lactose monohydrate, maize starch, soluble starch, magnesium stearate, yellow iron oxide (E172).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store protected from light, moisture and excessive heat.

6.5. Nature and contents of container

5 or 10 tablets in PVC/Aluminum blisters

6.6. Special precautions for disposal and other handling

Not applicable.

7. MARKETING AUTHORIZATION HOLDER

sanofi-aventis France
82, avenue Raspail
94250 Gentilly, France

8. MARKETING AUTHORIZATION NUMBER(S)

04936/07055/REN/2019

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Feb 1, 2020

10. DATE OF REVISION OF THE TEXT

[To be completed by the Marketing Authorization Holder]

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

GENERAL CLASSIFICATION FOR SUPPLY

List I.

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