ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Clomilen 50 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Clomiphene citrate 50 mg
Excipients:
For the exhaustive list of excipients: see section 6.1

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Clomiphene citrate is indicated for the treatment of anovulatory infertility resulting from functional disorders of the hypothalamo-hypophyseal axis (for instance normogonadotrophic anovulation, polycystic ovaries syndrome) in women desiring pregnancy.

4.2 Posology and method of administration

The recommended dose for the first course of Clomiphene citrate 50 mg tablet is 50 mg daily (1 tablet) for 5 days.

Therapy may be started at any time in the patient who has had no recent uterine bleeding.

A gynaecological examination is required before initiating the treatment.

If progestin-induced bleeding is planned, or if spontaneous uterine bleeding occurs before therapy, the regimen of 50 mg daily for 5 days should be started on or about the fifth day of the cycle.

When ovulation occurs at this dosage, there is no advantage to increasing the dose in subsequent cycles of treatment.

The assessment of the efficacy of the treatment (occurrence of ovulation), is usually insured by the temperature curve. The basal temperature rises after ovulating and maintain during 10 to 14 days. The other means available are the measure of plasma progesterone, in the middle of the luteal phase, and the ultrasound visualisation of the pre-ovulatory follicle.

If ovulation appears not to have occurred 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.

Increase of the dosage or duration of therapy beyond 100 mg/day for 5 days should not be undertaken.

Treatment beyond this is not recommended in the patient who does not exhibit evidence of ovulation.
The significance of match the coitus with the assumed fertility period should be reminded.

The examination of the cervical mucus can be useful, especially to match the ovulation with the artificial insemination.

A long term cyclic therapy is not recommended because, in the one hand, the relative safety of long-term therapy has not yet been conclusively demonstrated and in the second hand, since the majority of patients will ovulate following 3 courses, long-term cyclic therapy is not recommended, i.e. beyond a total of about 6 cycles (including 3 ovulatory cycles).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Pregnancy:
Clomiphene citrate 50 mg is not indicated during pregnancy.

Liver disease:
Clomiphene citrate 50 mg tablets is contraindicated in patients with liver disease or a history of liver dysfunction.

Abnormal uterine bleeding:
Clomiphene citrate 50 mg tablets is contraindicated in patients with abnormal uterine bleeding of undetermined origin.

Ovarian cyst:
Clomiphene citrate 50 mg tablets should not be given in the presence of an ovarian cyst, except polycystic ovary, since further enlargement of the cyst may occur. Patients should be evaluated for the presence of ovarian cyst prior to each course of treatment.

4.4 Special warnings and precautions for use

Good levels of endogenous oestrogen provide a favourable prognosis for ovulatory response induced by clomiphene citrate 50 mg tablets. The production of oestrogens can be estimated with a test to progestins (progestin-induced bleeding) or by the measurement of plasma estradiol concentration.
A low level of oestrogen, although clinically less favourable, does not preclude successful outcome of therapy.

Clomiphene citrate 50 mg tablets cannot be expected to substitute for specific treatment of other causes of ovulatory failure such as hyperprolactinaemia, thyroid or adrenal disorders.

Clomiphene citrate 50 mg therapy is inefficient in patients with primary pituitary failure or primary ovarian failure.

Other causes of infertility, potentially related, should be excluded or treated adequately before treatment with clomiphene citrate.

In order to avoid clomiphene citrate administration in the early during pregnancy, pregnancy should be excluded before initiating or reinitiating the therapy.

Ovarian cyst
A gynaecological examination is required prior to the first treatment course with Clomiphene citrate, and prior each consecutive course.
In the presence of an ovarian cyst, including ovarian endometriosis (except for polycystic ovaries), clomiphene citrate should not be administered, given the fact that a supplementary increase in the volume of the cyst can occur.

Ovarian Hyperstimulation Syndrome
Ovarian Hyperstimulation Syndrome (OHSS) has been reported in patients receiving Clomiphene citrate 50 mg tablets therapy for ovulation induction. In some cases, OHSS occurred following the cyclic use of Clomiphene citrate 50 mg tablet or when Clomiphene citrate 50 mg tablet was used in combination with

gonadotrophins. Severe cases of OHSS have rarely been reported with the following symptoms: pericardial effusion, anasarca, hydrothorax, acute abdomen, renal failure, pulmonary oedema, ovarian haemorrhage, deep venous thrombosis, torsion of the ovary and acute respiratory distress. If conception results, rapid progression to the severe form of the syndrome may occur.
To minimise the hazard of the abnormal ovarian enlargement associated with Clomiphene citrate 50 mg tablets therapy, the lowest dose consistent with expectation of good results should be used.
The patient should be instructed to inform the physician of any abdominal or pelvic pain, weight gain, discomfort or distension after taking Clomiphene citrate 50 mg tablets. Maximal enlargement of the ovary may not occur until several days after discontinuation of the course of Clomiphene citrate 50 mg tablets.
Some patients with polycystic ovary syndrome who are usually sensitive to gonadotropin may have an exaggerated response to usual doses of clomiphene citrate 5 mg tablets.

The patient who complains of abdominal or pelvic pains, discomfort, or distension after taking Clomiphene citrate 50 mg tablets should be examined because of the possible presence of an ovarian cyst or other cause. Due to fragility of enlarged ovaries in severe cases, abdominal and pelvic examination should be performed very cautiously. If abnormal enlargement occurs, Clomiphene citrate 5 mg tablets should not be given until the ovaries have returned to pre-treatment size. Ovarian enlargement and cyst formation associated with Clomiphene citrate 50 mg tablets therapy usually regress spontaneously within a few days or weeks after discontinuing treatment. Most of these patients should be managed conservatively. The dosage and/or duration of the next course of treatment should be reduced.

Uterine fibrosis
Caution should be exercised when using Clomiphene citrate 50 mg tablets in patients with uterine fibroids due to potential for further enlargement of the fibroids.

Multiple pregnancy
There is an increased chance of multiple pregnancy when conception occurs in relationship to Clomiphene citrate 50 mg tablets therapy, notably simultaneous intra-uterine and extra-uterine pregnancies. The potential complications and hazards of multiple pregnancy should be discussed with the patient. During the clinical investigation studies, the incidence of multiple pregnancy was 7.9 % among these, 6.9 % twin, 0.5 % triplet, 0.3 % quadruplet and 0.13 % quintuplet.
Of the twin pregnancies for which sufficient information was available, the ratio of monozygotic twin was 1:5.

Ectopic Pregnancy
There is an increased chance of ectopic pregnancy (including tubal and ovarian sites) in woman who conceive following Clomiphene citrate 50 mg tablets therapy.

Pregnancy Wastage and Birth Anomalies
Despite some isolated cases of congenital abnormalities reported after treatment with clomiphene citrate, it was not demonstrated that clomiphene citrate modifies the frequency of occurrence of congenital abnormalities in children from woman having had fertility issues (see section 4.6 Fertility, pregnancy and breast-feeding). The potential hazard of foetal or neonatal abnormalities related to the age of the patient or to a multiple pregnancy should be discussed with the patient.

There was no difference in reported incidence of birth defects whether Clomiphene citrate 50 mg tablets was given before the 19th day after conception or between the 20th and 35th day after conception. This incidence is within the anticipated range of general population.

Among the congenital abnormalities reported and related to clomiphene citrate induced ovulation, an increase in the proportion of neural tube deficiency can be noted.

There is no difference between the incidence of congenital abnormalities reported after the administration of clomiphene citrate up to the 19th day after conception or between the 20th and the 35th day after the conception.
This incidence is in the same range than the anticipated incidence in the general population.

Breast-feeding mothers
It was reported that clomiphene citrate reduces post-partum breast engorgement as well as lactation in some patients.

Visual Symptoms
Patients should be advised that blurring or other visual symptoms such as spots or flashes (scintillating scotoma) may occasionally occur during or shortly after therapy with Clomiphene citrate 50 mg tablets. These visual disturbances are usually reversible; however, cases of prolonged visual disturbance have been reported including after Clomiphene citrate 50 mg tablets discontinuation. The visual disturbances may be irreversible especially with increased dosage or duration of therapy. The significance of these visual symptoms is not understood. If the patient has any visual symptoms, treatment should be discontinued and ophthalmologic evaluation performed. Patients should be warned 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 sections 4.7 and 4.8).

Ovarian Cancer
There have been rare reports of ovarian cancer with fertility drugs: infertility itself is a primary risk factor. In the medical literature, some reports associated ovarian cancer and infertility medicines. Recent epidemiological and cohort data did not establish a relation between infertility treatments, including clomiphene citrate, and an increase in the risk of ovarian cancer. Some trials suggest that a prolonged used of clomiphene citrate (during 1 year or more) might reinforce the risk of developing an invasive ovarian tumour or an ovarian tumour that is at the limit of malignancy. Because of this uncertainty related to the increased risk of ovarian cancer, a long term therapy with treatment course over 6 months is not recommended.

Caution should be exercised when using Clomiphene citrate 50 mg tablets in patients with uterine fibroids due to potential for further enlargement of the fibroids.

Hypertriglyceridemia
Cases of hypertriglyceridemia have been reported (see section 4.8 Undesirable effects) in the post-marketing experience with Clomiphene citrate 50 mg tablets. Pre-existing or family history of hypertriglyceridemia and use of higher than recommended dose and/or longer duration of treatment with Clomiphene citrate 50 mg tablets are associated with risk of hypertriglyceridemia. Periodic monitoring of plasma triglycerides may be indicated in these patients.

Because of the presence of lactose, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

during the concurrent administration of clomiphene citrate (stimulation of the production of endogenous gonadotropins) and of gonadotropins, a significant increase of the risk of ovarian hyperstimulation as well as the risk of multiple pregnancies has been observed.

Such a combination can only be considered for precise indications and under daily rigorous monitoring of a gynaecologist.

4.6 Fertility, pregnancy and lactation

Fertility:
See section 4.4 “Special warnings and precautions for use: multiple pregnancies”.

Pregnancy:
Clomiphene citrate 50 tablets is contraindicated during pregnancy (see section 4.3 “Contraindications”). See also section 4.4 “Special warnings and precautions for use: Pregnancy Wastage and Birth Anomalies”.

Breast-feeding:
Clomiphene citrate 50 tablets is not indicated during lactation (see section 4.4 “Special warnings and precautions for use: Breast-feeding mothers”.

4.7 Effects on ability to drive and use machines

Patients should be warned that visual symptoms as “blurred vision” during treatment with clomiphene citrate or immediately after stopping the treatment.
That may render such activities as driving a car or operating machinery more hazardous than usual, particularly under conditions of variable lighting (see “Warning”).

4.8 Undesirable effects

Abstract of the safety profile
During the investigational studies, the more commonly reported adverse effects included ovarian enlargement (13.6 %), vasomotor flushes (10.4 %), abdominal-pelvic discomfort (distension, bloating) (5.5 %), nausea and vomiting (2.2 %), breast discomfort (2.1 %), visual symptoms (1.5 %), headache (1.3 %) and intermenstrual spotting or menorrhagia (1.3 %).

List of undesirable effects
The following CIOMS frequencies are used, if applicable:
Very common (≥ 1/10); common (≥1/100, <1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥1/10,000, <1/1,000); very rare (< 1/10,000) or unknown frequency.

Benign, malignant et unspecified neoplasms (and notably cysts and polyps)
Very rare: occurrence or worsening of hormonal or hormone-dependant tumours/neoplasms.

Metabolism and nutrition disorders
Unknown frequency: weight gain, hypertriglyceridemia, in some cases with pancreatitis.

Psychiatric disorders
Unknown frequency: anxiety, mood disorders (notably changing mood and irritability), nervousness, insomnia.

Nervous system disorders
Unknown frequency: transient paraesthesia and light-headedness.

Eye disorders
Uncommon: blurred visions, spots or flashes (scintillating scotoma), phosphenes, decreased visual acuity
Rare: cataract, optical neuritis,
Unknown frequency: recurring images, electroretinographic modifications, spasms of the retinal arterioles, detachment of the bottom part of the vitreous body

Heart disorders
Unknown frequency: tachycardia, palpitations

Vascular disorders
Unknown frequency: facial vasomotor disorders

Gastro-intestinal disorders
Unknown frequency: digestive intolerance, pancreatitis

Hepatobiliary disorders
Unknown frequency: BSP retention, elevated transaminases

Skin and subcutaneous tissue disorders

Very rare: alopecia, reversible with stopping the treatment
Unknown frequency: dermatitis, rash, allergic reactions; erythema multiform, bruising, angioneurotic oedema

Kidney and urinary tract disorders
Unknown frequency: pollakiuria

Reproductive system and breast disorders
Uncommon: with high doses: significant ovarian hyperstimulation, occurrence or increase in the risk to develop a cyst, occurrence or worsening of a pre-existing ovarian endometriosis.
Rare: at the recommended posology: ovarian hyperstimulation
Unknown frequency: breast tension, hypermenorrhoea, inter-menstrual bleedings, cervical mucus insufficiency, abdominal symptoms, cyclic pains of ovarian origin (Mittelschmerz), multiple pregnancies, notably simultaneous intra-uterine and extra-uterine pregnancies (including tubal and ovarian localisation), reduced endometrium thickness.

Investigations
Unknown frequency: increase in the desmosterol blood levels (in case of extended use).

Description of selected undesirable effects
Metabolism and nutrition disorders
Weight gain
Hypertriglyceridemia (frequency not known), in some cases with pancreatitis, has been observed in patients with pre-existing or a family history of hypertriglyceridemia and/or with dose and duration of treatment exceeding the label recommendation.

Eye disorders
Symptoms described usually as “blurring” or spots or flashed (scintillating scotoma) increase in incidence with increasing total dose.
These symptoms appear to be due to intensification and prolongation of after-images. After-images as such have also been reported. Symptoms often first appear or are accentuated with exposure to bright-light environment. Ophthalmologically definable scotoma, phosphenes and reduced visual acuity have been reported. Cataract and optical neuritis have rarely been reported. These visual disorders are usually reversible; nevertheless, persisting visual disorders have been reported, including after stopping the treatment. The visual disorders can be irreversible, especially in case of increase in posology or treatment duration (see section 4.4).

Vascular disorder
The facial vasomotor disorders, that remind flushing of menopause are rarely important, and disappear rapidly after stopping the treatment.

Hepatobiliary disorders
Bromsulfophtalein (BSP) retention of greater than 5 % was reported in 32 of 141 patients in whom it was measured.
Retention was usually minimal unless associated with prolonged continuous Clomiphene citrate 50 mg tablets administration or with apparently unrelated liver disease. In a later study in which patients were given 6 consecutive monthly courses of Clomiphene citrate 50 mg tablets (50 or 100 mg daily for 3 days) or matching placebo, BSP tests were done on 94 patients. Value in excess of 5 % retention were recorded in 11 patients, 6 of whom had taken drug and 5 placebo.

Reproductive system and breast disorders
Ovarian hyperstimulation
At recommended dosage, abnormal ovarian enlargement is infrequent although the usual cyclic variation in ovarian size may be exaggerated.

However, at higher doses, the potential risk

- Of significant ovarian hyperstimulation
- Of developing or increase a cyst
- Of developing or worsen a pre-existing ovarian endometriosis increases (see section 4.4 “Special warnings and precautions for use”).

This syndrome of ovarian hyperstimulation might exceptionally come with ascites. The majority of patients with this syndrome should be treated in a conservative way, because it regresses spontaneously.
The abdominal pains are often related to ovulation (Mittelschmerz), to pre-menstrual phenomena or to ovarian hyperstimulation.
Multiple pregnancies, and notably simultaneous intra-uterine and extra-uterine pregnancies, have been reported.
There is an increased chance of ectopic pregnancy (including tubal and ovarian localisation) in woman who conceive following Clomiphene citrate 50 mg tablets. See section 4.4 “Special warnings and precautions for use”.
Reduced endometrial thickness (frequency not known).

Investigation
If clomiphene citrate is administered during extended periods, it can interfere with cholesterol synthesis. Patients treated during extended periods might have an increased in blood desmosterol levels.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 reactions.

4.9 Overdose

Symptoms
Toxic effects of acute overdose of Clomiphene citrate 50 mg tablets consist in nausea, vomiting, flushes, blurred vision or flashes, scotoma, ovarian hypertrophy with abdominal or pelvic pains.
A severe ovarian hypertrophy can be accompanied by weight gain and ascites.
The maximum ovary volume increase can occur only several days after stopping the treatment with clomiphene citrate.

Treatment
Patients in reproductive age who absorbed a massive dose shall be followed during 2 to 3 weeks, monitored for ovarian hypertrophy (ultrasound monitoring and levels of oestrogens).

Acute intoxication with clomiphene citrate has never been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: sex hormone of the class of the selective oestrogen receptor modulator, ATC code: G03BG02

Mechanism of action
Clomiphene citrate if a non-steroidal agent belonging to the pharmacological group of selective oestrogen receptor modulators. Its main activity is a competitive antagonism of oestrogen.

The ovulatory response to cyclic Clomilen 50 mg tablets therapy is mediated through increased output of pituitary gonadotrophins, which in turn stimulates the maturation and endocrine activity of the ovarian follicle.

Pharmacodynamic effects
Clomiphene citrate binds the oestrogen receptor in the hypothalamus, maintaining the negative feedback loops. Compensatory measures modify the pulsatile secretion of GnRH by the hypothalamus to stimulate an increased secretion of gonadotrophins at the level of the pituitary gland, which command the activity at the level of the ovarian follicle. During a therapy with clomiphene citrate, LF and FSH levels increase to then decrease again after the end of the therapy, which lasts generally for 5 days. In case of success of the therapeutic course, one or more dominant maturing follicles appear, generating a flow of E2, triggering finally LF fluctuation of the mid-cycle and the ovulation.

5.2 Pharmacokinetic properties

Absorption
Orally administered ^{14}C labelled Clomiphene citrate was readily absorbed when administered to humans.

Elimination
Cumulative excretion of the ^{14}C label by way of urine and faeces averaged about 50 % of the oral dose after 5 days (with mean of urinary excretion of 7.8 % and mean of faecal excretion of 42.4 %).

Biotransformation
Clomiphene citrate undergoes an enterohepatic cycle.
Clomiphene citrate is a mixture of two geometrical isomers (cis(zuclomiphene) and trans(enclomiphene)).

5.3 Preclinical safety data

Carcinogenicity
Long term toxicity studies in animals have not been performed to evaluate the carcinogenic potential of Clomiphene citrate.

Teratogenicity
In spite of the absence of evidence that clomiphene citrate is teratogenic in man, congenital malformations have been observed after administrations of high doses of clomiphene citrate in pregnant rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica, lactose monohydrate, magnesium stearate, microcrystalline cellulose, maize starch, pregelatinised starch, purified water, sodium starch glycolate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in original container, do not store above 30 °C

6.5 Nature and contents of container

PVC-Aluminium blister of 10 tablets

6.6 Special precautions for disposal

Not applicable.

7. CATEGORY OF DISTRIBUTION

☐ Over-the counter medicine ☒ Prescription only medicines
List I

8. MARKETING AUTHORISATION HOLDER

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9. MANUFACTURER

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10. DATE OF REVISION OF THE TEXT

03/2019