SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CLOMID

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 320 mg tablet contains:
- Active ingredient: clomiphene citrate 50 mg.
- Excipient(s) with known effects: sucrose 67.50 mg, lactose 67.50 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CLOMID is indicated for the treatment of ovulatory failure in women desiring pregnancy, when a satisfactory ovulatory function has been demonstrated. Good levels of endogenous oestrogens (as estimated from vaginal smears, endometrial biopsy, assay of urinary oestrogens, or endometrial bleeding in response to progesterone) provide a favourable prognosis; however, a low level of oestrogens does not preclude successful outcome of therapy.

4.2 Posology and method of administration

Posology
Therapy may be started at any time in the patient who has not had recent menses. If progestin-induced bleeding is planned, or if spontaneous bleeding occurs immediately before planned 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. To improve the chances of pregnancy, an appropriate timing of sexual intercourses is essential.

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 can 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. A third course of therapy can be initiated as necessary under the same conditions. If ovulatory menses have not occurred after three courses, the diagnosis should be re-evaluated. Treatment beyond this is not recommended in the patient who does not exhibit evidence of ovulation. The majority of patients respond within three courses of therapy.
CLOMID should not be administered as monthly maintenance therapy in patients with recurrence of anovulatory menstrual cycles after suspension of treatment.

Method of administration
Oral use. The tablets should be taken with water.

4.3 Contraindications

CLOMID is contraindicated:
- in patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- during pregnancy (see section 4.6);
- in patients with hormone-dependent tumours;
- in patients with current liver disease or a documented history of liver dysfunction;
- in patients with menometrorrhagia;
- in patients with an ovarian cyst, with the exception of polycystic ovary, since further enlargement of the cyst may occur. Patients should be evaluated for the presence of an ovarian cyst prior to each course of treatment (see section 4.4).

4.4 Special warnings and precautions for use

Before starting CLOMID, it is essential to perform an accurate pelvic examination, which should be repeated before starting any subsequent course of therapy; it is also necessary to perform a clinical assessment of liver function.

CLOMID should not be given in the presence of an ovarian cyst or endometriosis involving the ovaries due to the risk of further enlargement of the cysts or of uterine fibroids.
However, in women with functional ovarian cysts, clomiphene citrate has shown to increase both ovulation and pregnancy rates without changing the size of cysts or causing any other complications.

In order to avoid accidental administration of CLOMID during the first period of pregnancy, basal temperature should be measured during all courses of therapy and ovulation should be monitored. A pregnancy test should be performed prior to each course of treatment.

Patients should be also advised of the potential risk to the foetus if clomiphene is used during pregnancy or if a pregnancy occurs during therapy (see section 4.6).

Special attention should be paid to patients of advanced reproductive age due to the higher incidence of anovulatory disorders or an increased tendency to develop endometrial cancer. Attention should also be paid to patients who have abnormal bleedings before the therapy; in particular, it is necessary to make sure that the presence of tumour lesions has been ruled out. In both categories of patients, a biopsy of the endometrium should be performed.

Some patients with polycystic ovary syndrome may have an exaggerated response to normal doses of CLOMID. The dosage and duration of the course of therapy should be reduced in such cases.

CLOMID is ineffective in patients with primary pituitary or primary ovarian failure. CLOMID cannot be expected to substitute for specific treatment of other causes of ovulatory failure, such as thyroid or adrenal disorders. For hyperprolactinaemia there is other preferred specific treatment. CLOMID is not first line treatment for low-weight related amenorrhoea, with infertility, and has no value if a high FSH blood level is observed following an early menopause.

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

Visual disturbances

Transitory visual disturbances, such as clouding, spotting, flickering, photophobia, double vision, scotoma, phosphenes and periphlebitis may occasionally occur during therapy with CLOMID. The frequency of such visual symptoms may increase with higher total doses or longer duration of therapy, although these disturbances are usually reversible; however, cases of visual disturbances that continued after therapy discontinuation have been reported. The visual disturbances may be irreversible especially with increased dosage or duration of therapy (see sections 4.7 and 4.8). These symptoms may render certain activities (such as driving a car or operating machinery) more hazardous than usual, particularly under conditions of variable lighting. If visual disturbances develop, treatment with CLOMID should be permanently discontinued.

Individual cases of central retinal vein occlusion (CRVO) and deep vein thrombosis have been reported in patients on clomiphene citrate.

Coagulation

Like many other hormone agents, clomiphene citrate may affect blood coagulation and reduce blood flow through the vessels.

Ovarian hyperstimulation

Although Ovarian Hyperstimulation Syndrome (OHSS) is an iatrogenic complication of ovarian stimulation almost exclusively associated with exogenous gonadotropin stimulation and only rarely observed after treatment with clomiphene citrate and spontaneous ovulation, patients should be advised to inform their doctor if they have abdominal or pelvic pain, weight increase, signs or feeling of abdominal distension. Maximal enlargement of the ovary induced by CLOMID, either physiological or abnormal, may not occur until several days after discontinuation of the recommended dose of CLOMID. The patient who complains of pelvic pain following administration of CLOMID should be carefully examined. If ovarian enlargement occurs, CLOMID should not be given until the ovaries have returned to pre-treatment size, and the dosage and/or duration of the next course of treatment should be reduced. The experience has shown that ovarian enlargement and cyst formation occurring concomitantly with CLOMID therapy regress spontaneously within a few days or weeks after discontinuing the treatment.

In order to minimize the risk of abnormal ovarian enlargement, the lowest CLOMID dose consistent with expectation of good results should be used.

Ovarian cancer

Some reports suggest that the risk of ovarian cancer is increased in women exposed to a heterogeneous group of ovulation-inducing drugs, including clomiphene citrate, although this risk seems to be higher in women who underwent 12 courses of therapy.

Multiple pregnancies

Clinical experience has shown an increased rate of multiple pregnancies (see section 4.6).

Extrauterine pregnancy

There is an increased chance of ectopic pregnancy (including tubal and ovarian sites) in women who conceive following CLOMID therapy. Multiple pregnancies, including simultaneous intrauterine and extrauterine pregnancies, have been reported (see section 4.8).

Pregnancy wastage and birth anomalies
Available data from epidemiological studies do not show any apparent cause-effect relationship between pre-conception exposure to clomiphene citrate and an increased risk of foetal defects or any particular birth anomaly (see section 4.6). Among the birth anomalies spontaneously reported in the published literature as individual cases, the proportion of neural tube defects has been high among pregnancies associated with ovulation induced by clomiphene citrate, but this has not been supported by data from population-based studies.
The physician should explain so that the patient understands the assumed risk of any pregnancy whether the ovulation was induced with the aid of CLOMID or occurred naturally.
The patient should be informed of the greater pregnancy risks associated with certain characteristics or conditions of any pregnant woman: e.g. age of female and male partner, history of spontaneous abortions, Rh genotype, abnormal menstrual history, infertility history (regardless of cause), organic heart disease, diabetes, exposure to infectious agents such as rubella, familial history of birth anomaly, and other risk factors that may be pertinent to the patient for whom CLOMID is being considered. Based upon the evaluation of the patient, genetic counselling may be indicated.
A possible elevation of risk of trisomies and Down syndrome has been suggested. However, as yet, the reported observations are too few to confirm or not confirm the presence of an increased risk that would justify amniocentesis other than for the usual indications because of age and family history.

Important information on some excipients
This medicinal product contains:
- sucrose: patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase deficiency should not take this medicinal product;
- lactose: patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

For those involved in sporting activities: use of this drug without therapeutic need is considered doping behaviour and may give a positive result in anti-doping tests.

4.5 Interaction with other medicinal products and other forms of interaction

There are no known clinically relevant interactions with other medicinal products.

4.6 Fertility, pregnancy and lactation

Pregnancy
This drug should not be used during pregnancy.
Available data from epidemiological studies do not show any apparent cause-effect relationship between pre-conception exposure to clomiphene citrate and an increased risk of foetal defects or any particular birth anomaly. However, limited cases of congenital malformations were observed in women treated with clomiphene. Malformations were observed in rats and rabbits that were administered CLOMID during pregnancy (see section 5.3).
Multiple pregnancies: Clinical experience has shown an increased incidence of multiple pregnancies when conception occurred during a course of therapy with CLOMID. Multiple follicular development is a relatively common event during treatment with clomiphene citrate; the risk of multiple pregnancy increased by approximately 8% overall for anovulatory women and by 2.6-7.4% in women treated for unexplained infertility. Before starting the treatment, both the patient and her partner should be informed of such risk and of the potential complications associated with multiple pregnancies.
Malformations in pregnancy: The overall incidence of malformations in pregnancy associated with CLOMID

use is within the limits reported in the literature for the general population. A possible increase in the risk for trisomies and Down syndrome has been suggested, but at present there are not sufficient observations to confirm or deny this hypothesis and to justify routine amniocentesis in the absence of other factors such as advanced age or a family history. A case of persistent hyperplastic primary vitreous (PHPV) was reported after maternal exposure to clomiphene citrate 100 mg daily for about three weeks of gestation. The potential ophthalmic adverse effects of clomiphene on the foetus have been investigated in rats and monkeys (see section 5.3). Recent studies have described comparable miscarriage rates as compared to those observed in spontaneous pregnancies (10%-23%).

Lactation

No studies have been conducted on the efficacy and safety of CLOMID during lactation, and it is not known whether CLOMID is excreted in maternal milk. Since many drugs are excreted in maternal milk, CLOMID should not be used in breastfeeding women. In some patients, CLOMID may reduce maternal milk production and the period of breastfeeding.

4.7 Effects on ability to drive and use machines

Patients should be warned that CLOMID may cause visual disturbances (see sections 4.4 and 4.8), which could affect their ability to drive or use machinery.

4.8 Undesirable effects

Some of the following undesirable effects may occur during therapy with CLOMID, as also reported in the post-marketing experience.
At the recommended doses, the undesirable effects are not remarkable and rarely affect the treatment.
The frequency and severity of the undesirable effects listed below depend on the dosage and duration of treatment.

Adverse reactions (Table 1) are listed by frequency, the most frequent first, using the following convention: common (≥ 1/100, <1/10), uncommon (≥ 1/1,000, <1/100); rare (≥ 1/10,000 to <1/1,000), very rare (<1/10,000), not known: frequency cannot be estimated from the available data.

The following undesirable effects include those reported with both short- and long-term use.

PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	
Very common	Pre-eclampsia, pregnancy complications, spontaneous abortion.
Common	Foetal death, ectopic pregnancy, incompetent cervix, premature labour, HELLP syndrome, gestational diabetes, placenta praevia, premature-preterm rupture of membranes, premature detachment of the placenta, postpartum haemorrhage, multiple pregnancy.
METABOLISM AND NUTRITION DISORDERS	
Common	Appetite decreased
Not known	Hypertriglyceridemia
Uncommon	Abnormal weight gain
PSYCHIATRIC DISORDERS	

Very common	Mood swings
Common	Postpartum depression
Uncommon	Insomnia, tension
Not known	Psychotic reaction NOS, paranoid psychosis, anxiety, depression, irritability, nervousness.
INVESTIGATIONS	
Very common	Bromsulphalein test results abnormal[1]
INFECTIONS AND INFESTATIONS	
Very common	Respiratory tract infection
Uncommon	Bronchitis
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	
Not known	Congenital cataract
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Very common	Back pain
NERVOUS SYSTEM DISORDERS	
Very common	Dizziness
Common	Headache, dysgeusia
Uncommon	Vertigo
Not known	Seizures, paraesthesia, pre-syncope, syncope, cerebrovascular accident, cerebral thrombosis, neurologic impairment, disorientation, speech disturbance
SKIN AND SUBCUTANEOUS TISSUE DISORDER	
Uncommon	Urticaria, allergic dermatitis, erythema multiforme, ecchymosis, angioedema
Not known	Alopecia[2], skin rash
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	
Very common	Breast tenderness, breast pain, dysmenorrhea, ovarian enlargement
Common	Breast discomfort, uterine bleeding, adnexa uteri pain, anovulatory bleeding
Uncommon	Haemorrhagic ovarian cyst, menorrhagia
Rare	Ovarian hyperstimulation syndrome[3], adnexal torsion[4]
Not known	Exacerbation of pre-existing endometriosis, reduced endometrial thickness
EYE DISORDERS	
Common	Visual impairment, scotoma, blurred vision, photophobia, double vision, photopsia.
Rare	Cataract
Not known	Retinal vein occlusion, optic neuritis
CARDIAC DISORDERS	
Not known	Tachycardia, palpitations
GASTROINTESTINAL DISORDERS	
Very common	Distension of the abdomen[5], flatulence
Common	Abdominal discomfort[5], abdominal pain[5], nausea[5], vomiting[5], diarrhoea[5], constipation, dyspepsia,

	oropharyngeal pain
Rare	Constipation
Not known	Pancreatitis
HEPATOBILIARY DISORDERS	
Not known	Increased transaminases
RENAL AND URINARY DISORDERS	
Uncommon	Polyuria, pollakiuria
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Very common	Fatigue
VASCULAR DISORDERS	
Very common	Hot flashes
Common	Periphlebitis[6]
Not known	Deep vein thrombosis
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL. CYSTS AND POLYPS)	
Not known	Endocrine neoplasm, ovarian cancer, malignant melanoma

Bromsulphalein test results abnormal[1]
Bromsulphalein retention of greater than 5% was reported in 32 of 141 patients in whom it was measured. Other liver function tests were usually normal. In a later study in which patients were given 6 consecutive monthly courses of CLOMID (50 and 100 mg daily for 3 days) or matching placebo, BSF tests were performed in 94 patients. Retention values in excess of 5% were recorded in 11 patients, 6 of whom were treated with CLOMID and 5 with placebo. One patient developed jaundice on treatment day 19 (50 mg daily); liver biopsy showed bile stasis without evidence of hepatitis.

Alopecia[2]
Modest, reversible hair loss was reported in a very limited number of patients, almost invariably occurring during prolonged courses of therapy.

Ovarian hyperstimulation syndrome[3]
Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of ovarian stimulation almost exclusively associated with exogenous gonadotropin stimulation, and is only rarely observed following treatment with clomiphene citrate. Due to fragility of enlarged ovaries in severe cases, abdominal and pelvic examination should be performed very cautiously.
Mild OHSS is relatively common. The first warning signs of OHSS are abdominal pain and distension, nausea, vomiting, diarrhoea and weight gain. Transient abnormalities of liver function and of tests indicative of liver dysfunction, which may be accompanied by morphological changes of liver biopsy, were reported in association with OHSS.
Severe OHSS is a rare occurrence; signs and symptoms include gross ovarian enlargement, progressive weight gain, severe abdominal pain, nausea and vomiting, hypovolaemia, ascites, oliguria, dyspnoea, pleural effusion. Other signs or symptoms include pericardial effusion, anasarca, hydrothorax, acute abdomen, hypotension, renal failure, pulmonary oedema, intraperitoneal ovarian haemorrhage, deep vein thrombosis, torsion of the ovary and respiratory distress.

Adnexal torsion[4]
Ovarian stimulation is regarded as a cause of adnexal torsion as a result of the increased volume and weight of the adnexa. The majority of reported cases were associated with gonadotropin therapy, and only a few cases were associated with treatment with clomiphene citrate. There is no sufficient evidence of the role of

gonadotropins and clomiphene citrate in the development of ovarian torsion.
Although adnexal torsion is a rare event, patients should be informed of the possible risk and the drug should be taken only when indicated.

-[5]: this undesirable effect may be the sign or symptom of mild ovarian hyperstimulation syndrome.

Ocular periphlebitis[6]

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 via the national reporting system at "www.aifa.gov.it/content/segnalazioni-reazioni-avverse ".

4.9 Overdose

There have been no reports of acute intoxication.
Possible signs and symptoms of chronic intoxication include nausea and/or vomiting, vasomotor flashes, visual blurring and scotomata, abdominal and/or pelvic pain, weight gain and ascites.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Synthetic ovulation stimulants.
ATC code: G03GB

The active ingredient of CLOMID is clomiphene citrate, a non-steroidal synthetic oestrogen agent for oral use, which stimulates ovulation in women with anovulatory cycles and cycles with insufficient luteal phase.
Clomiphene is a racemic mixture of two isomers, cis-clomiphene and trans-clomiphene, and was isolated during research on the analogs and derivatives of chlorotrianisene, which were identified for use in the treatment of oestrogen-dependent pathologies and for stimulating ovulation.
Several pharmaco-biological studies in animals reported that clomiphene acts as a weak oestrogen and as an anti-oestrogen.
The drug has demonstrated to be able to block the estrous cycle in normal female rats, to inhibit the uterotrophic effect of oestrogens in normal and castrated female rats, to obstruct the antiovulatory action of natural oestrogens and to inhibit the fixation of natural oestrogens in the specific uterine, breast, and possibly hypothalamic receptors. The anti-oestrogen activity of clomiphene seems to be associated with a central action on the hypothalamus and the pituitary gland. As a result of its inhibitory activity on hypothalamic oestrogen receptors and the subsequent increased release of pituitary gonadotropins (particularly FSH, which specifically acts on the mechanisms of follicle maturation in the ovaries), clomiphene mimics the physiological premenstrual increase in follicle-stimulating gonadotropin in a way that this, in turn, stimulates follicle maturation, which occurs normally at the beginning of each menstrual period. Therefore, clomiphene creates the required conditions for subsequent ovulation which is induced by the positive feedback triggered by the high oestrogen levels produced in the pituitary gland.
Clomiphene is devoid of either androgenic or antiandrogenic activity; it has no effect on the pituitary-adrenal and the pituitary-thyroid axes; it does not alter baseline ultrasound or has any influence on normal blood pressure or respiratory values even when used at doses largely exceeding those clinically recommended. The drug can increase basal body temperature, but does not modify or sometimes enhance the normal appearance

of vaginal cytologic changes typically occurring during progestin activity.

5.2 Pharmacokinetic properties

Clomiphene is rapidly absorbed following oral administration and is mainly excreted in the faeces. In studies conducted with the labelled compound, plasma half-life was estimated to be 24 hours following intraperitoneal administration in rats and 48 hours following intravenous administration in monkeys.
Enterohepatic circulation was demonstrated in both rats and monkeys. After 6 days of oral treatment in the latter, when about 90% of the administered dose had been eliminated in the faeces and, to a lesser extent, in the urine, the maximum residual concentration of ^{14}C was found in the liver and in the bile, while lower amounts were found in the adrenal glands, ocular tissue, pancreas, pituitary gland and ovaries. By intravenous route, high levels of ^{14}C were found in the ocular tissue of rats, rabbits and monkeys. The distribution pattern of the two isomers in the various tissues and organs was very similar to that of clomiphene containing the mixture of cis- and trans-clomiphene, as the highest concentrations were found in the liver, adrenal gland, eye, ovary and pituitary gland. A higher affinity of trans-clomiphene for adipose tissue was found, which may explain the lower and two-phase excretion of the isomer.
Studies in humans with ^{14}C-labelled drug also showed that absorption is rapid following oral administration, and that elimination mainly occurs in the faeces, by 51% within the first 5 days, while the remaining compound and its metabolites are slowly eliminated in the subsequent 5 weeks, much likely from an enterohepatic recirculation pool. In patients treated with 100 mg of clomiphene, concentrations of the two isomers (14.6 ng/mL of cis-clomiphene and 30.4 ng/mL of trans-clomiphene) were found in the plasma after 3 hours from administration; at a dose of 150 mg, concentrations were 42.3 and 80.9 ng/mL, respectively.
Clomiphene is metabolized by the microsomal enzymes of experimental animals to form desethylclomiphene, 4-hydroxyclomiphene and clomiphene-N-oxide.

5.3 Preclinical safety data

Acute toxicity
Acute toxicity from clomiphene is very low after either oral or parenteral administration. In studies conducted in various laboratories, DL50 values in mice were 1700-1919 mg/kg for oral administration, 350-390 mg/kg for intraperitoneal administration, and 86 mg/kg for intravenous administration. In rats, acute toxicity levels were even lower, with DL50 values of 5504-5750 mg/kg for oral administration and 449-530 mg/kg for intraperitoneal administration. This data demonstrates that DL50 values obtained from studies in mice and rats after oral administration are respectively about 1919 e 5750 times higher than the clinically recommended doses of the drug. The results from comparative tests performed after intraperitoneal and oral administration also demonstrated that there were no substantial differences between the values of DL50 for clomiphene and those reported for its two isomers cis-clomiphene and trans-clomiphene.

Chronic toxicity
The results of chronic toxicity tests for repeated treatments by oral route for 53 weeks in rats and dogs (doses of 5, 15, 40 mg/kg/day) and for 180 days in minipigs (5, 40 mg/kg/day) demonstrated that clomiphene, only when administered at higher than therapeutic doses, can cause undesirable effects that are attributable to the peculiar pharmacodynamic activity of the compound. Body weight changes and the appearance of alopecia can be associated with the drug's oestrogen activity, since it is known that oestrogens reduce body weight and cause hair growth changes. Cataract in the rat can be a consequence of clomiphene activity on cholesterol metabolism, resulting in an increase of desmosterol.

Fertility and teratogenicity
The toxic effects on both male and female reproductive systems may be the result of the pharmacological

activity of clomiphene, particularly of its peculiar mechanism of action in the central nervous system. Administration of clomiphene in mice, rats and rabbits during reproductive studies, usually at higher than clinically recommended doses, demonstrated adverse effects on fertility, gestation, and foetal and neonatal development. These changes, which are attributable to the oestrogen activity of clomiphene, seem to be influenced by the animal species used in the experiment, given that teratogenic effects were not observed in the monkeys even at doses remarkably higher than those used in women.
Malformations were observed in rats and rabbits who had been administered CLOMID in pregnancy; therefore, the drug should not be given during pregnancy.
Cataract was observed in rat foetuses but not in monkey foetuses: the formation of congenital cataract in rats was dose-dependent and was not found in rats exposed to 2 mg/kg of clomiphene citrate, while it was found in 3 of 128 foetuses exposed to 10 mg/kg and in 61% of those exposed to 50 mg/kg and 200 mg/kg. The only other ocular abnormalities observed were colobomas in those exposed to 50-200 mg/kg.

Genotoxicity
Mutagenesis studies conducted in vitro using Ames test and DNA repair tests, and in vivo studies to evaluate chromosomal aberrations by micronucleus assay provided negative results, as they did not demonstrate any mutagenic effects induced by clomiphene.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, lactose, soluble maize starch, magnesium stearate, maize starch, yellow iron oxide.

6.2 Incompatibilities

No specific incompatibilities have been noted.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

There are not special precautions for storage.

6.5 Nature and contents of container

Carton containing 10 x 50 mg tablets.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BRUNO FARMACEUTICI S.p.A. - Via delle Ande, 15 - 00144 ROMA

8. MARKETING AUTHORISATION NUMBER(S)

No. 020773026

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

June 2010

10. DATE OF REVISION OF THE TEXT

July 2021