Dostinex®

Cabergoline

0.5 mg tablets

Reference Market: Italy

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

DOSTINEX 0.5 mg tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
**active substance**: cabergoline 0.5 mg
excipient with a known effect: lactose
For the full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Tablets.

Dostinex 0.5 mg tablets are flat, oblong, white tablets, embossed with "PU" and a score line on one side and with "700" with a broken score line above and below the middle "0" on the other.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

**Inhibition/suppression of physiological lactation:**
DOSTINEX is indicated for the prevention of the physiological lactation immediately after delivery and for the suppression of ongoing lactation:

1) After delivery, when the mother decides not to breast–feed the child or when breast-feeding is contraindicated for mother- or child-related medical reasons.

2) After stillbirth or abortion.

DOSTINEX prevents the physiological lactation by inhibiting the secretion of prolactin.
Clinical trials showed that the administration of a single dose of 1 mg of DOSTINEX the first day post-partum is effective in inhibiting milk secretion and reducing breast congestion and pain in 70-90% of women. Only a minimum portion of patients reported recurrent mammary symptomatology of generally low severity at the third week after delivery.
About 85% of the women, who, overall, received 1 mg of cabergoline divided into four doses within two days, achieved the suppression of milk secretion and an improvement of the symptoms related to breast congestion and pain following lactogenesis.
The recurrence of breast symptoms after 10 days is rare.

**Treatment of hyperprolactinaemic disorders**
DOSTINEX is indicated for the treatment of dysfunctions related to hyperprolactinaemia, such as amenorrhoea, oligomenorrhoea, anovulation and galactorrhoea. DOSTINEX is indicated in patients with prolactin-secreting pituitary adenoma (micro- and macroprolactinoma), idiopathic hyperprolactinaemia or empty sella syndrome associated with hyperprolactinaemia, which represent key pathologies in the above-mentioned clinical conditions.
The weekly administration of 1-2 mg of DOSTINEX as chronic therapy was effective in normalizing serum prolactin concentrations in about 84% of hyperprolactinaemic patients. The resumption of regular menstrual cycles was observed in 83% of women who were previously amenorrhoeic. Based on the monitored progesterone levels, measured during the

luteal phase, the ovulation became stable in 89% of treated women, galactorrhoea disappeared in 90% of cases treated. In 50-90% of both female and male patients with micro- or macroprolactinoma, a decrease in the tumoral mass was observed.

## 4.2 Posology and method of administration

DOSTINEX should be administered by oral route.
Since, during clinical studies, DOSTINEX was mainly administered at meals and as the tolerability of this drug class is usually increased by food, DOSTINEX is recommended to be taken preferably with food.

**Inhibition/suppression of physiological lactation:**
For the inhibition of lactation, DOSTINEX should be administered the first day after delivery. The recommended dose is 1 mg (two tablets of 0.5 mg) administered in a single dose.
For the suppression of lactation, the recommended dose is 0.25 mg (half a tablet of 0.5 mg) every 12 hours for two days (total dose 1 mg).

**Treatment of hyperprolactinaemic disorders**
The dose of DOSTINEX initially recommended is of 0.5 mg/week administered in one or two intakes (half a tablet of 0.5 mg/week, for example on Monday and Thursday). The weekly dose should be gradually increased, preferably by adding 0.5 mg/week at monthly intervals until the optimal therapeutic response is achieved. The therapeutic dose is generally 1 mg/week, but it could vary from 0.25 mg to 2 mg/week. In hyperprolactinaemic patients, doses of DOSTINEX up to 4.5 mg/week are used.
The weekly dose can be administered once or divided into two or more intakes per week depending on the tolerability level of the patient.
When doses over 1 mg/week are indicated, it is recommended to distribute the weekly dose into multiple administrations, as the tolerability of these doses taken once weekly was assessed only in few patients.
Patients should be monitored during the dosing adjustment phase, to establish the lowest dose that produces the therapeutic response. The check of serum prolactin levels is recommended at monthly intervals, as a normalization of serum prolactin level is usually observed within 2-4 weeks, once the effective therapeutic regimen is achieved.
At the discontinuation of DOSTINEX, a recurrence of hyperprolactinaemia is normally observed. However, a persistent suppression of prolactin levels is observed for various months in some patients. In most women, ovulatory cycles persist at least for 6 months after discontinuation of DOSTINEX.

The maximum dose is 3 mg/day.

**Use in children**
Safety and efficacy of DOSTINEX were not established in subjects younger than 16 years.

**Use in elderly patients**
As a result of the indications according to which the use of DOSTINEX is recommended, experience in elderly patients is very limited. Available data does not show any particular risk.

## 4.3 Contraindications

Hypersensitivity to the active substance, to any of the excipients listed in section 6.1 or any ergot alkaloid.
History of pulmonary, pericardial or retroperitoneal fibrosis.
For long-term treatment: evidence of cardiac valvulopathy as determined by pre-treatment echocardiogram (See section 4.4 - Special warnings and precautions for use - Fibrosis and cardiac valvulopathy and possibly related clinical phenomena).

## 4.4 Special warnings and precautions for use

General:

As with other ergot derivatives, cabergoline should be given with caution to patients with severe cardiovascular disease, Raynaud's syndrome, peptic ulcer or gastrointestinal bleeding, or with a history of serious, particularly psychotic, mental disorders.

Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Serious adverse events such as hypertension, myocardial infarction, seizures, stroke or psychiatric disorders have been reported in women treated with cabergoline after childbirth to inhibit lactation. In some patients, the development of seizures or stroke was preceded by severe headache and/or transient vision disorders. Arterial pressure must be closely monitored during treatment. If hypertension, suggestive chest pain, severe, progressive or persistent headache (with or without vision disorders) or evidence of central nervous system toxicity develop, treatment with cabergoline must be discontinued and the patient examined immediately.

Hepatic insufficiency:

Lower doses should be considered in patients with severe hepatic insufficiency who receive prolonged treatment with DOSTINEX. Compared to healthy volunteers and those with milder forms of hepatic insufficiency, an increase in AUC has been seen in patients with severe hepatic insufficiency (Child-Pugh Class C) who received a single 1 mg dose.

Postural hypotension:

Postural hypotension can occur following administration of cabergoline. Care should be exercised when administering cabergoline concomitantly with other drugs known to lower blood pressure.

Fibrosis and cardiac valvulopathy and possibly related clinical phenomena:

Fibrotic disorders and serous membrane inflammations such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy involving one or more valves (aortic, mitral and tricuspid) or retroperitoneal fibrosis have occurred after prolonged use of ergot derivatives with agonist activity at the serotoninergic $5HT_{2B}$ receptors, such as cabergoline. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of cabergoline.

Erythrocyte sedimentation rate (ESR) has been found to be abnormally increased in association with pleural effusion/fibrosis. Chest x-ray examination is recommended in cases of unexplained ESR increases to abnormal values.

Valvulopathy has been associated with cumulative doses, therefore, patients should be treated with the lowest effective dose. At each visit, the benefit/risk balance of the treatment for the patient should be reassessed to determine the suitability of continued treatment with cabergoline.

Before initiating long-term treatment:

All patients must undergo a cardiovascular evaluation, including echocardiogram to assess the potential presence of an asymptomatic valvular disease.

It is also appropriate to perform an analysis of the erythrocyte sedimentation rate (ESR) or other inflammatory markers, a lung function test/chest X-ray and a renal function test prior to initiation of therapy.

In patients with valvular regurgitation, it is not known whether cabergoline treatment might worsen the underlying disease. If valvular fibrosis is detected, the patient should not be treated with cabergoline (see section 4.3 - Contraindications).

During long-term treatment:
Fibrotic disorders can have an insidious onset and patients should be regularly monitored to avoid the risk of possible manifestations of progressive fibrosis.

Therefore, during treatment, attention should be paid to the signs and symptoms of:

- Pleuro-pulmonary diseases such as dyspnoea, shortness of breath, persistent cough or chest pain.
- Renal insufficiency or ureteral/abdominal vascular obstruction that may occur with pain in the loin/flank and lower limb oedema, as well as any possible abdominal masses or tenderness that may indicate retroperitoneal fibrosis.
- Cardiac failure; since cases of valvular and pericardial fibrosis have often manifested as cardiac failure. Therefore, valvular fibrosis (and constrictive pericarditis) should be excluded if such symptoms occur.

Clinical diagnostic monitoring for the development of fibrotic disorders, as appropriate, is recommended. Following treatment initiation, the first echocardiogram must be performed within 3-6 months, thereafter, the echocardiographic monitoring should be determined by appropriate individual clinical assessment with particular emphasis on the above-mentioned signs and symptoms, but must always be performed at least every 6 to 12 months.
Cabergoline should be discontinued if an echocardiogram reveals new or worsened valvular regurgitation, valvular restriction or valve leaflet thickening (see section 4.3 - Contraindications).

The need for other clinical monitoring (e.g. physical examination including careful cardiac auscultation, X-ray, CT scan) should be determined on an individual basis.
Additional analyses such as erythrocyte sedimentation rate (ESR), and serum creatinine measurements should be performed, if necessary, to support a diagnosis of fibrotic disorder.

Somnolence/sudden sleep onset:
Cabergoline has been associated with somnolence. Dopamine agonists can be associated with sudden sleep onset episodes in patients with Parkinson's disease. A reduction of dosage or termination of therapy may be considered (see section 4.7 - Effects on ability to drive and use machines).

Inhibition/suppression of physiological lactation:
As with other ergot derivatives, cabergoline should not be administered to women with pregnancy-induced hypertension, for example, preeclampsia or post-partum hypertension, unless the potential benefit is judged to outweigh the possible risk.
A single dose of 0.25 mg of cabergoline should not be exceeded in nursing women treated for suppression of lactation to avoid the risk of postural hypotension. (See section 4.2 - Inhibition/suppression of physiological lactation and subsection above - Postural hypotension).

Treatment of disorders due to hyperprolactinaemia:
Because hyperprolactinaemia accompanied with amenorrhoea/galactorrhoea and infertility may be associated with pituitary tumours, a complete evaluation of the pituitary gland function is indicated before treatment with cabergoline is initiated.
Cabergoline restores ovulation and fertility in women with hyperprolactinaemic hypogonadism.
Before treatment with cabergoline is initiated, pregnancy should be excluded. Because clinical experience is still limited and the medicinal product has a long half-life, as a precautionary

measure it is recommended that once regular ovulatory cycles have been achieved, women seeking pregnancy discontinue cabergoline one month before intended conception.

Because pregnancy might occur prior to resumption of menstruation, a pregnancy test is recommended at least every 4 weeks during the amenorrhoeic period and, once menstruation resumes, every time a menstrual cycle is delayed by more than 3 days. Women who wish to avoid pregnancy should be advised to use mechanical contraception during treatment with cabergoline and after discontinuation of cabergoline until anovulation.

As a precautionary measure, women who become pregnant during treatment should be monitored to detect any signs of pituitary enlargement, since expansion of pre-existing pituitary tumours may occur during gestation.

Psychiatric disorders
Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists, including DOSTINEX. A reduction in the dose/gradual withdrawal and final discontinuation should be considered if such symptoms develop.

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

No information is available on interactions between cabergoline and other ergot alkaloids; therefore, the concomitant use of these medicinal products during long-term treatment with cabergoline is not recommended.

Since cabergoline exerts its therapeutic effect by direct stimulation of dopamine receptors, it should not be concurrently administered with drugs that have dopamine-antagonist activity (such as phenothiazines, butyrophenones, thioxanthenes, metoclopramide), since these might reduce the inhibitory effects of cabergoline on prolactin secretion.
As with other ergot derivatives, cabergoline should not be used with macrolide antibiotics (e.g. erythromycin) due to possibility of an increase in cabergoline bioavailability.

## 4.6 Pregnancy and lactation

Pregnancy

No adequate and well-controlled studies concerning the use of cabergoline in pregnant women have been conducted. Studies conducted on animals have not shown any teratogenic effects, but a reduction in fertility and embryotoxicity have been observed contemporaneously with the pharmacodynamic activity (see section 5.3).

Following a twelve-year observational study on the effects of cabergoline therapy on pregnancy, information is currently available on 256 pregnancies. Seventeen of these 256 pregnancies (6.6%) resulted in major congenital malformations or abortion. Information is available on 23/258 infants who had a total of 27 neonatal abnormalities, both major and minor. Musculoskeletal malformations were the most common neonatal abnormalities (10), followed by cardio-pulmonary abnormalities (5). There is no information on perinatal disorders or long-term development of infants exposed to intra-uterine cabergoline. Based on recent published literature, the prevalence of major congenital malformations in the general population has been reported to be 6.9% or greater. Rates of congenital abnormality vary

between different populations. It is not possible to accurately determine if there is an increased risk, as no control group was included.
Before DOSTINEX administration, pregnancy should be excluded.

Cabergoline should be used in pregnancy only if clearly indicated and after careful assessment of the benefit/risk balance (see section 4.4 "Special warnings and precautions for use" - Treatment of disorders due to hyperprolactinaemia).

In consideration of the long half-life of the drug (79-115 hours) and the limited data available on intrauterine exposure, women who are planning a pregnancy should, once they achieve regular ovulatory cycles, interrupt cabergoline a month before attempting to conceive. This will prevent possible foetal exposure to the drug and will not interfere with the possibility of conception since ovulatory cycles persist in some cases for 6 months after drug withdrawal. If conception occurs during therapy, treatment should be discontinued as soon as pregnancy is confirmed to limit foetal exposure to the drug.

Breast-feeding
In rats, cabergoline and/or its metabolites are excreted in milk. No information is available on the excretion in breast milk in humans; however, mothers should be advised not to breast-feed in case of failed lactation inhibition/suppression by cabergoline. Since it inhibits lactation, cabergoline should not be administered to mothers with hyperprolactinaemic disorders who wish to breast-feed their infants.

## 4.7 Effects on ability to drive and use machines

During the initial phase of treatment, patients should be careful when performing actions that require a fast and accurate reaction.
Patients being treated with cabergoline and experiencing episodes of somnolence and/or sudden sleep onset should be informed to refrain from driving or engaging in activities where impaired attention may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also section 4.4 - Special warnings and precautions for use – Somnolence/sudden sleep onset).

## 4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with DOSTINEX with the following frequencies: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <11/100), rare (≥1/10,000, <11/1,000), very rare (<11/10,000), not known (cannot be estimated from the available data).

| MedDRA System Organ Class | Frequency | Undesirable effects |
|---|---|---|
| Cardiac disorders | Very common | Valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion) |
| | Uncommon | Palpitations |
| | Not known | Angina pectoris |
| Respiratory, thoracic and mediastinal disorders | Uncommon | Dyspnoea, pleural effusion, fibrosis (including pulmonary fibrosis), epistaxis |
| | Very rare | Pleural fibrosis |
| | Not known | Respiratory disorders, respiratory failure, |

| | | |
|---|---|---|
| | | pleuritis, chest pain |
| Immune system disorders | Uncommon | Hypersensitivity reactions |
| Nervous system disorders | Very common | Headache*, dizziness/vertigo |
| | Common | Somnolence |
| | Uncommon | Transient hemianopsia, syncope, paraesthesia |
| | Not known | Sudden sleep onset, tremor |
| Eye disorders | Not known | Impaired vision |
| Psychiatric disorders | Common | Depression |
| | Uncommon | Increased libido |
| | Not known | Aggressiveness, delusion, hypersexuality, pathological gambling, psychotic disorder, hallucinations |
| Vascular disorders | Common | Dostinex generally exerts a hypotensive effect in patients on long-term treatment; orthostatic hypotension, hot flushes** |
| | Uncommon | Digital vasospasm, fainting |
| Gastrointestinal disorders | Very common | Nausea*, dyspepsia, gastritis, abdominal pain* |
| | Common | Constipation, vomiting** |
| | Rare | Epigastric pain |
| General disorders and administration site conditions | Very common | Asthenia***, fatigue |
| | Uncommon | Oedema, peripheral oedema |
| Hepatobiliary disorders | Not known | Altered hepatic function |
| Skin and subcutaneous tissue disorders | Uncommon | Rash, alopecia |
| Musculoskeletal and connective tissue disorders | Uncommon | Leg cramps |
| Reproductive system and breast disorders | Common | Breast pain |
| Investigations | Common | Asymptomatic lowering of blood pressure (systolic pressure ≥20 mmHg and diastolic pressure ≥10 mmHg) |
| | Uncommon | A decrease in haemoglobin values has been observed in amenorrhoeic women during the first few months after the resumption of menstruation |
| | Not known | Blood creatinine phosphokinase increased, liver function test abnormal |

* Very common in patients treated for hyperprolactinaemic disorders; common in patients treated for inhibition/suppression of lactation
** Common in patients treated for hyperprolactinaemic disorders; uncommon in patients treated for inhibition/suppression of lactation
*** Very common in patients treated for hyperprolactinaemic disorders; uncommon in patients treated for inhibition/suppression of lactation

**Impulse control disorders**
Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists, including DOSTINEX (see section 4.4 “Special warnings and precautions for use”).

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after marketing 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 according to their local country requirements.
https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse

## 4.9 Overdose

Symptoms of overdose would likely be those caused by over-stimulation of dopamine receptors, such as nausea, vomiting, gastric disorders, postural hypotension, confusion/psychosis or hallucinations.
General supportive measures should be taken to remove any unabsorbed drug and maintain blood pressure, if necessary.
In addition, the administration of dopamine antagonist drugs may be advisable.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Prolactine inhibitors
ATC code: G02CB03

DOSTINEX is an ergot derivative with dopaminergic action and a potent and long-lasting effect of inhibition of prolactin levels.
Via the direct stimulation of $D_2$ dopaminergic receptors present on the pituitary lactotropic cells, it inhibits the secretion of prolactin. In rats, the compound reduces the secretion of prolactin at oral doses of 3-25 mcg/kg, and *in-vitro* at the concentration of 45 pg/ml. Moreover, DOSTINEX exerts a central dopaminergic effect via the stimulation of the $D_2$ receptor at oral doses higher than those effective in lowering the serum prolactin levels.
The long-lasting effect of the drug on the reduction of prolactin levels is probably due to the long persistence in the target organ, as suggested by the slow clearance of total pituitary radioactivity, after single oral administration of the labelled product to rats ($t_{1/2}$ of about 60 hours).

The pharmacodynamic effects of DOSTINEX were studied in healthy volunteers, puerperae and hyperprolactinaemic patients. After a single oral dose of DOSTINEX (0.3-1.5 mg), a significant reduction of the serum prolactin levels is observed in all the study populations. The effect is fast (it starts within 3 hours after the administration) and persistent (up to 7-28 days in healthy volunteers and hyerprolactinaemic patients and up to 14-21 days in puerperae). The lowering effect of prolactin is dose-related both in terms of entity and duration of the effect.
Concerning any endocrine effects not related to the antiprolactinaemic action, data available in humans confirm the experimental results which denote that DOSTINEX is characterized by a very selective action with no effects on the baseline secretion of other pituitary hormones or cortisol. The single pharmacodynamic effect of DOSTINEX not related to the therapeutic effects refers to the reduction of blood pressure. The peak hypotensive effect of DOSTINEX in single dose appears during the first 6 hours after the drug intake and is dose-dependent in both entity and incidence.

## 5.2 Pharmacokinetic properties

The pharmacokinetic and metabolic profiles of DOSTINEX were studied in healthy volunteers of both sexes and in hyperprolactinaemic patients.

After oral administration, the labelled product was rapidly absorbed in the gastrointestinal tract, as evidenced by the plasma peak of radioactivity (between 0.5 and 4 hours after the administration).
Ten days after the administration, 18% and 72% of radioactivity were found in urine and stools, respectively. In urine, a rate of unchanged product corresponding to 2-3% of the dose was identified.

The main metabolite identified in urine is 6-allyl-8ß-carboxy-ergoline, corresponding to 4-6% of the dose. Three other metabolites were identified and measured in urine in the rate of 3%. It was noticed that the metabolites are less potent than DOSTINEX in inhibiting the secretion of prolactin *in vitro*. The biotransformation of DOSTINEX was also studied in the blood plasma of male healthy volunteers treated with labelled cabergoline: a fast and massive biotransformation was found.
The low urinary excretion of the unchanged product was confirmed also in the studies with the non-radioactive product. The half-life of DOSTINEX, calculated on the percentages of urinary excretion, is very long (63-68 hours in healthy volunteers, 79-115 hours in hyperprolactinaemic patients).
On the basis of the elimination half-life, the steady-state conditions are reached after 4 weeks, as confirmed by the mean peak of plasma levels of DOSTINEX obtained after single administration (37 ± 8 pg/ml) and after 4 weeks of repeated administrations (101 ± 43 pg/ml).
*In-vitro* experiments demonstrated that the drug, at the concentrations of 0.1-10 ng/ml, binds up to plasma proteins for 41-42%.
It does not seem that food influences the absorption and availability of DOSTINEX.

### 5.3 Preclinical safety data

Evidence indicated maternotoxic effects but no teratogenic effects in mice given cabergoline at doses up to 8 mg/kg/day (approximately 55 times the maximum recommended human dose) during the period of organogenesis.
A dose of 0.012 mg/kg/day (approximately 1/7 the maximum recommended human dose) during the period of organogenesis in rats caused an increase in post-implantation embryofoetal losses. These losses could be due to the inhibitory properties of cabergoline on prolactin secretion in rats. At daily doses of 0.5 mg/kg/day (approximately 19 times the maximum recommended human dose) during the period of organogenesis in rabbits, cabergoline caused maternotoxicity characterized by a loss of body weight and decreased food consumption. Doses of 4 mg/kg/day (approximately 150 times the maximum recommended human dose) during the period of organogenesis in rabbits caused an increased occurrence of various malformations. However, in another study in rabbits, no treatment-related malformations or embryotoxicity were observed at doses up to 8 mg/kg/day (approximately 300 times the maximum recommended human dose).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Lactose
Leucine

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

Do not use Dostinex after the expiry date which is stated on the Carton/ Bottle label after EXP:. The expiry date refers to the last day of that month.

**6.4 Special precautions for storage**

Store below 30◦C

**6.5 Nature and contents of container**

Type I amber glass bottles with screw cap and safety closure containing silica gel.
High-density polyethylene (HDPE) bottles with childproof cap, containing silica gel.
Bottle with 2 tablets
Bottle with 4 tablets
Bottle with 8 tablets

not all pack sizes or presentation may be marketed

**6.6 Special precautions for disposal and other handling**

Keep out of the sight and reach of children.

The bottles of DOSTINEX are supplied with a desiccant in the caps. This desiccant should not be removed.
Please close accurately the bottle after use.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 7. FURTHER INFORMATION

**MARKETING AUTHORIZATION HOLDER**
Pfizer Italia S.r.l.
Via Isonzo, 71
Latina
Italy.

**MANUFACUTRED, PACKED & RELEASED BY**
Pfizer Italia s.r.l. Località Marino Del Tronto 63100 Ascoli Piceno,Italy

## 8. DATE OF REVISION OF THE TEXT

October 2020.

**THIS IS A MEDICAMENT**

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the Pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

**Keep all medicaments out of reach and sight of children**

**Council of Arab Health Ministers**
**Union of Arabic Pharmacists**