SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Addnok 8mg sublingual tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

8mg sublingual tablets:

Each sublingual tablet contains buprenorphine hydrochloride corresponding to 8mg buprenorphine

Excipient(s): 8mg sublingual tablets: Lactose 191mg

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Sublingual Tablet

Appearance:

8mg tablets: Oval, biconvex, white tablets with “8” embossed on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment

4.2 Posology and method of administration

Adults:

Treatment with Addnok sublingual tablets is intended for use in adults who have agreed to be treated for addiction to opioids.

Treatment must be under the supervision of a physician experienced in the management of opiate dependence/addiction.

When treatment with Addnok is initiated, the physician should be aware of the partial agonist profile of the buprenorphine molecule. Buprenorphine binds to μ and κ opioid receptors and may trigger withdrawal symptoms in opioid-dependent patients.

Baseline liver function tests and documentation of viral hepatitis status is recommended prior to commencing therapy. Patients who are positive for viral hepatitis, on concomitant medication (see section 4.5) and/or have existing liver dysfunction are at risk of accelerated liver injury. Regular monitoring of liver function is recommended (see section 4.4).

Administration of Addnok is sublingual. The physician must advise the patient that the sublingual route is the only effective and safe route of administration for this medicinal product. The sublingual tablet is to be placed under the tongue until dissolved, which usually occurs within 5 to 10 minutes.

The tablet should not be swallowed, crushed or chewed.

Induction therapy:

The initial dose is 0.8 to 4mg administered as a single daily dose.

Opioid-dependent drug addicts who have not undergone phaseout: one dose of Addnok sublingual tablet(s) administered sublingually at least 6 hours after the last dose of opioid, or when the first signs of withdrawal appear.

Patients receiving methadone: before starting treatment with Addnok, the dose of methadone should be reduced to a maximum of 30mg/day. Addnok may trigger symptoms of withdrawal in patients treated with methadone.

Dosage adjustment and maintenance:

The dose of Addnok should be increased progressively according to the clinical effect of the individual patient, 16mg daily is often sufficient. The maximum daily dose should not exceed 24mg.

Especially during initiation of treatment, daily dispensing of buprenorphine is recommended. After stabilisation has been achieved, patients considered trustworthy may be given a supply of the drug sufficient for several days of treatment. Furthermore local requirements should be followed with regard to dispensing.

Dosage reduction and termination of treatment:

After a satisfactory period of stabilisation has been achieved, the dosage may be reduced gradually to a lower maintenance dose.

When deemed appropriate, treatment may be discontinued. The availability of sublingual tablets in doses of 0.4mg, 2mg and 8mg, allows for a downward titration of the dosage. Patients should be monitored following termination of buprenorphine treatment because of the potential for relapse.

Elderly:

The same dosage as adults

Children (under the age of 18 years):

Addnok should not be used for treatment of children under the age of 18 years, as experience with treatment of children is insufficient.

For further information, see the national guidelines for buprenorphine treatment.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients

Severe respiratory insufficiency

Severe hepatic insufficiency

Acute alcoholism or delirium tremens

4.4 Special warnings and precautions for use

Warnings

Addnok sublingual tablets are recommended only for treatment of opioid drug dependence.
National requirements should be followed with regard to dispensing.
Discontinuation of treatment may cause withdrawal symptoms that may be delayed.
Due to the lack of data in adolescents (age 15 - <18), buprenorphine should be used only with caution in this age group.
Patients should be closely monitored during the switching period from methadone to buprenorphine since withdrawal symptoms have been reported.
The physician should consider the risk of abuse and misuse (e.g. iv. administration), particularly at the initiation of treatment.

Diversion:
Diversion refers to the introduction of Addnok into the illicit market either by patients or by individuals who obtain the medicinal product through theft from patients or pharmacies. This diversion may lead to new addicts using Addnok as the primary drug of abuse with the risk of overdose, spread of blood borne viral infections, respiratory depression and hepatic injury. The physician should consider the risk of diversion of buprenorphine into the illicit market before prescribing buprenorphine.

The risk of overdose or treatment dropout is greater if the patient is under treated with buprenorphine and continues to self-medicate withdrawal symptoms with opioids , alcohol or other sedatives and hypnotics (in particular benzodiazepines).

Buprenorphine is a partial agonist at the μ opiate receptor and chronic administration produces dependence of the opioid type.

Precipitated Withdrawal:
When initiating treatment with buprenorphine the physician must be aware of the partial agonist profile of buprenorphine and that it can precipitate withdrawal in opioid-dependent patients particularly if administered less than 6 hours after the last use of heroin or other short-acting opioids, or if administered less than 24 hours after the last dose of methadone (see section 4.2). Conversely, withdrawal symptoms may also be associated with suboptimal dosing.
Buprenorphine can cause drowsiness, which may be exacerbated by other centrally acting agents such as alcohol, tranquilisers, sedatives and hypnotics (see section 4.5).
Animal studies, as well as clinical experience, have demonstrated that buprenorphine may cause dependence but at a lower level than morphine.
Discontinuation of treatment may result in a withdrawal syndrome that may be delayed.

Buprenorphine can cause orthostatic hypotension.
Buprenorphine is an opioid and may mask pain as a disease symptom.
Medicinal products that inhibit the enzyme CYP3A4 may cause increased concentrations of buprenorphine. A reduction of the buprenorphine dose may be necessary. In patients who are already treated with CYP3A4 inhibitors the dose of buprenorphine should be titrated carefully since a reduced dose may be sufficient in these patients (see section 4.5).
Concomitant use of monoamine oxidase inhibitors (MAOI) can increase the efficacy of opioids based on experience with morphine.
Due to the lack of data in adolescent age 15 - <18, Addnok should not be used in this age group.

Respiratory depression:
Some cases of death due to respiratory depression have been reported, particularly in cases when used in combination with benzodiazepines (see section 4.5), or when buprenorphine was not used as prescribed. Cases of death have been reported in connection with concomitant administration of buprenorphine and other medical products that causes central nervous system depression such as alcohol or other opioids.

Hepatitis, hepatic disorders:
Cases of acute hepatic injury have been reported in opioid-dependent addicts both in clinical trials and in post-marketing adverse reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of cytolytic hepatitis, hepatic failure, hepatic necrosis, hepatorenal syndrome and hepatic encephalopathy and death.
In many cases the presence of pre-existing liver enzyme abnormalities, genetic disease, infection with hepatitis B or hepatitis C virus concomitant use of other potentially hepatoxic medicines, alcohol abuse, anorexia, and on-going injecting drug use may have a causative or contributory role.
These supplemental factors should be considered before prescribing Addnok and during treatment. If a hepatic event is suspected, further biological and aetiological investigation is required. Depending upon the findings, the medicinal product may be discontinued cautiously in order to prevent withdrawal symptoms and to prevent a return to illicit drug use.
If the treatment is continued, hepatic function should be monitored closely.

Paediatric use
No data is available in children less than 15 years of age; therefore, buprenorphine should not be used in children under the age of 15.

Precautions for use
As with other opioids caution should be exercised to patients with:

- asthma or respiratory insufficiency (cases of respiratory depression, have been reported with buprenorphine, see section 4.3);
- renal insufficiency (30 % of the administered dose is eliminated by the renal route; thus renal elimination may therefore be prolonged if renal function is affected);
- hepatic insufficiency (hepatic metabolism of buprenorphine may be altered, see section 4.3);

- head injuries;
- increased intracranial pressure;
- hypotension;
- prostatic hypertrophy;
- urethral stenosis

As inhibiters of CYP3A4 (see section 4.5) may increase the concentration of buprenorphine, it is recommended that patients, already treated with inhibitors of CYP3A4, should have their dosage of Addnok adjusted carefully since a reduced dose may be sufficient in these patients.

Addnok sublingual tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Serotonin syndrome
Concomitant administration of Addnok sublingual tablets and other serotonergic agents, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
The following combinations are not recommended:
Alcohol:
Addnok should not be taken together with alcoholic drinks or medicines containing alcohol. Alcohol increases the sedative effect of buprenorphine which will impair the ability to drive or use machinery (see section 4.7).

Addnok should be used with caution in combination with:

Benzodiazepines:
This combination may cause death due to respiratory depression of central origin.
Therefore dosages must be individually titrated and the patient should be monitored closely. The possibility of drug abuse should also be considered (see section 4.4).

Other central nervous system depressants:
Other opioid derivatives (analgesics and antitussives (such as morphine, methadone, dextropropoxyphene, codeine, dextromethorphan and noscapine), certain antidepressants, sedative H1-receptor antagonists, barbiturates, anxiolytics other than benzodiazepines, neuroleptics, clonidine and related substances:
This combination increases central nervous system depression and therefore causes a reduced ability to drive and use machinery.

Monoamine oxidase inhibitors (MAOI):
Possible exaggeration of the effects of opioids based on experience with morphine.

To date, no notable interaction has been observed with cocaine.

Pharmacokinetic interactions
The effect of other medicinal products on buprenorphine

CYP3A4 inhibitors:
Buprenorphine is metabolised by CYP3A4. An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased C_{max} and AUC (area under the curve) of buprenorphine (approximately 70 % and 50 % respectively) and to a lesser extent, of norbuprenorphine.
Concomitant administration of buprenorphine and potent CYP3A4 inhibitors (such as HIV protease inhibitors like ritonavir, nelfinavir, saquinavir and indinavir or azole antifungal agents such as ketoconazole or itraconazole, erythromycin, gestodene, troleandomycin) can lead to markedly increased plasma concentrations of buprenorphine or norbuprenorphine. The combination should be avoided or monitored closely since a dose reduction may be required.

CYP3A4 inducers:
The interaction between buprenorphine and CYP3A4 inducers has not been investigated. Therefore it is recommended that patients receiving Addnok should be closely monitored if enzyme inducers such as phenobarbital, carbamazepine, phenytoin, rifampicin are co-administered.

Effect of buprenorphine on other medicinal products
Buprenorphine has been shown to be a CYP2D6 and CYP3A4 inhibitor in vitro. The risk of inhibition with therapeutic concentrations in vivo seems low, but can not be excluded. When buprenorphine (predominantly at high doses) is combined with medicinal products that are CYP2D6 or CY3A4 substrates the plasma concentrations of these medicinal products may be increased and the risk of dose dependent adverse reactions may occur. Buprenorphine does not inhibit the enzyme CYP2C19 in vitro. The effect on other enzymes that metabolises medicinal products has not been investigated.

Addnok sublingual tablets should be used cautiously when co-administered with:

- Serotonergic medicinal products, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of Addnok in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

During the last three months of pregnancy, continuously use of buprenorphine, regardless of the dosage, may be responsible for a withdrawal syndrome in neonates. Buprenorphine should not be used during second and third trimester of pregnancy. At the end of pregnancy, if high doses have to been given occasionally or if continuously use is necessary, neonatal monitoring should be considered, to prevent a risk of respiratory depression or a withdrawal symptom in children.

Breast-feeding

In rats buprenorphine is excreted in mother's milk. In high doses buprenorphine has potential to inhibit milk production. Therefore buprenorphine should not be used during the breast-feeding period in opioid adapted women.

4.7 Effects on ability to drive and use machines

Before stabilization is achieved and opioid tolerance is fully developed, Addnok may have major influence on the ability to drive and use machines.

Addnok can cause drowsiness, particularly when taken together with other centrally acting substances, including alcohol. Therefore caution is advised if motor vehicles or machines are used (see section 4.4).

4.8 Undesirable effects

The occurrence of undesirable effects depends on the patient's tolerance threshold, which is higher in drug adapted patients than in the general population.

Organ class	Common (≥1/100 to <1/10)	Rare ≥1/10.000 to <1/1.000)
Immune system disorders		Angioneurotic oedema, anaphylactic shock.
Psychiatric disorders		Hallucinations
Nervous system disorders	Headaches, cases of fainting, vertigo	
Respiratory, thoracic and		Respiratory depression*, bronchial spasm

mediastinal disorders		
Gastrointestinal disorders	Constipation, nausea, vomiting	
Hepatobiliary disorders		Necrosis of the liver, hepatitis**
Renal and urinary disorders		Urine retention
Vascular disorders	Orthostatic hypotension	
General disorders and administration site conditions	Insomnia, drowsiness, asthenia, sweating	

* see section 4.4 and 4.5

** see section 4.4

In patients with marked drug dependence, buprenorphine may initially produce an antagonist effect similar to that associated with naloxone.

In cases of intravenous misuse local reactions, sometimes septic, and potentially serious acute hepatitis have been reported (see section 4.4).

Spontaneous abortion has been reported with buprenorphine. It is not possible to establish a causal relationship, since cases typically involve other drug use or risk factors for spontaneous abortion (see section 4.6).

A neonatal abstinence syndrome has been reported among newborns of women who have received buprenorphine during pregnancy. The syndrome may be milder and more protracted than that from short acting full μ-opioid agonists. The nature of the syndrome may vary depending upon the mother's drug use history (see section 4.6).

4.9 Overdose

Buprenorphine seems to have a wide therapeutic margin of safety due to its partial opioid agonist properties.

In cases of accidental overdose, the respiratory and cardiac status of the patient must be monitored closely and relevant symptomatic treatment should be initiated. The major symptom, requiring intervention is respiratory depression, which could lead to respiratory arrest and death.

If the patient vomits, care must be taken to prevent aspiration of the vomit.

Treatment: Symptomatic treatment of respiratory depression and standard procedures for intensive care should be implemented.

Patent airways and if necessary assisted or controlled ventilation must be assured.

The patient should be transferred to an environment within which full resuscitation facilities are available.

Use of an opioid antagonist (e.g. naloxone) is recommended, despite the modest effect it may have in reversing the respiratory symptoms of buprenorphine, as buprenorphine is strongly attached to the receptor of morphine.

The recommended dose range of naloxone in these cases is 2-8mg, repeated at suitable intervals.

If an opioid antagonist is used (e.g. naloxone), the long duration of action of buprenorphine should be taken into consideration.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Drugs used in opioid dependence, ATC code: N07 BC01

Buprenorphine is a partial opioid agonist/antagonist which attaches to the μ- and κ-receptors of the brain. Its activity in opioid maintenance treatment is attributed to its slowly reversible binding to the μ-receptors which over a longer period reduces the adapted patients need for drugs.

Buprenorphine has a wide therapeutic index due to its partial agonist/antagonist effect, which limits its suppressing effects on especially the cardiac and respiratory function.

5.2 Pharmacokinetic properties

Absorption

When taken orally, buprenorphine undergoes pronounced first-pass hepatic metabolism with N-dealkylation and glucuroconjugation in the small intestine.

Per oral use of this medication is therefore inappropriate.

Peak plasma concentrations are achieved 90 minutes after sublingual administration and the maximal dose-concentration relationship is linear, between 2mg and 16mg.

Distribution

The absorption of buprenorphine is followed by a rapid distribution phase and a half-life of 2 to 5 hours.

Biotransformation

Buprenorphine is metabolised by 14-N-dealkulation and glucoroconjugation of the parent molecule and the dealkylated metabolite.

N-desalkyl-buprenorphine is an μ-agonist with intrinsic activity. Norbuprenorphine contributes to the overall pharmacological effect, however it is unknown to what extent.

Elimination

Elimination of buprenorphine is bi- or tri- exponential, with a long terminal elimination phase of 32 hours. This is in part due to re-absorption of buprenorphine after intestinal hydrolysis of the conjugated derivative, and in part due to the highly lipophilic nature of the molecule.

Buprenorphine is essentially eliminated in the faeces by biliary excretion of the glucuroconjugated metabolites (70 %). The residual 30 % is eliminated in the urine.

5.3 Preclinical safety data

The potential risk for humans is unknown. Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential. Studies in rats and rabbits have evidenced foetotoxicity including post-implantation loss. In addition, maternal oral administration at high doses during gestation and lactation resulted in a slight delay in the development of some neurological functions (surface righting reflex and startle response) in neonatal rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Mannitol (E421)

Maize starch

Citric acid, anhydrous (E330)

Sodium citrate (E331)

Povidone (E1201)

Magnesium stearate (E470b)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This product does not require any special storage conditions

6.5 Nature and contents of container

Blister (PVC/PVDC/Aluminium)

Pack sizes:

7, 14 and 28 sublingual tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal

Medicines no longer required should not be disposed of via wastewater or the municipal sewage system. Patients should be instructed to return them to a pharmacy or to ask their pharmacist how to dispose of them in accordance with the national regulations. These measures will help to protect the environment.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 28444/0015

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