

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Molterfin 2 mg sublingual tablets.

Molterfin 8 mg sublingual tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2 mg sublingual tablets:

Each sublingual tablet contains buprenorphine hydrochloride corresponding to 2 mg buprenorphine.

8 mg sublingual tablets:

Each sublingual tablet contains buprenorphine hydrochloride corresponding to 8 mg buprenorphine.

Excipient(s) with known effect:

2 mg sublingual tablets: Lactose 48 mg.

8 mg sublingual tablets: Lactose 191 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sublingual Tablet

Appearance:

2 mg tablets: Oval, biconvex, white tablets with "2" embossed on one side.

8 mg 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

Posology

Adults:

Treatment with Molterfin 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 Molterfin 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.

Induction therapy:

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

In case an initial dose below 2 mg is required, another medicinal product of buprenorphine sublingual tablets should be used for that strength, since Molterfin is available only as 2 mg and 8 mg dose strength.

Opioid-dependent drug addicts who have not undergone phaseout: one dose of Molterfin 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 Molterfin, the dose of methadone should be reduced to a maximum of 30 mg/day. Molterfin may trigger symptoms of withdrawal in patients treated with methadone.

Dosage adjustment and maintenance:

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

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 2 mg and 8 mg, allows for a downward titration of the dosage. In case slower downtitration in smaller steps should be required, other medicinal products of buprenorphine sublingual tablets with lower dose strengths should be used. 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):

Molterfin 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.

Method of administration

Administration of Molterfin 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.

Treatment goals and discontinuation

Before initiating treatment with Molterfin, a treatment strategy including treatment duration and treatment goals, should be agreed together with the patient. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with Molterfin, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal (see section 4.4).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe respiratory insufficiency.
- Severe hepatic insufficiency.
- Acute alcoholism or delirium tremens

4.4 Special warnings and precautions for use

Warnings

Molterfin 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.

The physician should consider the risk of abuse and misuse (e.g. iv. administration), particularly at the initiation of treatment.

Tolerance and opioid use disorder (abuse and dependence):

Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Molterfin. Abuse or intentional misuse of Molterfin may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with Molterfin and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2).

Patients will require monitoring for signs of drug-seeking behavior (e.g. too early requests for refills). This includes the review of concomitant opioids and psychoactive drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Diversion:

Diversion refers to the introduction of Molterfin 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 Molterfin as the primary drug of abuse with the risk of overdose, spread of blood borne viral infections, respiratory depression and hepatic injury.

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. Conversely, withdrawal symptoms may also be associated with suboptimal dosing.

Due to the lack of data in adolescent age 15 - <18, Molterfin should not be used in this age group.

Respiratory depression:

Cases of death due to respiratory depression have been reported, particularly in cases when used in combination with benzodiazepines and gabapentinoids (pregabalin and gabapentin) (see section 4.5) or when buprenorphine was not used as prescribed.

Sleep-related breathing disorders:

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related

hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Hepatitis, hepatic disorders:

Serious cases of acute hepatic injury have been reported in connection with abuse, especially by i.v. route. These hepatic injuries have mainly been observed at high doses and may be a result from mitochondrial toxicity.

Pre-existing or gained mitochondrial degradation (genetic disease, virus infections especially chronic hepatitis C, alcohol abuse, anorexia, other mitochondrial toxins such as acetylsalicylic acid, isoniazide, valproate, amiodarone, anti-retro-virale nucleoside analogue etc.) may increase the occurrence of such hepatic injuries.

These supplemental factors should be considered before prescribing Molterfin as well as during monitoring of the 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 recurrent abuse.

If the treatment is continued, the liver function should be monitored closely. Serious cases of acute hepatic injury have also been reported in a context of misuse, especially by intravenous route. These hepatic injuries have mainly been observed at high doses and can be exacerbated by viral infections, particularly chronic hepatitis C, alcohol abuse, anorexia and the concurrent use of other potentially hepatotoxic drugs.

Serotonin syndrome

Concomitant administration of Molterfin 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.

Opioid withdrawal symptoms may occur, if buprenorphine is administered to an opioid-addicted patient less than 6 hours after the last intake of opioids (see section 4.2).

As for other opioids, caution should be exercised in patients who use buprenorphine and have:

- a head injury and increased intracranial pressure
- hypotension
- prostatic hypertrophy and urethral stricture

As buprenorphine is an opioid, pain as a symptom of a disease, may be inhibited.

Buprenorphine may cause drowsiness, which may be exacerbated by concurrent use of other centrally acting substances, such as alcohol, sedatives and hypnotics (see section 4.5).

Orthostatic hypotension may occur.

Studies in animals, as well as clinical investigations have demonstrated that buprenorphine may cause dependence.

Therefore it is important to follow directions for induction of treatment, dose adjustment and monitoring of the patient (see section 4.2).

Precautions for use

Caution should be exercised to patients with:

Asthma or respiratory insufficiency (cases of respiratory depression, have been reported with buprenorphine).

Renal insufficiency (30 % of the administered dose is eliminated by the renal route. The renal elimination may therefore be prolonged if renal function is affected).

Hepatic insufficiency (hepatic metabolism of buprenorphine may be altered).

As inhibitors 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 Molterfin adjusted carefully since a reduced dose may be sufficient in these patients.

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

The following combinations are not recommended:

Alcohol:

Alcohol increases the sedative effect of buprenorphine which will impair the ability to drive or use machinery.

Molterfin should not be taken together with alcoholic drinks or medicines containing alcohol.

The following combinations should be used with precaution:

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 derivates (analgesics and antitussives (such as morphine, 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. The concomitant use of Molterfin with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).

Anticholinergics or medicinal products with anticholinergic activity:

Concomitant administration of buprenorphine with anticholinergics or medications with anticholinergic activity (e.g. tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects.

MAO-inhibitors (monoamin oxidase inhibitors):

Possible exaggeration of the effects of opioids, based on experience with morphine.

Serotonergic medicinal products

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).

Pharmacokinetic interactions

CYP3A4 inhibitors:

An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased C_{max} and AUC of buprenorphine (70 % and 50 % respectively) and to a lesser extent norbuprenorphine.

Patients receiving Molterfin should be closely monitored and may require dose-reduction if potent CYP3A4 inhibitors (such as protease inhibitors as ritonavir, nelfinavir and indinavir or azole antifungal agents such as ketoconazole or itraconazole) are co-administered.

CYP3A4 inducers:

The interaction of buprenorphine and CYP3A4 inducers has not been investigated. Therefore it is recommended that patients receiving Molterfin 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 seems low, but can not be excluded. When buprenorphine (predominantly at high doses) is combined with medicinal products that are CYP2D6 or CYP3A4 substrates the plasma levels of these medicinal products may rise and dose dependent undesirable effects may occur. Buprenorphine does not inhibit CYP2C19 in vitro. The effect on other enzymes that metabolises medicinal products has not been investigated.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

During the last three months of pregnancy, continuous 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 be given occasionally or if continuous use is necessary, neonatal monitoring should be considered, to prevent a risk of respiratory depression or a withdrawal symptom in children.

Breastfeeding

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, Molterfin may have major influence on the ability to drive and use machines.

Molterfin 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)	Not known (cannot be estimated from the available data)
Immune system disorders		Angioneurotic oedema, anaphylactic shock.	
Psychiatric disorders		Hallucinations.	
Nervous system disorders	Headaches, cases of fainting, vertigo.		
Respiratory, thoracic and mediastinal disorders		Respiratory depression*, bronchial spasm.	
Gastrointestinal disorders	Constipation, nausea, vomiting.		Dental caries.
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.

Drug dependence

Repeated use of Molterfin can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (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

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).

Neonatal abstinence syndrome

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).

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 listed in Appendix V*.

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 2-8 mg, 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 2 mg and 16 mg.

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 glucuroconjugation 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

Strip (Aluminium/PA/PET/PVC).

Pack sizes:

7, 14 and 28 sublingual tablets.
Bundle pack for hospital use with 140 (5 x 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

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

08-11-2024