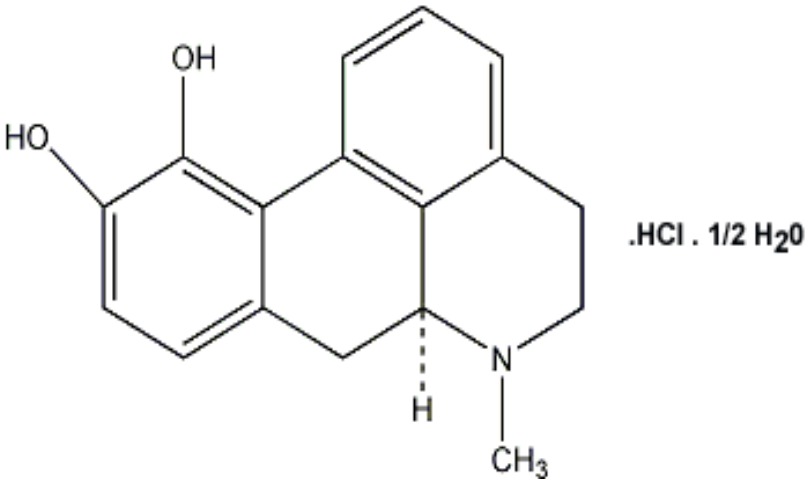
Uprimaâ 2 mg

PRODUCT NAME
Apomorphine Hydrochloride Sublingual

Trade Name
Uprimaâ

DESCRIPTION
Apomorphine is a dopaminergic agonist with affinity for both D1 like and D2 like receptors in sites within the brain known to be involved in the mediation of erection.

Apomorphine hydrochloride (HCl) is chemically designated 4H - dibenzo [de,g] quinoline-10,11-diol,5,6,6a,7-tetrahydro-6-methyl,hydrochloride,hemihydrate,(R)-or (6a,R)- 5,6,6a,7 - tetrahydro - 6 methyl - 4H - dibenzo [de,g] quinoline - 10, 11 - diol, hydrochloride, hemihydrate. Its molecular formula is $C_{17}H_{17}NO_2$. HCl. $1/2H_2O$ and molecular weight is 312.8. Apomorphine HCl has the following structure :



Apomorphine HCl is a white to greysh minute glistening crystal or powder and melts with decomposition between 225 C and 236 C. Apomorphine HCl is soluble in alcohol and chloroform and slightly soluble in water (1 gram in 50 ml).

Apomorphine has no narcotic pharmacological similarity to opiates.

Apomorphine HCl tablets are available in two dosage strengths, each administered as a sublingual (SL) tablet. Each tablet contains 2 mg apomorphine HCl, equivalent to 1.71 mg of apomorphine respectively, with the following inactive ingredients:
microcrystalline cellulose, hydroxypropylmethylcellulose, citric acid, magnesium stearate, asorbic acid, edetate disodium dihydrate, colloidal silicon dioxide, ferric oxide, acesulfame potassium, orange mint flavor and sufficient amount of mannitol to attain final tablet weight.

CLINICAL PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group : Drugs used in erectile dysfunction (ATC code : G04B E). Apomorphine is a sublingual therapy for the treatment of erectile dysfunction and operates through a central mechanism af action. It is predominantly a D2-like dopaminergic agonist with selectivity for D2, D3, and D4 receptors that is from 10-100 fold greater than for D1 and D5 in relevant cells. It acts within the central nervous system, particularly the hypothalamic region of the brain, which is known to be involved in the mediation of erection. The erectogenic effects of apomorphine arise through dopaminergic signalling via oxytocinergic pathways. These signals subsequently mediate local actions of nitric oxide, the conversion of GTP to cGMP, and subsequent smooth muscle relaxation in the corpus cavernosum, leading to corporal engorgement and erection.

The clinical pharmacodynamic profile of apomorphine is consistent with its dopaminergic activity.

In Phase III studies, Uprima at 2 mg was statistically superior to placebo for the primary endpoint of percentage of intercourse attempts resulting in erections firm enough for intercourse, showing a response of about 45 % with 2 mg (as compared to about 35 % with placebo).

The median onset time to erection for Uprima was approximately 18 – 19 minutes (confidence intervals approximately 16 – 21 minutes).

Pharmacokinetic properties
Following sublingual administration, apomorphine reaches peak plasma concentrations relatively quickly (see below). Apomorphine is rapidly cleared from plasma, with an apparent elimination half-life of approximately 3 hours. Due to extensive first pass metabolism, Uprima appears to be nearly ineffective when swallowed, with only 1 – 2 % of the activity seen after intravenous or subcutaneous administration.

Absorption: apomorphine is rapidly absorbed from the sublingual cavity and can be detected in plasma within 10 minutes after placing the tablet under the tongue. Peak plasma concentrations are attained in about 40 – 60 minutes. Increasing dosage strengths of Uprima sublingual tablets provide dose-proportional increases in C_{max} and AUC . The bioavailability of apomorphine from sublingual tablets, relative to subcutaneous administration, is approximately 17 – 18 %.

Distribution: apomorphine is approximately 90 % bound to plasma proteins, primarily albumin. Binding is independent of concentration between 1.0 and 1000 ng/ml, which exceeds the concentration range achieved with the recommended doses.

Metabolism: apomorphine is extensively metabolized, primarily through conjugation with glucuronic acid or sulphate. Apomorphine is also metabolized by N-demethylation, leading to the formation of norapomorphine, which is converted to glucuronide and sulphate conjugates. The major metabolite in plasma of subjects receiving a single sublingual dose of apomorphine is apomorphine sulphate. The glucuronides of apomorphine and norapomorphine are found in plasma at lower concentrations. These conjugates are not expected to be pharmacologically active. *In vitro* data suggest that Uprima at the recommended doses, is not likely to inhibit the metabolism of other drugs by cytochrome P450 isoforms CYP1A2, 3A4, 2C9, 2C19, or 2D6.

Elimination: following a 2 mg sublingual dose of [^{14}C] apomorphine, radioactivity was eliminated in both urine (93 %) and faeces (16 %). Less than 2 % of the apomorphine dose was excreted in

urine as free apomorphine.

Special Populations:

Elderly
The pharmacokinetics of apomorphine (5 mg) were investigated in healthy male subjects older than 65 years. The t_{max} was 36 % longer and the C_{max} was 21 % lower in elderly subjects than in young subjects. The AUC was 11 % larger in the elderly. See Dosage and administration .

Renal insufficiency
The AUC of apomorphine was increased by 4 % in subjects with mild renal insufficiency (creatinine clearance 40 – 80 ml/min/1.73 m^2), 52 % in moderate cases (10 – 40 ml/min/1.73 m^2) and 67 % in severe cases (< 10 ml/min/1.73m^2). Apparent terminal elimination half-life of apomorphine was predicted to increase by 0.24 hour with each 10ml/min/1.73 m^2 decrease in creatinine clearance C_{max} was not significantly affected. See Dosage and administration

Hepatic insufficiency
Mean C_{max} and AUC were 16 – 62 % and 35 – 68 % higher, respectively, in subjects with varying degrees of hepatic insufficiency compared with normal subjects. The apparent terminal elimination half-life of apomorphine 2 mg was 1.8 – 3.5 hours in patients with hepatic insufficiency compared with 1.9 hours in normal subjects. See Dosage and administration .

Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity. Apomorphine has no effect on fertility in male rats. Findings observed in animals included behavioural disorders, retinal atrophy, Leydig cell tumours, and haematological changes. All of these events occurred at exposure levels much higher than dose used in clinical trials, were species-specific, and they are not considered relevant to the clinical use of Uprima.

INDICATIONS AND USAGE

Treatment of erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

In order for Uprima to be effective, sexual stimulation is required.

Uprima is not indicated for use by women.

CONTRAINDICATIONS

Uprima is contraindicated in the following situations:
In patients with known hypersensitivity to the active substance or any of the excipients in the tablet formulation.
In patients with severe unstable angina, recent myocardial infarction, severe heart failure or hypotension and other conditions where sexual activity is inadvisable.

WARNING AND PRECAUTIONS

Special warnings and special precautions for use

A medical history and a complete physical examination should be conducted in order to diagnose erectile dysfunction and determine the underlying causes before pharmacological treatment is considered. Before commencement of any treatment for erectile dysfunction, the potential cardiac risks inherent in resuming sexual activity in an individual patient, assessed according to his medical condition and history, should be considered by the physician.

It is not known if Uprima is effective in patients with spinal cord injuries, multiple sclerosis, and in patients who have undergone prostatectomy or pelvic surgery. Efficacy in diabetic patients has not been established.

Agents for the treatment of erectile dysfunction should be used with caution in patients with anatomical penile deformity (such as angulation, cavernosal fibrosis, or Peyronie's disease) , as Uprima has not been sufficiently studied in these populations.

Uprima may uncommonly produce a transient vasovagal syndrome that may manifest as a self-limiting fainting/syncope (incidence < 0.2 % at the recommended dose regimen). Nearly all (>90 %) syncopal episodes were preceded by a prodrome of symptoms that included mild to severe nausea, vomiting, pallor, sweating/hot flushes, and dizziness or lightheadedness. If patients experience prodromal symptoms they should not attempt to stand up, but should lie down and raise their legs until their symptoms resolve.

Uprima should be used with caution in patients with uncontrolled hypertension, known hypotension or those with a history of postural hypotension. Acute decreases in blood pressure have been noted after Uprima administration. Elderly patients may be more prone to such occurrences and are more susceptible to any deleterious consequences.

Uprima should be used with caution in patients taking antihypertensives or nitrate medications owing to the potential for hypotension (see Interaction with other medicinal products and other forms of interaction).

Uprima should be used with caution in patients with compromised renal or hepatic function (see Dosage and Administration).

The safety and efficacy of Uprima in combination with other treatments for erectile dysfunction has not been studied. Therefore, the use of such combinations is not recommended.

DRUG INTERACTIONS

Interaction with other medicinal products and other forms of interaction

Since apomorphine is primarily metabolized by sulphation and glucuronidation, compounds that inhibit or induce cytochrome P450 isoforms are not expected to affect the pharmacokinetics of apomorphine.

The combination of Uprima with both nitrates and antihypertensives (angiotensin-converting

enzyme (ACE) inhibitors, β-blockers, calcium channel blockers, and alpha blockers) has been studied. The only significant findings were in the group of patients who were taking nitrates. A proportion (4/40) of these patients experienced vasovagal symptoms and significant standing blood pressure decreases when Uprima was administered at higher than the recommended dose (5 mg). It is therefore recommended that caution be observed when administering Uprima to patients taking nitrates.

Interaction studies and/or clinical experience with ondansetron hydrochloride, prochlorperazine maleate, and domperidone indicate that these agents may be given safely with Uprima. No studies have been performed with Uprima in combination with other antiemetics, hence other combinations are not recommended.

Uprima should not be given in combination with other centrally-acting dopamine agonists or antagonists because of the potential for pharmacodynamic interactions.

No formal drug interaction studies have been performed with other agents for erectile dysfunction, antidepressants, anticonvulsants, or other CNS-active agents, however clinical experience has not indicated the presence of interactions.

Interaction studies in volunteers where alcohol was given with Uprima indicated that concurrent alcohol intake may cause an increase in the incidence and extent of hypotension. Additionally, intake of alcohol can diminish sexual performance.

Pregnancy and lactation
Uprima is not indicated for use in women

Animal reproduction studies have not been conducted with Uprima. It is not known whether Uprima can cause foetal harm in pregnant women or whether it can affect female reproduction capacity. Also, it is not known whether apomorphine passes into breast milk.

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and the use machines have been performed. Because some patients can experience dizziness, lightheadedness, and, uncommonly, syncope, they should not engage in activities such as driving or operating machinery for at least 2 hours after administration of Uprima or until any such symptoms are fully resolved.

ADVERSE REACTIONS

Undesirable effects
Over 4000 patients have received at least one dose of Uprima in clinical trials. The most common (> 1/100, < 1/10) adverse drug reactions noted in patients taking 2 – 3 mg Uprima are nausea and headache, both occurring in approximately 7 % of patients, and dizziness, occurring in approximately 4 % of patients.

Other commonly (> 1/100, < 1/10) observed adverse drug reactions are yawning, rhinitis, pharyngitis, somnolence, infection, pain, increased cough, flushing, taste disorder, and sweating. These adverse events were generally mild and transient.

Uncommonly (> 1/1000, < 1/100), Uprima may produce a transient vasovagal syndrome that can lead to self-limiting fainting/syncope. (See warnings and precautions).

OVERDOSAGE

Uprima in high doses may induce vomiting. If the tablets are swallowed the bioavailability of apomorphine will be reduced by first pass metabolism. There is no specific antidote available for Uprima. Treatment should be supportive and symptomatic. It is advised that vital signs such as blood pressure and heart rate are monitored. Measures to avoid possible orthostatic hypotension should be taken. The use of domperidone maleat, a peripherally acting dopamine antagonist used to counter emetic effects, may be considered.

DOSAGE AND ADMINISTRATION

For sublingual use. The tablet should be placed under the tongue and allowed to dissolve.

Use in adults

One tablet should be administered approximately 20 minutes prior to sexual activity. It is recommended that the patient be started at the 2 mg dose. A minimum time period of 8 hours should be allowed to elapse prior to administering a subsequent dose.

Each patient should be instructed by a medical professional on the proper administration technique for Uprima. The patient should be adviced to drink a small amount of water before taking Uprima to optimize the dissolution of the tablet. One tablet of Uprima should be placed under the tongue. In the majority of patients the tablet will be completely dissolved within 10 minutes. If any residual amount remains in the mouth after 20 minutes it may be swallowed. In order for Uprima to be effective, sexual stimulation is required. The patient should initiate sexual activity and proceed to intercourse when he feels ready. The median onset of effect is approximately 18-19 minutes after the tablet is placed under the tongue; the onset time varies from patient to patient.

Use in the elderly

No dosage adjustment is required in elderly patients.

Use in patients with impaired renal function

In patients with renal insufficiency an increase in apomorphine AUC values and prolongation of the elimination half-life was observed, however, C_{max} was not significantly altered. The maximum dosage should therefore be limited to 2 mg in patients with severely impaired renal function.

Use in patients with impaired hepatic function

In patients with hepatic insufficiency significant increases were observed in apomorphine AUC values, C_{max} and elimination half-life. Owing to the potential for a higher risk of adverse events in this population, patients with significantly impaired hepatic function should only be given Uprima if the benefits outweigh the risks. Such patients may be initiated at the 2 mg dosage level and care exercised in any dose increase.

Use in children

Uprima is not indicated for use in children.

HARUS DENGAN RESEP DOKTER

Presentation
Box of blister of 2 sublingual tablets.

Storage and Handling
Stored between 15^0C – 25^0C. Do not freeze, protect from light and moisture.
Store in original package.

Manufactured by	Imported by
Abbott Laboratories Ltd.	P.T.Abbott Indonesia
Queenborough Kent	Jl.Raya Bogor Km.37
ME 11 5EL United Kingdom	Depok Indonesia