

ANNEX I

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Uprima 2 mg sublingual tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg apomorphine hydrochloride, equivalent to 1.71 mg apomorphine. For excipients see 6.1.

3. PHARMACEUTICAL FORM

Sublingual tablet.

2 mg tablet is a brick red, pentagon-shaped tablet embossed with “2” on one side and the Abbott logo on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of men with 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.

4.2 Posology and method of 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. The dose may be increased on subsequent administrations to 3 mg if necessary to reach the desired clinical effect.

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 advised to drink a small amount of water before taking Uprima to optimise 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.

4.3 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.

4.4 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 anti-hypertensives or nitrate medications owing to the potential for hypotension (see section 4.5 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 section 4.2 Posology and method of administration).

Uprima is not indicated for use by women.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Since apomorphine is primarily metabolised 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 anti-hypertensives (angiotensin-converting enzyme (ACE) inhibitors, β -blockers, calcium channel blockers, and α_1 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.

4.6 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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and 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.

4.8 Undesirable effects

Over 4000 patients have received at least one dose of Uprima in clinical trials. The most common adverse drug reactions noted in patients taking 2 or 3 mg Uprima were nausea and headache, both occurring in approximately 7 % of patients, and dizziness, occurring in approximately 4 % of patients.

Table 1 displays adverse reactions from clinical trial experience and post-marketing experience. Adverse reactions from postmarketing experience are identified with an asterisk.

The adverse reactions are displayed by system organ class. Within the system organ class adverse reactions are listed by frequency, using the following groupings: common (>1/100, < 1/10), uncommon (>1/1000, <1/100), very rare (<1/10,000).

Table 1. Adverse Reactions		
System Organ Class	Frequency	Adverse Reaction
Infections	Common	Infection
Immune System Disorders	Very rare	Hypersensitivity Reactions (including Angioedema)*
Nervous System Disorder	Common	Headache, Dizziness, Somnolence
	Uncommon	Vasovagal Autonomic Syndrome, Syncope ¹
Vascular Disorders	Common	Vasodilation (Flushing)
Respiratory, Thoracic and Mediastinal Disorders	Common	Rhinitis, Pharyngitis, Yawning, Increased Cough
Gastrointestinal Disorders	Common	Nausea, Dyspepsia
	Uncommon	Stomatitis*, Mouth Ulceration*
Skin And Subcutaneous Tissue Disorders	Common	Sweating
General Disorders and Administration Site Conditions	Common	Pain, Taste Disorder

¹See section 4.4 Special warnings and precautions for use.

*Adverse reactions from postmarketing experience.

4.9 Overdose

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 maleate, a peripherally acting dopamine antagonist used to counter emetic effects, may be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 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 of 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 and 3 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 2mg (as compared to about 35% with placebo) and about 50% with 3 mg (as compared to about 30% with placebo).

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

5.2 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 metabolised, primarily through conjugation with glucuronic acid or sulphate. Apomorphine is also metabolised 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 section 4.2 Posology and method of administration for dosage recommendations.

Renal insufficiency

The AUC of apomorphine was increased by 4% in subjects with mild renal insufficiency (creatinine clearance 40 – 80 ml/min/1.73 m²), 52% in moderate cases (10 – 40 ml/min/1.73 m²) and 67% in severe cases (<10 ml/min/1.73 m²). Apparent terminal elimination half-life of apomorphine was predicted to increase by 0.24 hour with each 10 ml/min/1.73 m² decrease in creatinine clearance. C_{max} was not significantly affected. See section 4.2 Posology and method of administration for dosage recommendations.

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 section 4.2 Posology and method of administration for dosage recommendations.

5.3 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 those used in clinical trials, were species-specific, and they are not considered relevant to the clinical use of Uprima.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Hypromellose
Citric acid
Magnesium stearate
Ascorbic acid
Disodium edetate
Silicon dioxide
Red iron oxide (E172)
Acesulfame potassium
Orange mint flavour (WONF WL-28499)
Mannitol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Aluminium foil/foil cold-form blister packs containing 1, 2, 3, 4 and 8 sublingual tablets.
Not all pack sizes may be marketed.

6.6 Instructions for use and handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Abbott Laboratories Ltd
Queenborough
Kent ME11 5EL
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/180/001-005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28.05.01

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Uprima 3 mg sublingual tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 3 mg apomorphine hydrochloride, equivalent to 2.56 mg apomorphine. For excipients see 6.1.

3. PHARMACEUTICAL FORM

Sublingual tablets.

3 mg tablet is a brick red, triangle-shaped tablet embossed with “3” on one side and the Abbott logo on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of men with 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.

4.2 Posology and method of 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. The dose may be increased on subsequent administrations to 3 mg if necessary to reach the desired clinical effect. 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 advised to drink a small amount of water before taking Uprima to optimise 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.

4.3 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.

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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.

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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 anti-hypertensives or nitrate medications owing to the potential for hypotension (see section 4.5 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 section 4.2 Posology and method of administration).

Uprima is not indicated for use by women.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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

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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.

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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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and 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.

4.8 Undesirable effects

Over 4000 patients have received at least one dose of Uprima in clinical trials. The most common adverse drug reactions noted in patients taking 2 or 3 mg Uprima were nausea and headache, both occurring in approximately 7 % of patients, and dizziness, occurring in approximately 4 % of patients.

Table 1 displays adverse reactions from clinical trial experience and postmarketing experience. Adverse reactions from postmarketing experience are identified with an asterisk.

The adverse reactions are displayed by system organ class. Within the system organ class adverse reactions are listed by frequency, using the following groupings: common (>1/100, < 1/10), uncommon (>1/1000, <1/100), very rare (<1/10,000).

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	Uncommon	Vasovagal Autonomic Syndrome, Syncope ¹
Vascular Disorders	Common	Vasodilation (Flushing)
Respiratory, Thoracic and Mediastinal Disorders	Common	Rhinitis, Pharyngitis, Yawning, Increased Cough
Gastrointestinal Disorders	Common	Nausea, Dyspepsia
	Uncommon	Stomatitis*, Mouth Ulceration*
Skin And Subcutaneous Tissue Disorders	Common	Sweating
General Disorders and Administration Site Conditions	Common	Pain, Taste Disorder

¹See section 4.4 Special warnings and precautions for use.

*Adverse reactions from postmarketing experience.

4.9 Overdose

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 maleate, a peripherally acting dopamine antagonist used to counter emetic effects, may be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in erectile dysfunction (ATC code: G04B E).

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

In Phase III studies, Uprima at 2 mg and 3 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) and about 50% with 3 mg (as compared to about 30% with placebo).

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

5.2 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 metabolised, primarily through conjugation with glucuronic acid or sulphate. Apomorphine is also metabolised 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 section 4.2 Posology and method of administration for dosage recommendations.

Renal insufficiency

The AUC of apomorphine was increased by 4% in subjects with mild renal insufficiency (creatinine clearance 40 – 80 ml/min/1.73 m²), 52% in moderate cases (10 – 40 ml/min/1.73 m²) and 67% in severe cases (<10 ml/min/1.73 m²). Apparent terminal elimination half-life of apomorphine was predicted to increase by 0.24 hour with each 10 ml/min/1.73 m² decrease in creatinine clearance. C_{\max} was not significantly affected. See section 4.2 Posology and method of administration for dosage recommendations.

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 section 4.2 Posology and method of administration for dosage recommendations.

5.3 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 those used in clinical trials, were species-specific, and they are not considered relevant to the clinical use of Uprima.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Hypromellose
Citric acid
Magnesium stearate
Ascorbic acid
Disodium edetate
Silicon dioxide
Red iron oxide (E172)
Acesulfame potassium
Orange mint flavour (WONF WL-28499)
Mannitol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Aluminium foil/foil cold-form blister packs containing 1, 2, 4, 8 and 12 sublingual tablets.
Not all pack sizes may be marketed.

6.6 Instructions for use and handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Abbott Laboratories Ltd
Queenborough
Kent ME11 5EL
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/180/006-010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28.05.2001

10. DATE OF REVISION OF THE TEXT

ANNEX II

ANNEX III

LABELLING AND PACKAGE LEAFLET

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What Uprima is and what it is used for
2. Before you take Uprima
3. How to take Uprima
4. Possible side effects
5. Storing Uprima
6. Further information

Uprima 2 mg sublingual tablets

apomorphine hydrochloride

Each tablet contains 2 mg of apomorphine hydrochloride, equivalent to 1.71 mg of apomorphine.

The other ingredients are: microcrystalline cellulose, hypromellose, citric acid, magnesium stearate, ascorbic acid, disodium edetate, silicon dioxide, red iron oxide (E172), acesulfame potassium, Orange mint flavour (WONF WL-28499) and mannitol.

The Marketing Authorisation holder and the manufacturer of Uprima is Abbott Laboratories Ltd, Queenborough, Kent ME11 5EL, United Kingdom

1. WHAT UPRIMA IS AND WHAT IT IS USED FOR

Uprima tablets are sub-lingual tablets each containing 2 mg of apomorphine (as hydrochloride). The 2 mg tablet is available in packs of 1, 2, 3, 4 and 8 sublingual tablets. Not all pack sizes may be marketed.

Uprima 2 mg tablets are brick red in colour and are pentagon shaped embossed with 2 on one side and the Abbott logo on the other side.

Uprima is a medicine known as a dopaminergic agonist which helps men achieve an erection by stimulating the region of the brain, called the hypothalamus, thereby helping to produce the natural signals which start the erection process in the penis. Sexual stimulation is necessary for Uprima to work. Uprima is different to morphine and has no morphine-like properties.

Uprima is a therapy for the treatment of men with erectile dysfunction (sometimes called ED or impotence). This is a condition in which a man cannot get, or keep, a hard penis (erection) sufficient for satisfactory sexual performance.

2. BEFORE YOU TAKE UPRIMA

Do not take Uprima if:

- You have ever had an allergic reaction to apomorphine or any of the ingredients in Uprima. Possible signs of an allergic reaction include rash, itching, swollen face or lips and shortness of breath. Tell your Doctor if you get any of these.
- You have severe unstable angina, recent myocardial infarction, severe heart failure or hypotension, and other medical conditions which could make sexual activity dangerous. Always consult your Doctor about your medical history.

You should tell your Doctor if:

- You have a deformity or disease of the penis as these may require special care when using medicines such as Uprima.
- You experience severe dizziness/lightheadedness or feel faint after taking Uprima, especially if you also have severe nausea or vomiting, sweating, become pale or become unusually hot. In these cases you should not attempt to stand up. If you experience these symptoms or feel faint for any reason you should lie down and raise your legs. The feeling of faintness should go away.
- You are taking nitrates (often used for the relief of angina or chest pains) or any medicines for hypertension (high blood pressure).
- You have liver or kidney problems. Your suitability for Uprima and/or the appropriate dose may need to be considered by your doctor.
- You have abnormally high or low blood pressure or are prone to dizzy spells or fainting.
- You are taking any other treatment for erectile dysfunction. Uprima should not be used with any other treatment for erectile dysfunction.

Uprima should not be given to children under the age of 18. No dose adjustment is required for the elderly.

Taking Uprima with food and drink:

Taking alcohol with Uprima can increase any undesirable effects, in particular low blood pressure. In addition, taking alcohol can make it more difficult to obtain an erection.

Pregnancy/Breast-feeding:

Not for use in women.

Driving and using machines:

Because some patients can experience dizziness, lightheadedness and, uncommonly fainting, it is recommended that you do not drive or operate machinery for at least 2 hours after taking Uprima or until any such symptoms are fully resolved.

Taking other medicines:

Please inform your doctor if:

- You are taking nitrates (often used for the relief of angina or chest pains) or any medicines for hypertension (high blood pressure).
- You are taking drugs which affect the dopamine system (often used to treat Parkinson's disease, disturbances of the mind or to prevent vomiting).

You should also inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

3. HOW TO TAKE UPRIMA

Your Doctor will decide the dose of Uprima which is suitable for you. Do not take more tablets than your Doctor has prescribed. All patients should begin with the 2 mg tablet. If your erection is not sufficient for satisfactory sexual activity at this dose and you have not experienced side effects, you may increase the dose to the 3 mg tablet following consultation with your doctor. You should not take more than 3 mg in any 8 hour period.

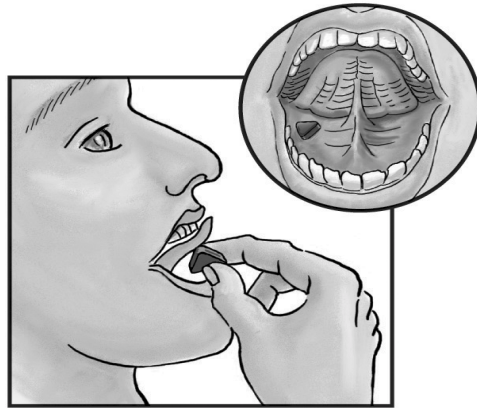


Figure 1

When taking Uprima:

- Swallow a small amount of water to help moisten your mouth
- Place one tablet of Uprima under your tongue (see Figure 1). The tablet will not work if you swallow it.
- Let the tablet dissolve under your tongue – this usually takes about 10 minutes (if any tablet residue is left after 20 minutes it may be swallowed).
- Sexual activity may begin as soon as the Uprima is placed under your tongue and you may proceed with intercourse when you and your partner are ready.
- Typically erections may be achieved in under 20 minutes, although this varies from person to person.

You should not take more than 3 mg Uprima in any 8 hour period.

If Uprima does not help you get a satisfactory erection tell your Doctor as your dose may need adjustment.

You should only take Uprima as directed. If you take too many tablets or the wrong dose, contact your Doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Uprima can have side effects. These are generally mild and transient in nature.

Common undesirable effects are nausea, headache, dizziness, yawning, sleepiness, infection, sore throat, pain, increased cough, rhinitis, flushing, taste disorder, heartburn and sweating.

Uncommonly, fainting has occurred. If you feel faint, follow the instructions given under '**You should tell your doctor if:**'

Uncommon undesirable effects are mouth reactions including stomatitis (inflammation of the mucous membrane of the mouth) and mouth ulcers. Very rare undesirable effects are allergic

reactions, including angioedema (swelling of the skin and mucous membranes involving the face, lips and/or tongue).

If you have chest pains during intercourse, you should stop immediately and contact your doctor.

If you have any undesirable effect which is severe or prolonged you should tell your Doctor. If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING UPRIMA

Keep out of the reach and sight of children

Store your Uprima in the original package. Do not use this medicine after the expiry date shown on the pack, or if the pack has been damaged or tampered with.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved on {date}

PACKAGE LEAFLET

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What Uprima is and what it is used for
2. Before you take Uprima
3. How to take Uprima
4. Possible side effects
5. Storing Uprima
6. Further information

Uprima 3 mg sublingual tablets

apomorphine hydrochloride

Each tablet contains 3 mg of apomorphine hydrochloride, equivalent to 2.56 mg of apomorphine.

The other ingredients are: microcrystalline cellulose, hypromellose, citric acid, magnesium stearate, ascorbic acid, disodium edetate, silicon dioxide, red iron oxide (E172), acesulfame potassium, Orange mint flavour (WONF WL-28499) and mannitol.

The Marketing Authorisation holder and the manufacturer of Uprima is Abbott Laboratories Ltd, Queenborough, Kent ME11 5EL, United Kingdom

1. WHAT UPRIMA IS AND WHAT IT IS USED FOR

Uprima tablets are sub-lingual tablets each containing 3 mg of apomorphine (as hydrochloride). The 3 mg tablet is available in packs of 1, 2, 4, 8 and 12 sublingual tablets. Not all pack sizes may be marketed.

Uprima 3 mg tablets are brick red in colour and are triangle shaped embossed with 3 on one side and the Abbott logo on the other side.

Uprima is a medicine known as a dopaminergic agonist which helps men achieve an erection by stimulating the region of the brain, called the hypothalamus, thereby helping to produce the natural signals which start the erection process in the penis. Sexual stimulation is necessary for Uprima to work. Uprima is different to morphine and has no morphine-like properties.

Uprima is a therapy for the treatment of men with erectile dysfunction (sometimes called ED or impotence). This is a condition in which a man cannot get, or keep, a hard penis (erection) sufficient for satisfactory sexual performance.

2. BEFORE YOU TAKE UPRIMA

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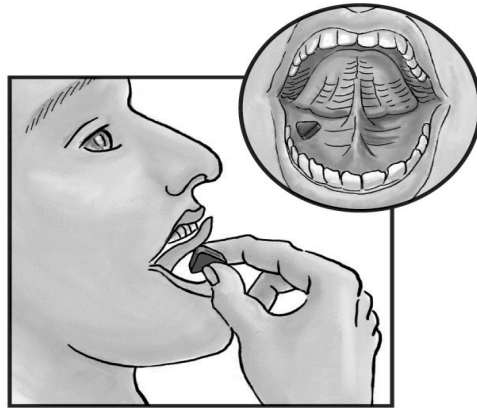


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