PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# Pr**KYNMOBI®**

apomorphine hydrochloride

Soluble film, 10 mg, 15 mg, 20 mg, 25 mg and 30 mg, Sublingual

USP

Antiparkinson Agent

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**RECENT MAJOR LABEL CHANGES**

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|---|---|
| 7 Warnings and Precautions, Hematologic, Hemolytic Anemia | 12/2022 |

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**Sections or subsections that are not applicable at the time of authorization are not listed**

## PART I: HEALTH PROFESSIONAL INFORMATION

## 1 INDICATIONS

KYNMOBI (apomorphine hydrochloride) is indicated for:

- the acute, intermittent treatment of "OFF" episodes in patients with Parkinson's disease (PD)

### 1.1 Pediatrics

**Pediatrics (<18 years of age):** The safety and efficacy of apomorphine sublingual film have not been evaluated in patients under 18 years of age, and its use is not recommended in this patient population.

### 1.2 Geriatrics

**Geriatrics (> 65 years of age):** Treatment response and safety profile of patients 65 years of age and older are similar. Caution is advised as older patients tend to have a longer disease history and more co-morbidities. See 7.1.4 Geriatrics.

## 2 CONTRAINDICATIONS

Apomorphine hydrochloride is contraindicated in patients:

- Hypersensitive to apomorphine hydrochloride or to any ingredient (including sodium metabisulfite) in the KYNMOBI formulation or component of the packaging (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING). Patients with a sulfite sensitivity may experience various allergic-type reactions, including anaphylactic symptoms and life-threatening asthmatic attacks. Patients who experienced any hypersensitivity/allergic reaction to KYNMOBI should not take KYNMOBI again. See 7 WARNINGS AND PRECAUTIONS, Immune, - Hypersensitivity; and - Sulfite Sensitivity.
- Using concomitant drugs of the 5HT3 antagonist class including antiemetics (e.g., ondansetron, granisetron, palonosetron). There have been reports of profound hypotension and loss of consciousness when subcutaneous apomorphine was administered with ondansetron. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension/Orthostatic Hypotension/Syncope; and 9.4 Drug-Drug Interactions, 5HT3 antagonists.
- With severe renal or hepatic impairment (see 10.3 Pharmacokinetics, Special Populations and Conditions).

## 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

**Serious Warnings and Precautions**

**Sudden Onset of Sleep and Somnolence**

Patients receiving treatment with dopaminergic agents, such as apomorphine, have reported suddenly falling asleep while engaged in activities of daily living, including while driving. This may occur anytime (i.e. is NOT limited to the initiation of therapy), and without forewarning signs of somnolence.

For additional details, and patient instructions, see 7 WARNINGS AND PRECAUTIONS, Neurologic, Sudden Onset of Sleep and Somnolence.

# 4 DOSAGE AND ADMINISTRATION

## 4.1 Dosing Considerations

- KYNMOBI (apomorphine hydrochloride soluble film) is for sublingual use only. It must be administered whole and not cut, chewed or swallowed. Patients may need caregiver help for administration, e.g. due to their "OFF" status. See 4.4 Administration.
- **Medical Supervision** should be provided during:
    - initial administration instructions, to ensure appropriate use of the sublingual film by the patient and/or caregiver (see 4.4 Administration, and Patient Medication Information, Instructions for Use); and
    - dose initiation and titrations, to monitor for response and side effects, especially in patients with a history of hypotension, cardiovascular disease, or those who are currently using antihypertensive medication, and in patients with renal and/or hepatic impairment. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular; and 4.2.5 Special Populations);
- **Antiemetic Pre-treatment**: Pre-treatment with a concomitant antiemetic (e.g. domperidone) may be considered to minimize the risk of nausea and vomiting (see 7 WARNINGS AND PRECAUTIONS, Gastrointestinal, Nausea and Vomiting).
    - The antiemetic can be started up to three days prior to the initial dose of apomorphine sublingual film. Dose and duration of concomitant antiemetic treatment should be consistent with dosing recommendations for the antiemetic and the need for concomitant treatment should be re-assessed periodically.
    - The concomitant use of apomorphine and drugs, including antiemetics, of the 5HT3 antagonist class is contraindicated. See 2 CONTRAINDICATIONS, and 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions).
- **Renal and/or Hepatic Insufficiency** (see 4.2.5 Special Populations):
    - Contraindicated in severe insufficiency
    - Not recommended in moderate insufficiency

## 4.2 Recommended Dose and Dosage Adjustment

### 4.2.1 Dosing Overview

Each apomorphine sublingual film dose is dissolved sublingually, as needed, for the acute intermittent treatment of "OFF" episodes. See details below, under 4.2.2 Titration; 4.2.3 Maintenance; and 4.2.4 Re-treatment and Discontinuation.

- **Dose**:
    - The starting dose is 10 mg. Initiate in "OFF" state, and monitor.
    - Titrate at the next observed OFF period, by 5 mg increments, based on tolerability and response.
    - Therapeutic dose range: 10 mg to 30 mg per dose.
    - Maintain at the lowest tolerable dose that provides an effective response.
    - The total daily dose should not exceed 90 mg.

- **Dose frequency**:
    - Administer one film for one "OFF" episode. Do not repeat dosing for the same episode even if the response is less than optimal.
    - Doses (for distinct episodes) should be separated by at least 2 hours.
    - Do not administer more than 5 films per day. The average frequency of dosing in the clinical studies was approximately 2 times per day.
- **Discontinue** treatment when no longer effective, or associated with significant adverse effects.
- **Re-starting** treatment:
    - Contraindicated when stopped due to hypersensitivity reactions.
    - Not recommended when stopped due to oral adverse reactions.
    - If paused for non-safety reasons, re-start at previously determined ~~last~~ maintenance dose.

### 4.2.2 Titration

Apomorphine sublingual film must be titrated to balance optimal response and tolerability before starting the maintenance treatment. The recommended starting dose of apomorphine sublingual film is 10 mg. Dose titration should be initiated with 10 mg when patients are in an "OFF" state. In clinical studies of KYNMOBI, the "OFF" state was achieved by instructing patients to not take their regular morning dose of carbidopa/levodopa or any other adjunctive Parkinson's disease medications, and to take their last dose of carbidopa/levodopa and any other adjunctive Parkinson's disease medications no later than midnight the night before.

If the patient tolerates the dose but does not respond adequately (i.e., does not turn "ON"), the patient should be instructed to resume the usual Parkinson's disease medication. Continue up-titration with apomorphine sublingual film under medical supervision, generally within 3 days, at the next observed "OFF" period.

Continue to titrate in a similar manner in 5 mg increments until an effective and tolerable dose is achieved, up to 30 mg (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).

### 4.2.3 Maintenance

After instructions and initial titration, the patient maintains the established dose to manage the "OFF" episodes at home. Caregiver assistance may be required for the patients who are unable to self-administer apomorphine sublingual film.

If a single dose of apomorphine sublingual film is ineffective for a particular "OFF" episode, a second dose should not be given for that "OFF" episode. The efficacy or safety of administering a second dose for a single "OFF" episode has not been studied.

Do not administer a subsequent dose of apomorphine sublingual film for a new "OFF" episode sooner than 2 hours after the last dose.

Treatment dose may require adjustment during the maintenance period, and this should be conducted under medical supervision. Treatment should be maintained with the lowest effective dose of apomorphine sublingual film that reasonably balances optimal response and tolerability.

### 4.2.4 Re-treatment and Discontinuation

Patients who have had an interruption in therapy for non-safety related reasons may be restarted on the maintenance dose previously determined in titration.

Apomorphine sublingual film rechallenge is not generally recommended after discontinuation due to an oral adverse reaction as these reactions may recur and may be more severe than the initial reaction. Apomorphine sublingual film rechallenge is contraindicated if it has been discontinued because of a local or systemic hypersensitivity reaction of any severity, as it may trigger a more serious and severe reaction.

Treatment should be discontinued when apomorphine hydrochloride is no longer effective or is associated with significant adverse effects. Prior to discontinuation, patients should be informed about potential withdrawal symptoms, and then monitored. See 7 WARNINGS AND PRECAUTIONS, Neurologic, Dopamine Agonist Withdrawal Syndrome (DAWS).

### 4.2.5 Special Populations

**Pediatrics (<18 years of age)**

Health Canada has not authorized an indication for pediatric use.

**Patients with Renal Impairment**

No dose adjustment is required for patients with mild renal impairment. Apomorphine is not recommended in patients with moderate renal impairment unless the benefits outweigh potential risks. Use of apomorphine in patients with severe renal impairment is contraindicated (see 2 CONTRAINDICATIONS and 10.3 Pharmacokinetics, Special Populations, Renal Insufficiency).

**Patients with Hepatic Impairment**

No dose adjustment is required for patients with mild hepatic impairment. Apomorphine is not recommended in patients with moderate hepatic impairment unless the benefits outweigh potential risks. Use of apomorphine in patients with severe hepatic impairment is contraindicated (see 2 CONTRAINDICATIONS and 10.3 Pharmacokinetics, Special Populations, Hepatic Insufficiency).

### 4.4 Administration

Apomorphine soluble film is indicated for sublingual administration only, and must be administered whole. It will disintegrate in about 3 minutes. Patients should not cut, chew or swallow the film.

The patient should be adequately instructed on how to use apomorphine sublingual films to ensure proper administration and appropriate use (refer to the Patient Medication Information, Instructions for Use section). When the patient's OFF symptoms are likely to interfere with self-administration, a caregiver should also be appropriately instructed, especially for patients with significant motor dysfunctions and requiring assistance.

## 5 OVERDOSAGE

In pooled clinical studies (n=556) conducted with KYNMOBI (apomorphine hydrochloride) sublingual film there were no cases of overdose. No specific antidotes for apomorphine are known.

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| For management of a suspected drug overdose, contact your regional poison control centre. |

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table 1 – Dosage Forms, Strengths, Composition and Packaging**

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|---|---|---|
| Sublingual | Soluble film≠<br><br>10 mg, 15 mg, 20 mg, 25 mg, 30 mg≠<br><br>apomorphine hydrochloride | disodium EDTA dihydrate<br>dye (FD&C Blue #1, Granular, 05603)<br>glycerin (natural)<br>glyceryl monostearate (Imwitor 491)<br>hydroxyethyl cellulose (Natrosol 250G Pharm)<br>hydroxypropyl cellulose (Nisso HPC-SSL)<br>maltodextrin (M180)<br>(-)-menthol (Emprove® crystals)<br>pyridoxine hydrochloride<br>sodium hydroxide<br>sodium metabisulfite<br>sucralose<br>white ink (ammonia, butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, shellac and titanium dioxide) |

KYNMOBI (apomorphine hydrochloride) soluble film is a blue to green rectangular single film with a white printed number identifying the strength (e.g., "10" is 10 mg). KYNMOBI comes in dosage strengths of 10 mg, 15 mg, 20 mg, 25 mg and 30 mg. Each soluble film is individually packaged in a sealed foil pouch.

Films are supplied in cartons of 30 films and cartons of 2 films.

## 7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX .

- **Sudden Onset of Sleep and Somnolence**

### General

***Falls***

Patients with Parkinson's disease (PD) are at risk of falling due to underlying postural instability, possible autonomic instability, and syncope caused by the blood pressure lowering effects of the drugs used to treat PD, including dopamine agonists like apomorphine (see 10 CLINICAL PHARMACOLOGY).

During the titration phase of the controlled clinical trial, falls were reported as an adverse reaction in 4% of patients treated with KYNMOBI. During the maintenance phase of the controlled clinical trial, 6% of KYNMOBI-treated patients had events that could reasonably be considered falls compared to 2% of placebo-treated patients.

***Fibrotic Complications***

Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, pleural thickening, and cardiac valvulopathy have been reported in some patients treated with ergot-derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur. Although these adverse reactions are believed to be related to the ergoline structure of these dopamine agonists, whether other, non-ergot derived dopamine agonists, such as apomorphine, can cause these reactions is unknown.

**Cardiovascular**

***Hypotension/Orthostatic Hypotension/Syncope***

Dopamine agonists, including apomorphine, may cause orthostatic hypotension or hypotension at any time. Patients with Parkinson's disease may also experience orthostatic hypotension. For these reasons, Parkinson's disease patients being treated with apomorphine may require monitoring for signs and symptoms of orthostatic hypotension, especially in patients who have a history of hypotension, cardiovascular disease or who are currently using antihypertensive medication. Patients should be informed of this risk. See also 7 WARNINGS AND PRECAUTIONS, General, Falls.

During the titration phase of the controlled clinical trial, syncope, pre-syncope, hypotension or orthostatic hypotension were reported as adverse reactions in 4% of patients. During the maintenance phase of the controlled clinical trial, syncope, pre-syncope, hypotension or orthostatic hypotension were reported as adverse reactions in 2% of patients treated with KYNMOBI, compared with 0% of patients who received placebo.

In the controlled clinical trial, 43% of KYNMOBI-treated patients and 36% of placebo-treated patients had a reduction of 20 mmHg or more in standing minus supine/sitting systolic blood pressure, or a reduction of 10 mmHg or more for standing minus supine/sitting diastolic blood pressure.

In pooled clinical studies (n=556), 2 – 3% of KYNMOBI-treated patients had an adverse event of hypotension and/or orthostatic hypotension.

In pooled clinical studies, 0.4% of KYNMOBI-treated patients during titration (n=556) and 2% during maintenance treatment (n=408) experienced syncope.

The hypotensive effects of apomorphine may be increased by the concomitant use of alcohol, antihypertensive medications, and vasodilators (especially nitrates). Patients should avoid alcohol when using apomorphine (see 9 DRUG INTERACTIONS). Monitor blood pressure for hypotension and orthostatic hypotension in patients taking apomorphine with concomitant antihypertensive medications and/or vasodilators (see 9 DRUG INTERACTIONS).

***Cardiac and Cerebral Ischemia***

Apomorphine has been shown to reduce resting systolic and diastolic blood pressure and may have the potential to trigger or exacerbate coronary and/or cerebral ischemia in patients with or without known cardiovascular and cerebrovascular disease. Before initiating treatment with apomorphine, patients with a cardiovascular disease history should be assessed to determine suitability. If patients develop signs and symptoms of coronary or cerebral ischemia, prescribers should re-evaluate the continued use of apomorphine.

In the controlled clinical trial, one KYNMOBI-treated patient (n=54) experienced a fatal cardiac arrest. In pooled clinical studies (n=408), acute coronary syndrome events (including myocardial infarction and angina) were infrequent.

***Nitroglycerin***

Caution is advised when using apomorphine in patients who are prescribed nitroglycerin. Patients taking apomorphine should lie down before and after taking sublingual nitroglycerin. In a study of healthy participants, the hypotensive effect of subcutaneous apomorphine on systolic and diastolic blood pressure was exacerbated by the concomitant use of alcohol or sublingual nitroglycerin (0.4 mg). A similar study has not been performed with KYNMOBI.

***QTc Prolongation***

KYNMOBI is associated with QTc interval prolongation (see 10.2 Pharmacodynamics, Prolongation of the QTc Interval). Many drugs that cause QTc prolongation are suspected to increase the risk of torsade de pointes.

Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QTc prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Particular care should be exercised when administering KYNMOBI to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging drug. Risk factors for torsade de pointes in the general population include, but are not limited to, the following: female gender; age 65 years or older; baseline prolongation of the QTc interval; presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; family history of sudden cardiac death at <50 years; cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, left ventricular hypertrophy, cardiomyopathy, conduction system disease); history of arrhythmias (especially ventricular arrhythmias, atrial fibrillation, or recent conversion from atrial fibrillation); electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia) or conditions leading to electrolyte disturbances (e.g., eating disorders); bradycardia (<50 beats per minute); acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma); and diabetes mellitus.

When drugs that prolong the QTc interval are prescribed, healthcare professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug.

***Cardiac valvulopathy***

See 7 WARNINGS AND PRECAUTIONS, General, Fibrotic Complications regarding reports of cardiac valvulopathy.

**Dependence/Tolerance**

In premarketing clinical experience, KYNMOBI did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior.

However, there are rare post-marketing reports of abuse of medications containing apomorphine or levodopa. In general, these reports consist of patients taking increasing doses of medication in order to achieve a euphoric state.

**Driving and Operating Machinery**

Advise patients to exercise caution when driving or operating a vehicle or potentially dangerous

machinery. See 7 WARNINGS AND PRECAUTIONS, Neurologic, Sudden Onset of Sleep and Somnolence.

**Gastrointestinal**

***Oral Mucosal Irritation***

During the titration phase of the controlled clinical trial, oral soft tissue pain or paresthesia were reported as adverse reactions in 2% of patients treated with KYNMOBI. During the maintenance phase of the controlled clinical trial, oral soft tissue pain or paresthesia were reported as adverse reactions in 13% of patients treated with KYNMOBI, compared with 2% of patients who received placebo.

In general, oral mucosal irritation reactions were mild to moderate in severity, and usually resolved with treatment discontinuation.

Apomorphine sublingual film rechallenge is not generally recommended after discontinuation as oral adverse reactions may recur and be more severe than the initial reaction.

Oral hypersensitivity adverse reactions may also occur during treatment with apomorphine sublingual film (see 7 WARNINGS AND PRECAUTIONS, Immune, Hypersensitivity).

***Nausea and Vomiting***

Apomorphine may cause nausea and vomiting when administered at recommended doses (see 8.2 Clinical Trial Adverse Reactions). Treatment with an antiemetic (e.g. domperidone) may be considered to minimize the risk of nausea or vomiting (see 4.1 Dosing Considerations).

5HT3 antagonists including antiemetics (for example, ondansetron, granisetron, palonosetron) are contraindicated (see 2 CONTRAINDICATIONS; and 9.4 Drug-Drug Interactions, 5HT3 Antagonists).

Antiemetics with anti-dopaminergic actions (e.g., haloperidol, chlorpromazine, promethazine, prochlorperazine) have the potential to worsen symptoms in patients with Parkinson's disease and should be avoided.

**Hematologic**

***Hemolytic Anemia***

Hemolytic anemia requiring hospitalization has been reported with apomorphine treatment in the postmarketing setting. Many of the reported cases included a positive direct antiglobulin test (Coombs test), suggesting a potential immune-mediated hemolysis. Severe anemia, angina and dyspnea have occurred with hemolytic anemia. Some patients were treated with high dose glucocorticoids or blood transfusions. Hemolytic anemia can appear at any time after apomorphine treatment. If a patient develops anemia while taking apomorphine sublingual film, consider a workup for hemolytic anemia. If hemolytic anemia occurs, consider discontinuing apomorphine treatment.

**Immune**

***Hypersensitivity***

Oral soft tissue swelling (lips, tongue, gingiva, and mouth) was reported as an adverse reaction in 15% of patients treated with KYNMOBI during the maintenance phase of the controlled clinical study (n=54), compared with 0% of patients who received placebo; 11% of patients discontinued KYNMOBI because of this event.

Swelling of the face, oral allergy syndrome, hypersensitivity or urticaria were reported as an adverse reaction in 6% of patients treated with KYNMOBI during the maintenance phase (n=54) of the controlled clinical study, compared with 0% of patients who received placebo; 4% of patients

discontinued KYNMOBI because of this event.

It is not known whether these events are related to apomorphine, sodium metabisulfite, or another KYNMOBI excipient.

Once a hypersensitivity reaction has been identified with or without systemic hypersensitivity reactions, apomorphine sublingual film should be discontinued. The patients should not be rechallenged, as the reaction is likely to worsen (see 7 WARNINGS AND PRECAUTIONS, Gastrointestinal, Oral Mucosal Irritation).

***Sulfite Sensitivity***

KYNMOBI contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is estimated at 1% and 5% in populations with asthma.

**Neurologic**

***Sudden Onset of Sleep and Somnolence***

Patients receiving treatment with dopaminergic agents have reported suddenly falling asleep while engaged in activities of daily living, including operating a motor vehicle, which sometimes resulted in accidents.

Physicians should alert patients of the reported cases of sudden onset of sleep, bearing in mind that these events are NOT limited to initiation of therapy. Patients should also be advised that sudden onset of sleep has occurred without warning signs. If drowsiness or sudden onset of sleep should occur, patients should immediately contact their physician.

Until further information is available on the management of this unpredictable and serious adverse event, patients should be warned not to drive or engage in other activities where impaired alertness could put themselves and others at risk of serious injury or death (e.g., operating machines). Substituting other dopamine agonists may not alleviate these symptoms, as episodes of falling asleep while engaged in activities of daily living have also been reported in patients taking these products.

While dose reduction clearly reduces the degree of somnolence, there is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

Presently, the precise cause of this event is unknown. It is known that many Parkinson's disease patients experience alterations in sleep architecture, which results in excessive daytime sleepiness or spontaneous dozing, and that dopaminergic agents can also induce sleepiness.

**Clinical Trial Data:** During the titration phase study (n=141) of the controlled clinical study, somnolence was reported as an adverse reaction in 11% of patients treated with KYNMOBI. During the maintenance phase study (n=54) of the controlled clinical study, somnolence was reported as an adverse reaction in 13% of patients treated with KYNMOBI, compared with 2% of patients who received placebo.

In pooled clinical studies, 11% of KYNMOBI-treated patients during titration (n=556), and 9% during maintenance treatment (n=408) experienced somnolence (see 8.2 Clinical Trial Adverse Reactions).

***Dyskinesias***

Apomorphine may cause dyskinesia or exacerbate pre-existing dyskinesia.

During the titration phase (n=141) of the controlled clinical study, dyskinesia was reported as an adverse reaction in 1% of patients treated with KYNMOBI. During the maintenance phase (n=54) of the controlled clinical study, dyskinesia was not reported as an adverse reaction in patients treated with KYNMOBI, compared with 2% of patients who received placebo.

In pooled clinical studies, 3% of KYNMOBI-treated patients during titration (n=556) and 5% during maintenance treatment (n=408) reported dyskinesia or worsening of dyskinesia. In the pooled clinical studies, 0% of KYNMOBI-treated patients during titration studies, and 1% during maintenance studies, withdrew from studies due to dyskinesias.

***Neuroleptic Malignant Syndrome***

A symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in other antiparkinsonian therapies. Apomorphine sublingual film however may be discontinued without tapering. After discontinuation, it may be reinitiated, unless the discontinuation was the result of a hypersensitivity reaction.

***Dopamine Agonist Withdrawal Syndrome (DAWS)***

A drug withdrawal syndrome has been reported during tapering or after discontinuation of dopamine agonists. Withdrawal symptoms do not respond to levodopa, and may include apathy, anxiety, depression, fatigue, sweating, panic attacks, insomnia, irritability and pain. The syndrome has been reported in patients who did or did not develop impulse control disorders. Prior to discontinuation, patients should be informed about potential withdrawal symptoms, and closely monitored during tapering and after discontinuation. In case of severe withdrawal symptoms, temporary re-administration of apomorphine at the lowest effective dose to manage these symptoms may be considered.

**Ophthalmologic**

***Retinal Pathology in Albino Rats***

In a 2-year carcinogenicity study of apomorphine in albino rats, retinal atrophy was detected at all subcutaneous doses tested (up to 0.8 mg/kg/day or 2 mg/kg/day in males or females, respectively; less than the maximum recommended human dose (MRHD) of 20 mg/day on a body surface area [mg/m2] basis). Retinal atrophy/degeneration has been observed in albino rats treated with other dopamine agonists for prolonged periods (generally during 2-year carcinogenicity studies). Retinal findings were not observed in a 39-week subcutaneous toxicity study of apomorphine in monkeys at doses up to 1.5 mg/kg/day, a dose similar to the MRHD on a mg/m2 basis. The clinical significance of the finding in rats has not been established but cannot be disregarded because it may involve the disruption of a mechanism that is universally present in vertebrates (e.g., disk shedding).

**Psychiatric**

***Hallucinations/Psychotic-Like Behaviour***

Apomorphine should not be considered for patients with a major psychotic disorder unless the potential benefits outweigh the risks and uncertainties. In addition, certain medications used to treat psychosis may exacerbate the symptoms of Parkinson's disease and may decrease the effectiveness of

apomorphine (see 9 DRUG INTERACTIONS).

Patients who develop psychotic symptoms during apomorphine treatment should be clinically assessed and continued only if the clinical benefit outweighs the risk.

During the maintenance phase (n=54) of the controlled clinical study, hallucinations, delusions, disorientation or confusion were reported as adverse reactions in 6% of patients treated with KYNMOBI, compared with 2% of patients who received placebo. No patient developed hallucinations or psychotic-like behavior during the titration phase (n=141).

In pooled clinical studies, 0.2% KYNMOBI-treated patients during titration studies (n=556) and 4% during maintenance treatment studies (n=408) had hallucinations and/or psychotic-like behaviour. Events experienced during maintenance treatment were considered serious for two patients, one of whom discontinued the study.

***Impulse Control Disorders***

Impulse control disorders including compulsive behaviours such as intense urges to gamble, increased sexual urges, intense urges to spend money, binge eating, compulsive eating, punding and/or other intense urges have been reported in Parkinson's disease and Restless Legs Syndrome patients treated with dopamine agonists. Because patients may not recognize these behaviors as abnormal, it is important for physicians to specifically ask patients and caregivers to identify new behaviour patterns. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking apomorphine.

In pooled clinical studies (n=556), less than 1% of KYNMOBI-treated patients had impulse control disorder and/or compulsive behaviours.

**Reproductive Health: Female and Male Potential**

- **Function**

  Priapism

  Apomorphine use is associated with increased incidences of penile erection. They may develop into prolonged painful erections in some patients. Severe priapism may require medical attention.

  In pooled clinical studies (n=556), there were less than 1% of KYNMOBI-treated male patients who reported priapism.

**Respiratory**

See 7 WARNINGS AND PRECAUTIONS, General, Fibrotic Complications regarding reports of pulmonary infiltrates, pleural effusion, and pleural thickening.

**Skin**

***Melanoma***

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear.

For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using apomorphine for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

## 7.1 Special Populations

### 7.1.1 Pregnant Women

There are no adequate data on the developmental risk associated with use of apomorphine in pregnant women. Apomorphine should not be used in this patient population.

In animal reproduction studies, apomorphine had adverse developmental effects in rats (increased neonatal deaths) and rabbits (increased incidence of malformation) when administered during pregnancy at clinically relevant doses. These doses were also associated with maternal toxicity.

Apomorphine (0.3, 1, or 3 mg/kg/day) administered by subcutaneous injection to female rats throughout gestation and lactation, resulted in increased offspring mortality at the highest dose tested, which was associated with maternal toxicity. There were no effects on developmental parameters or reproductive performance in surviving offspring. The no-effect dose for developmental toxicity (1 mg/kg/day) is less than the MRHD on a mg/m2 basis.

### 7.1.2 Breast-feeding

There are no data on the presence of apomorphine in human milk, the effects of apomorphine on the breastfed infant, or the effects of apomorphine on milk production. Apomorphine should not be used unless its potential benefits outweigh the risk and uncertainties.

### 7.1.3 Pediatrics

**Pediatrics (<18 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

### 7.1.4 Geriatrics

In pooled clinical studies, there were 280 patients younger than age 65 and 276 patients 65 years of age or older treated with at least one dose of KYNMOBI. Rates of treatment-emergent adverse events reported in clinical trials were similar in patients age 65 and older compared with patients less than 65.

The most common adverse event for both age groups during maintenance treatment was nausea (22.9% of patients younger than 65 years of age and 19.2% of patients 65 years of age or older).

### 7.1.5 Renal Impairment

Use of apomorphine in patients with severe renal impairment is contraindicated (see 2 CONTRAINDICATIONS, 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY).

### 7.1.6 Hepatic Impairment

Use of apomorphine in patients with severe hepatic impairment is contraindicated (see 2 CONTRAINDICATIONS, 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY).

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

Oral soft tissue reactions to KYNMOBI (including swelling) were very common and prompted discontinuation in 11% of clinical trial patients. In general, oral mucosal irritation reactions were mild to moderate in severity, and usually resolved with treatment discontinuation. Nausea, dizziness, and somnolence were also very common. Hypotension, orthostatic hypotension, syncope and falls were common, as were hallucinations, delusions, disorientation, vomiting, headache, rhinorrhea, fatigue and hyperhidrosis. Apomorphine may cause sudden sleep onset.

See also 7 WARNINGS AND PRECAUTIONS, e.g. subsections:

- General, Falls
- Cardiovascular, Hypotension / Orthostatic Hypotension / Syncope
- Gastrointestinal, Oral Mucosal Irritation
- Immune, Hypersensitivity
- Neurologic, Sudden Onset of Sleep and Somnolence.

The KYNMOBI safety database included 556 patients with Parkinson's disease who received at least one (1) dose of KYNMOBI.

### 8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety data described below is based on one randomized, double-blind, placebo-controlled, 12-week study in patients with Parkinson's disease (see 14 CLINICAL TRIALS).

In this study, patients were titrated to their optimal effective and tolerated dose. There were 141 patients who received at least one (1) dose of KYNMOBI. Individual doses in this trial ranged from 10 mg to 35 mg and were administered up to 5 times per day. The mean age of patients in this study was 63 years (range 43 to 86 years), 63% were male and 93% were Caucasian.

Table 2 presents the adverse reactions that occurred in at least 5% of patients treated with KYNMOBI during the maintenance phase of the study, and with an incidence greater than in patients who received placebo. Overall, the types and incidences of adverse reactions were comparable in the Titration (n=141) and Maintenance (n=54) phases of the study.

**Table 2 – Adverse Reactions Reported by at Least 5% of Patients Treated with KYNMOBI during the Maintenance Phase, and with an Incidence Greater than Placebo**

| | Titration | Maintenance | |
|---|---|---|---|
| | KYNMOBI (N=141) % | KYNMOBI (N=54) % | Placebo (N=55) % |
| **Gastrointestinal disorders** | | | |
| Nausea | 21 | 28 | 4 |
| Oral/pharyngeal soft tissue swelling[1] | 1 | 15 | 0 |
| Oral/pharyngeal soft tissue pain and paraesthesia[2] | 2 | 13 | 2 |
| Oral ulceration and stomatitis[3] | 2 | 7 | 0 |
| Oral mucosal erythema | 4 | 7 | 4 |
| Vomiting | 4 | 7 | 0 |
| Dry mouth | 1 | 6 | 0 |
| **Nervous system disorders** | | | |
| Somnolence | 11 | 13 | 2 |
| Dizziness | 11 | 9 | 0 |
| Headache | 8 | 6 | 0 |
| **Respiratory, thoracic, and mediastinal disorders** | | | |
| Rhinorrhea | 6 | 7 | 0 |
| **General disorders and administration site conditions** | | | |
| Fatigue | 3 | 7 | 0 |
| **Injury, poisoning, and procedural complications** | | | |
| Fall | 4 | 6 | 2 |
| Laceration | 1 | 6 | 0 |
| **Skin and subcutaneous tissue disorders** | | | |
| Hyperhidrosis | 4 | 6 | 4 |
| **Immune system disorders** | | | |
| Hypersensitivity[4] | 0 | 6 | 0 |

[1] Includes lip swelling, lip edema, oropharyngeal swelling, gingival edema, edema mouth, swollen tongue, and pharyngeal edema

[2] Includes throat irritation, glossodynia, oral pain, oral paresthesia, oropharyngeal pain, gingival pain, and oral hypoesthesia

[3] Includes lip ulceration, oral mucosal blistering, stomatitis, cheilitis, and tongue ulceration

[4] Includes hypersensitivity, swelling face, oral allergy syndrome and urticaria

In this study, no clear relationship was observed between adverse events and total daily dose (i.e. considering dose and number of doses administered per day at time of the adverse event).

Oropharyngeal Adverse Events:

In the titration phase of the controlled clinical study, 1% of KYNMOBI-treated patients (n=141) experienced oral/pharyngeal soft tissue swelling, 2% experienced oral/pharyngeal soft tissue pain and paresthesia, 2% experienced oral ulceration and stomatitis, 4% experienced oral mucosal erythema and 0% experienced a hypersensitivity reaction.

In the maintenance phase of the controlled clinical study, 15% of KYNMOBI-treated patients (n=54) experienced oral/pharyngeal soft tissue swelling, 13% experienced oral/pharyngeal soft tissue pain and paresthesia, 7% experienced oral ulceration and stomatitis, 7% experienced oral mucosal erythema and 6% experienced a hypersensitivity reaction.

Adverse events of Special Interest

In the pooled safety data from the maintenance phase of studies conducted in 383 Parkinson's patients, the following adverse events of special interest have been reported in KYNMOBI-treated patients : Erythema, Stomatitis, Oral Ulcers or Oral Irritation 33.2%; Dizziness 7.0%, Hypotension 1.3%, Orthostatic Hypotension 2.6%; Fall 7.0%, Contusion 2.6% and Laceration 1.8%; Somnolence 7.6% and Insomnia 1.8%; Allergic/Sensitivity Response to the Formulation 13.8%; Dyskinesias 5.0%; Hallucination 2.1%, Hallucination visual 1.0% and Psychotic disorder 0.5%; Syncope 1.8%, Presyncope 1.0%; Acute Coronary Syndrome, Myocardial Infarction, Angina 1.0%.

### 8.3 Less Common Clinical Trial Adverse Reactions

Following is a list of MedDRA terms that reflect adverse events reported by patients treated with KYNMOBI during the maintenance phase of the study (n=54). The events listed are events that are plausibly drug-related and reported with a greater incidence than placebo. Events listed in Table 2 are not included. Although the events reported occurred during treatment with KYNMOBI, they were not necessarily caused by it.

**Cardiac disorders:** Cardiac arrest
**Eye disorders**: Lacrimation increased, vision blurred
**Gastrointestinal disorders:** Glossodynia, lip oedema, lip swelling, lip ulceration, cheilitis, eructation, gingival oedema, gingival pain, hypoaesthesia oral, mouth ulceration, oedema mouth, oral mucosal blistering, paraesthesia oral, salivary hypersecretion, stomatitis, swollen tongue, tongue polyp, tongue ulceration
**General disorders and administration site conditions:** Chills, chest pain
**Immune system disorders:** Hypersensitivity, oral allergy syndrome
**Investigations:** Electrocardiogram QT prolonged
**Nervous system disorders:** Ageusia, drooling, dysgeusia, memory impairment
**Psychiatric disorders:** Delusion, hallucination, visual, initial insomnia, irritability, obsessive-compulsive disorder
**Reproductive system and breast disorders:** Spontaneous penile erection
**Respiratory, thoracic and mediastinal disorders:** Oropharyngeal swelling, throat irritation, yawning, dyspnoea, nasal congestion, oropharyngeal pain, pharyngeal erythema, pharyngeal oedema, sinus congestion
**Skin and subcutaneous tissue disorders:** swelling face, urticaria
**Vascular disorders:** Flushing, orthostatic hypotension

### 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Not applicable.

### 8.5 Post-Market Adverse Reactions

The following adverse events have been identified during post-authorization use of apomorphine. When these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Hematologic**: Hemolytic anemia requiring hospitalization has been reported with apomorphine treatment in the postmarketing setting (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Hemolytic Anemia).

# 9 DRUG INTERACTIONS

## 9.1 Serious Drug Interactions

| Serious Drug Interactions |
| --- |
| **5HT3 antagonists**: The concomitant use of drugs of the 5HT3 antagonist class is contraindicated. This includes antiemetics such as ondansetron. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension/Orthostatic Hypotension/Syncope, and 9.4 Drug-Drug Interactions, 5HT3 antagonists. |

## 9.2 Drug Interactions Overview

Apomorphine is a dopamine agonist and should be used only after due consideration in patients taking dopamine antagonists (e.g. neuroleptics). The hypotensive effect of apomorphine on systolic and diastolic blood pressure may be exacerbated by alcohol, and by other drugs such as 5HT3 receptor antagonists, antihypertensive agents, vasodilators, and nitroglycerin. The concomitant use of apomorphine with drugs that disrupt electrolyte levels should be avoided. Caution is advised in the concomitant use of other drugs that also prolong QTc interval.

There is a low potential for apomorphine to cause a drug-drug interaction due to competition for metabolizing enzymes or drug transporters, though it may induce CYP 1A2.

## 9.3 Drug-Behavioural Interactions

### Alcohol

In a study of healthy participants, concomitant administration of high dose (0.6 g/kg) or low dose (0.3 g/kg) ethanol with subcutaneous apomorphine caused greater decreases in blood pressure compared to subcutaneous apomorphine alone.

When high dose ethanol and subcutaneous apomorphine were concomitantly administered to participants, the mean largest decrease (the mean of each participant's largest drop in blood pressure measured within the 6-hour period following administration of subcutaneous apomorphine) for supine systolic and diastolic blood pressure was 9.1 mm Hg and 10.5 mm Hg, respectively. The mean largest standing systolic and diastolic blood pressure decrease was 11.3 mm Hg and 12.6 mm Hg, respectively. In some individuals, the decrease was as high as 61 mm Hg and 51 mm Hg, respectively, for standing systolic and diastolic blood pressure.

When low dose ethanol and subcutaneous apomorphine were concomitantly administered, the mean largest decrease in supine systolic and diastolic blood pressure was 10.2 mm Hg and 9.9 mm Hg, respectively. The mean largest decrease in standing systolic and diastolic blood pressure was 8.4 mm Hg and 7.1 mm Hg, respectively. In comparison, the mean largest decrease in supine systolic and diastolic blood pressure when subcutaneous apomorphine was administered alone was 6.1 mm Hg and 7.3 mm Hg, respectively, and in standing systolic and diastolic blood pressure was 6.7 mm Hg 8.4 mm Hg, respectively.

A similar study has not been performed with apomorphine sublingual film.

Patients should avoid drinking alcohol when using KYNMOBI (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

### 9.4 Drug-Drug Interactions

**Carbidopa/levodopa**

Levodopa pharmacokinetics were unchanged when subcutaneous apomorphine and levodopa were co-administrated in patients. However, motor response differences were significant. The threshold levodopa concentration necessary for an improved motor response was reduced significantly, leading to an increased duration of effect without a change in the maximal response to levodopa therapy.

**CYP1A2 Induction**

Apomorphine sulfate is the main metabolite of apomorphine. In *in vitro* studies using primary human hepatocyte cultures, apomorphine sulfate was shown to induce CYP1A2 in a concentration-dependent manner. Although induction results based on *in vitro* experiments are not necessarily predictive of response *in vivo*, caution needs to be exercised when apomorphine is coadministered with drugs that depend on this enzyme for clearance

**5HT3 Antagonists**

Based on reports of profound hypotension and loss of consciousness when subcutaneous apomorphine was administered with ondansetron during clinical trials, the concomitant use of apomorphine sublingual film with 5HT3 receptor antagonists including antiemetics (for example, ondansetron, granisetron, palonosetron) is contraindicated (see 2 CONTRAINDICATIONS; 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension/Orthostatic Hypotension/Syncope).

**Antihypertensive Medications and Vasodilators**

In pooled clinical studies, KYNMOBI-treated patients receiving concomitant antihypertensive medications or vasodilators (n = 209) compared to patients not receiving these concomitant drugs (n = 347) during titration experienced: orthostatic hypotension (3% vs 3%), fall (2% vs 2%) and hypotension (1% vs 3%) (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

**Nitroglycerin**

Caution is advised when using apomorphine in patients who are prescribed nitroglycerin. Patients taking apomorphine should lie down before and after taking sublingual nitroglycerin (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

In a study of healthy participants, concomitant administration of 0.4 mg sublingual nitroglycerin with subcutaneous apomorphine caused greater decreases in blood pressure compared to subcutaneous apomorphine alone. When nitroglycerin and subcutaneous apomorphine were concomitantly administered to healthy participants, the mean largest decrease (the mean of each subject's largest drop in blood pressure measured within the 6-hour period following administration of subcutaneous apomorphine) in supine systolic and diastolic blood pressure (measured over 6 hours) was 9.7 mm Hg and 9.3 mm Hg, respectively [see Clinical Pharmacology (12.3)]. The mean largest decrease in standing systolic and diastolic blood pressure was 14.3 mm Hg and 13.5 mm Hg, respectively. Some individuals experienced very large decreases in standing systolic and diastolic blood pressure, up to a maximum decrease of 65 mm Hg and 43 mm Hg, respectively. In comparison, the mean largest decrease in supine systolic and diastolic blood pressure when subcutaneous apomorphine was administered alone was 6.1 mm Hg and 7.3 mm Hg, respectively, and in standing systolic and diastolic blood pressure was 6.7 mm Hg and 8.4 mm Hg, respectively.

A similar study has not been performed with apomorphine sublingual film.

**Other QTc-Prolonging Drugs**

Caution should be exercised when prescribing apomorphine concomitantly with drugs that prolong the QT/QTc interval (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

In addition to the Class Ia and Class III antiarrhythmic drugs, other drugs that have been associated with QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples found below. Chemical/ pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QTc prolongation and/or torsades de pointes:

Class 1C antiarrhythmics (e.g., flecainide, propafenone); antipsychotics (e.g., chlorpromazine, haloperidol); antidepressants (e.g., fluoxetine, tricyclic/tetracyclic antidepressants e.g., amitriptyline, imipramine, maprotiline); opioids (e.g., methadone); macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, tacrolimus); quinolone antibiotics (e.g., ciprofloxacin); antimalarials (e.g., quinine, chloroquine); azole antifungals (e.g., ketoconazole); domperidone; 5HT3 receptor antagonists (e.g., ondansetron); kinase inhibitors (e.g., sunitinib); histone deacetylase inhibitors (e.g., vorinostat); beta-2 adrenoceptor agonists (e.g., salmeterol).

Current information sources should be consulted for more comprehensive lists of drugs that cause QTc prolongation.

**Drugs that Cause Electrolyte Depletion**

The concomitant use of apomorphine with drugs that can disrupt electrolyte levels should be avoided. Such drugs include, but are not limited to, the following:

- loop, thiazide, and related diuretics;
- laxatives and enemas;
- amphotericin B;
- high dose corticosteroids

**Dopamine Antagonists**

Since apomorphine is a dopamine agonist, it is possible that concomitant use of dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes), may diminish the effectiveness of apomorphine. Patients with major psychotic disorders, treated with neuroleptics, should be treated with dopamine agonists only if the potential benefits outweigh the risks.

**Other Drugs Eliminated Via Hepatic Metabolism**

The potential for apomorphine to interact with concomitant medications to cause a metabolism or transporter based drug-drug interaction is low.

**COMT Interactions**

A pharmacokinetic interaction of apomorphine with catechol-O-methyl transferase (COMT) inhibitors or drugs metabolized by this route is unlikely since apomorphine appears not to be metabolized by COMT.

### 9.5 Drug-Food Interactions

Interactions with food have not been established.

### 9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

### 9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

## 10 CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

Apomorphine is a non-ergoline dopamine agonist with high in vitro binding affinity for the dopamine D4 receptor, and moderate affinity for the dopamine $D_2$, $D_3$, and $D_5$, and adrenergic $\alpha 1_D$, $\alpha_{2B}$, $\alpha_{2C}$ receptors. The precise mechanism of action of apomorphine as a treatment for "OFF" episodes associated with Parkinson's disease is unknown, although it is believed to be due to stimulation of post-synaptic dopamine $D_2$-type receptors within the caudate-putamen in the brain.

### 10.2 Pharmacodynamics

**Prolongation of the QTc Interval**

The effects of KYNMOBI on the QTc interval were evaluated in a randomized, double-blind, positive- and placebo-controlled 3-period crossover study in 40 patients with Parkinson's disease. Patients were titrated with KYNMOBI to doses in the range of 10 mg to 60 mg based on efficacy and tolerability prior to entering the 3-way crossover period. In the randomised crossover phase, 36 subjects received apomorphine at therapeutic doses in the 10 mg to 25 mg range, 3 subjects received a supratherapeutic dose of 35 mg, and 1 subject received a supratherapeutic dose of 50 mg.

Apomorphine was associated with QTcF prolongation at the 60 min and 2 h post-dose time points, with a maximum difference from placebo in mean change from baseline QTcF of 6.2 ms (90% CI 2.7, 9.7) at 60 min.

**Decreases in Blood Pressure**

In the controlled clinical trial, 43% of KYNMOBI-treated patients and 36% of placebo-treated patients had a reduction of 20 mmHg or more for standing minus supine/sitting systolic blood pressure, or 10 mmHg or more for standing minus supine/sitting diastolic blood pressure.

In studies of healthy participants, effects on blood pressure were additive when subcutaneous apomorphine was concomitantly administered with nitroglycerin or alcohol.

Similar studies have not been performed with apomorphine sublingual film. See 9 DRUG INTERACTIONS

### 10.3 Pharmacokinetics

Pharmacokinetic data for KYNMOBI show that the peak concentration and exposure of apomorphine vary significantly between individuals, similar to the data from the subcutaneous formulations. The sources of the variation are not clear.

**Absorption**

Following sublingual administration of 15 mg of apomorphine, the time to maximum concentration (Tmax) ranged from 0.5 to 1 hour. Apomorphine exhibits less than dose proportional increase in exposures over a dose range of 10 mg to 35 mg (1.2 times the highest recommended dosage) following

a single sublingual administration of apomorphine sublingual film in patients with Parkinson's disease.

**Distribution:**

Following sublingual administration of 15 mg of apomorphine, the geometric mean (CV%) of the apparent volume of distribution was 3630 L (66%).

**Metabolism:**

Apomorphine is mainly metabolized in the liver. The major metabolic pathways for apomorphine are sulfation and glucuronidation by multiple sulfotransferase (SULT) and glycosyltransferase (UGT) enzymes with limited N-demethylation catalyzed by multiple enzymes, including CYP2B6, CYP2C8 and CYP3A4/5, followed by conjugation. The major metabolite for apomorphine is apomorphine sulfate, with apomorphine glucuronide and norapomorphine glucuronide as minor metabolites.

**Elimination**

Apomorphine metabolites are eliminated mainly in the urine. Following sublingual administration of 15 mg of apomorphine, the geometric mean (CV%) of the apparent clearance was 1440 L/h (68%), and the geometric mean of the terminal elimination half-life is about 1.7 hours (range about 0.8 hour to 3 hours).

**Special Populations and Conditions**

The apparent clearance of apomorphine does not appear to be influenced by age, gender, race, weight, duration of Parkinson's disease, levodopa dose, use of antiemetic, or duration of therapy.

- **Hepatic Insufficiency** Studies with KYNMOBI in patients with hepatic impairment have not been conducted. In a study with subcutaneous apomorphine comparing patients with hepatic impairment (moderately impaired as determined by the Child-Pugh classification method) to healthy matched volunteers, the $AUC_{0-\infty}$ and $C_{max}$ values were increased by approximately 10% and 25%, respectively, following a single administration.

  Data from the published literature and other publicly available sources indicate that in another study, utilizing sublingual tablet(s) of apomorphine in patients with mild, moderate or severe hepatic insufficiency based on the Child-Pugh classification, increases were observed in apomorphine mean $AUC_{0-\infty}$ and mean $C_{max}$ (Mean $AUC_{0-\infty}$ for mild, moderate and severe hepatic patients was 59%, 35%, and 68% higher; $C_{max}$ was 16%, 36%, and 62% higher, respectively than the estimates for patients with normal hepatic function) (see 4.2.5 Special Populations, Patients with Hepatic Impairment).

- **Renal Insufficiency** The impact of mild renal impairment on the pharmacokinetics of apomorphine sublingual films was evaluated using a population pharmacokinetic analysis, based on data collected in clinical studies, compared with patients with normal renal function. Results indicated the exposure estimates were similar. Studies with KYNMOBI in patients with moderate to severe renal impairment have not been conducted.

  In a study with subcutaneous apomorphine comparing renally-impaired patients (moderately impaired as determined by estimated creatinine clearance) to healthy matched volunteers, the $AUC_{0-\infty}$ and $C_{max}$ values were increased by approximately 16% and 50%, respectively, following a single administration. The mean time to peak concentrations and the mean terminal half-life of apomorphine were unaffected by the renal status of the individual.

  Data from the published literature and other publicly available sources indicate that in another study, where sublingual tablet(s) of apomorphine was administered, the mean $AUC_{0-\infty}$ of

apomorphine was increased by 4% in male patients with mild renal impairment (creatinine clearance ($CL_{cr}$) 40-80 mL/min/1.73 $m^2$), by 52% in moderate renal impairment ($CL_{cr}$ 10-40 mL/min/1.73 $m^2$) and by 67% in severe renal impairment ($CL_{cr}$ less than 10 mL/min/1.73 $m^2$) (see 4.2.5 Special Populations, Patients with Renal Impairment).

## 11 STORAGE, STABILITY AND DISPOSAL

Store KYNMOBI at 15 - 30°C.

Keep KYNMOBI in the foil pouch, protected from light, until ready to use.

## 12 SPECIAL HANDLING INSTRUCTIONS

None.

## PART II: SCIENTIFIC INFORMATION

## 13 PHARMACEUTICAL INFORMATION

### Drug Substance

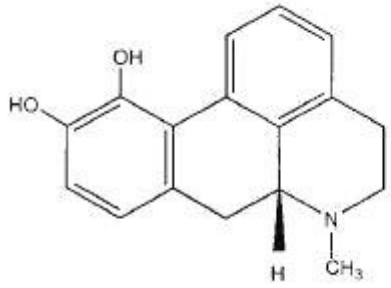
Proper name: apomorphine hydrochloride

Chemical name: 6aβ-Aporphine-10,11-diol hydrochloride hemihydrate

Molecular formula and molecular mass: $C_{17}H_{17}NO_2 \cdot HCL \cdot ½\ H2O$

312.79

Structural formula:




· HCl ·1/2 $H_2O$

Physicochemical properties: Apomorphine hydrochloride is white to grayish glistening crystals or white powder that is soluble in water at 80°C. The solubility profile of apomorphine hydrochloride is as follows:

| Solvent | Solubility |
|---|---|
| Water at 80°C | Soluble |
| Water | Sparingly soluble |
| Alcohol | Sparingly soluble |
| Chloroform | Very slightly soluble |
| Ether | Very slightly soluble |

## 14 CLINICAL TRIALS

### 14.1 Trial Design and Study Demographics

**Table 3 - Summary of patient demographics for clinical trials in "OFF" Episodes Associated with Parkinson's Disease**

| Study # | Trial design | Dosage, route of administration and duration | Study patients (n) | Mean age (Range) | Sex |
|---|---|---|---|---|---|
| CTH-300 (Study 1) | Randomized, double-blind, placebo-controlled, parallel-group Phase 3 study | KYNMOBI, 10 mg – 35 mg sublingually based on effective and tolerable dose<br>OR<br>Placebo<br>12 weeks | N = 109<br>KYNMOBI: 54<br>Placebo: 55 | 62.7 years (43 – 79 years)<br>41.3% ≥ 65 years | 62.4% males<br>37.6% females |

The efficacy of KYNMOBI in the acute treatment of "OFF" episodes associated with Parkinson's disease was studied in one randomized, double-blind, placebo-controlled, parallel-group study in 109 levodopa (L-dopa) responsive patients with Parkinson's disease complicated by motor fluctuations ("OFF" Episodes).

All patients in this study received concomitant levodopa at baseline and 51% of patients were using a concomitant oral dopaminergic agonist, 41% monoamine oxidase B inhibitors, 21% amantadine derivatives and 8% other dopaminergic agents.

Patients were at least 18 years of age (range 43 – 79 years) and had at least one well-defined "OFF" episode per day (mean 3.9 episodes per day) with a total daily "OFF" time duration of greater than or equal to 2 hours during the waking day. Patients with atypical or secondary Parkinson's disease, a major psychiatric disorder, clinically significant hallucinations and/or impulse control disorder(s) were excluded from the study.

Patients were titrated to an effective and tolerable dose of KYNMOBI, once the patient was confirmed to be in an "OFF" state after withholding their morning dose of levodopa. Patients were initiated with 10 mg of KYNMOBI. If the patient responded to the 10 mg KYNMOBI dose, they were randomized at that dose in a blinded fashion to KYNMOBI or matching placebo in a 1:1 ratio. If the patient tolerated the test dose but did not adequately respond, higher doses were administered on subsequent days in 5 mg increments, up to a maximum dose of 35 mg, until a full ON was achieved as determined by the investigator and the patient. Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS III) was measured pre-dose, and at 15, 30, 45, 60 and 90 minutes post-dose.

The primary endpoint of the study was mean change from pre-dose to 30 minutes post-dose in the MDS-UPDRS III at the 12-week visit of the maintenance treatment phase. Part III of MDS-UPDRS contains 18 items designed to assess the severity of the cardinal motor findings (e.g., tremor, rigidity, bradykinesia, postural instability, etc.) in patients with Parkinson's disease. The key secondary endpoint was the percentage of patients with a subject-rated full "ON" response within 30 minutes post-dose at the 12-week visit of the maintenance treatment phase. A full "ON", as assessed by the patient, was defined as: a period of time where medication was providing benefit with regard to mobility, stiffness

and slowness and where a patient felt he/she could perform normal daily activities; AND the response was comparable to or better than their normal response to PD medications prior to enrolling in the study.

Patients enrolled in the study were experiencing the following types of "OFF": morning akinesia (84.4%), wearing "OFF" (99.3%), delayed "ON" (66.0%), dose failure (42.6%) and sudden "OFF" (46.1%).

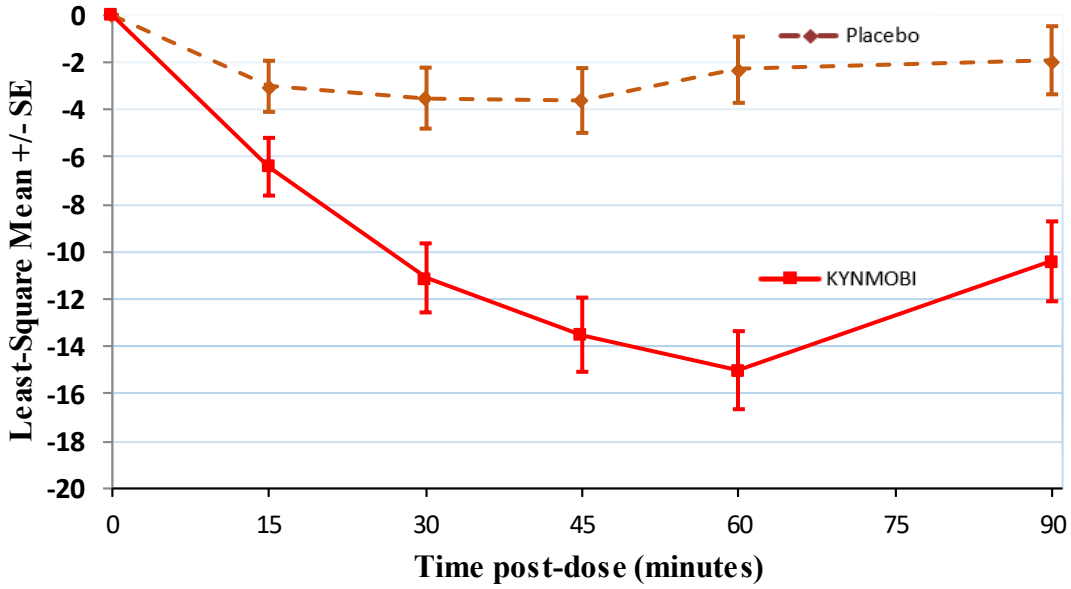
### 14.2 Study Results

The overall mean (SD) pre-dose MDS-UPDRS Part III score at the last titration visit at which the dose at randomization was given was 43.1 (14.71) points, with similar mean scores for the treatment groups that the patients were assigned to in the maintenance phase (placebo: 43.1 points ± 14.38; KYNMOBI: 43.2 points ± 15.17).

A total of 34 (63%) KYNMOBI-treated patients and 46 (84%) placebo-treated patients completed the week 12 visit. At the 12-week visit of the maintenance treatment phase, the KYNMOBI treatment group (using doses of 10 to 35 mg) showed a least squares (LS) mean improvement (i.e., reduction in score) from pre-dose MDS-UPDRS III score after 30 minutes post-dose of -11.1 points (95% CI: -14.0, -8.2) versus -3.5 points for the placebo group (95% CI: -6.1, -0.9). The LS mean treatment difference between KYNMOBI and placebo was -7.6 (95% CI: -11.5, -3.7; p = 0.0002).

Figure 1 describes the LS mean change in MDS-UPDRS III score from pre-dose over time for KYNMOBI and placebo at week 12.

**Figure 1 - Estimated Least Square Mean Change (± standard error) from Pre-dose in the MDS-UPDRS III Score to 15, 30, 45, 60 and 90 Minutes Post-dose at week 12 – Mixed Model for Repeated Measures (MMRM, modified Intent-to-Treat Population)**




The key secondary endpoint of the study was the percentage of patients with a subject-rated full "ON" response within 30 minutes at week 12. A higher percentage of patients on KYNMOBI achieved a subject-rated full "ON" response within 30 minutes at week 12 versus placebo.

## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL TOXICOLOGY

**Genotoxicity:** Apomorphine was mutagenic in the in vitro bacterial reverse mutation (Ames) and the in vitro mouse lymphoma thymidine kinase +/- assays. Apomorphine was clastogenic in the in vitro chromosomal aberration assay in human lymphocytes and in the in vitro mouse lymphoma thymidine kinase +/- assay. Apomorphine was negative in the in vivo micronucleus assay in mice.

**Carcinogenicity:** Lifetime carcinogenicity studies of apomorphine were conducted in male (0.1, 0.3, or 0.8 mg/kg/day) and female (0.3, 0.8, or 2 mg/kg/day) rats. Apomorphine was administered by subcutaneous injection for 22 months or 23 months, respectively. In males, there was an increase in Leydig cell tumors at the highest dose tested, which is less than the MRHD (20 mg) on a mg/m$^2$ basis. This finding is of questionable significance because the endocrine mechanisms believed to be involved in the production of Leydig cell tumors in rats are not relevant to humans. No drug-related tumors were observed in females; the highest dose tested is similar to the MRHD on a mg/m$^2$ basis.

In a 26-week carcinogenicity study in p53-knockout transgenic mice, there was no evidence of carcinogenic potential when apomorphine was administered by subcutaneous injection at doses up to 20 mg/kg/day (male) or 40 mg/kg/day (female).

**Reproductive and Developmental Toxicology:** Apomorphine was administered subcutaneously at doses up to 3 mg/kg/day (approximately 1.5 times the MRHD on a mg/m$^2$ basis) to male and female rats prior to and throughout the mating period and continuing in females through gestation day 6. There was no evidence of adverse effects on fertility or on early fetal viability. A significant decrease in testis weight was observed in a 39-week study in cynomolgus monkey at all subcutaneous doses tested (0.3, 1, or 1.5 mg/kg/day); the lowest dose tested is less than the MRHD on a mg/m$^2$ basis.

In a published fertility study, apomorphine was administered to male rats at subcutaneous doses of 0.2, 0.8, or 2 mg/kg prior to and throughout the mating period. Fertility was reduced at the highest dose tested.

No adverse developmental effects were observed when apomorphine (0.3, 1, or 3 mg/kg/day) was administered by subcutaneous injection to pregnant rats throughout organogenesis; the highest dose tested is 1.5 times the MRHD of 20 mg/day on a mg/m$^2$ basis. Administration of apomorphine (0.3, 1, or 3 mg/kg/day) by subcutaneous injection to pregnant rabbits throughout organogenesis resulted in an increased incidence of malformations of the heart and/or great vessels at the mid and high doses; maternal toxicity was observed at the highest dose tested. The no-effect dose for adverse developmental effects is less than the MRHD on a mg/m$^2$ basis.

Apomorphine (0.3, 1, or 3 mg/kg/day), administered by subcutaneous injection to females throughout gestation and lactation, resulted in increased offspring mortality at the highest dose tested, which was associated with maternal toxicity. There were no effects on developmental parameters or reproductive performance in surviving offspring. The no-effect dose for developmental toxicity (1 mg/kg/day) is less than the MRHD on a mg/m$^2$ basis.

## PATIENT MEDICATION INFORMATION

### READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

**PrKYNMOBI®**

**Apomorphine hydrochloride soluble film**

Read this carefully before you start taking **KYNMOBI** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **KYNMOBI**.

**Serious Warnings and Precautions**

**There have been reports of patients falling asleep suddenly, without warning, when taking drugs to treat Parkinson's disease that are similar to KYNMOBI.**

**While taking KYNMOBI, to avoid putting yourself and others at risk for serious injury or death, you should not:**

- **Drive**
- **Use machines, or**
- **Take part in activities that require you to be alert**

**If you start falling asleep suddenly, without warning, contact your healthcare professional right away.**

### What is KYNMOBI used for?

KYNMOBI is used, as needed, to treat OFF episodes in adults with Parkinson's disease. An OFF episode is when your Parkinson's movement symptoms (e.g., tremor, slowness, stiffness and difficulty moving) are unexpectedly not controlled by your regular Parkinson's medication. KYNMOBI is for use with other drugs to treat Parkinson's disease and does not replace the other drugs prescribed by your healthcare professional to treat your Parkinson's symptoms.

### How does KYNMOBI work?

KYNMOBI belongs to a group of drugs called dopamine agonists. It is not known exactly how it works. It seems to improve some of the chemical imbalance in the part of the brain affected by Parkinson's disease.

### What are the ingredients in KYNMOBI?

Medicinal ingredients: Apomorphine hydrochloride

Non-medicinal ingredients: disodium EDTA dihydrate, FD&C Blue #1, glycerin (natural), glyceryl monostearate, hydroxyethyl cellulose, hydroxypropyl cellulose, maltodextrin, menthol crystals, pyridoxine hydrochloride, sodium hydroxide, sodium metabisulfite, sucralose and white ink (ammonia, butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, shellac and titanium dioxide).

**KYNMOBI comes in the following dosage forms:**

Soluble films of 10 mg, 15 mg, 20 mg, 25 mg and 30 mg

**Do not use KYNMOBI if:**

- Are allergic to apomorphine hydrochloride or to any of the ingredients in KYNMOBI. KYNMOBI contains a sulfite called sodium metabisulfite. Sulfites can cause severe, life-threatening allergic reactions and asthma attacks in some people. If you have an allergic reaction to KYNMOBI you should not take it again.
- Are taking certain drugs used to treat nausea or vomiting such as ondansetron, granisetron and palonosetron. You could have very low blood pressure and loss of consciousness if you take KYNMOBI and these drugs.
- Have severe liver or kidney disease.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take KYNMOBI. Talk about any health conditions or problems you may have, including if you:**

- Have difficulty staying awake during the daytime
- Have suspicious, undiagnosed changed patches of pigmented skin, including irritated or irregular moles, or moles in which you have noticed changes or a history of skin cancer (melanoma)
- Have dizziness
- Have fainting spells
- Have asthma
- Have a history of fibrosis
- Are allergic to any medicines containing sulfites
- Have severe uncontrolled involuntary movements that can look like fidgeting, writhing or swaying called dyskinesia
- Have liver or kidney problems
- Have any unusual conditions related to your eyes or eyesight
- Have had a stroke or other brain problems
- Have any mental disorders or have seen or heard things that are not there (hallucinations)
- Drink alcohol
- Are pregnant or plan to become pregnant. It is not known if KYNMOBI will harm your unborn baby. KYNMOBI should not be used if you are pregnant.
- Are breastfeeding or plan to breastfeed. It is not known if KYNMOBI passes into your breast milk. You and your healthcare provider should decide if you will take KYNMOBI or breastfeed. You should not do both.

**Other warnings you should know about:**

- KYNMOBI can cause problems with your heart rhythm called QTc prolongation. You may have no symptoms or you may have dizziness, feeling like your heart has skipped or added a beat, fainting or seizures. If these symptoms continue, they can lead to sudden death. You may be more at risk if you have had or have:
    - a heart attack
    - congestive heart failure
    - an irregular heartbeat or heart rhythm
    - a blockage in one or more of your arteries that affects blood flow to your heart

- an abnormally rapid heart rate
- heart palpitations (feeling like your heart has skipped a beat or added an extra beat)
- a family history of sudden cardiac death at less than 50 years of age
- problems of electrocardiogram (ECG) abnormality called "Long QT syndrome"
- diabetes
- imbalances in the electrolytes in your body (potassium, magnesium and calcium)

- KYNMOBI may cause low blood pressure at any time or when you go from sitting or lying down to standing. Your blood pressure may be monitored while you are taking KYNMOBI especially if you are taking medication for high blood pressure, if you have a history of low blood pressure or if you have any heart problems.
- KYNMOBI can cause neuroleptic malignant syndrome. This is a disorder that causes you to have a high fever, confusion, altered states and stiffness in your muscles.
- When reducing your dose of KYNMOBI or stopping treatment, you may have withdrawal symptoms. These include lack of interest, anxiety, depression, fatigue, sweating, panic attacks, insomnia, irritability and pain.
- While taking KYNMOBI, you may have unusual urges and/or behaviors such as excessive:
  - gambling
  - sexual behavior
  - eating
  - spending

You or your caregiver should tell the healthcare professional if either of you notice that you have new or changes to your behavior.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**Serious Drug Interactions**

- Do NOT take KYNMOBI if you are taking certain drugs used to treat nausea or vomiting, such as ondansetron, granisetron and palonosetron.

**The following may interact with KYNMOBI:**

- Other medicines used to treat Parkinson's disease, including levodopa
- Alcohol. You should avoid alcohol when using KYNMOBI. It can worsen your side effects.
- Drugs to lower your blood pressure such as antihypertensive drugs or vasodilators
- Drugs that can affect the levels of electrolytes (salts) in your body:
  - Diuretics
  - Laxatives and enemas
  - Certain antibiotics
  - High doses of steroids
- Certain drugs that have an effect on your heart rate, such as:
  - antiarrhythmics (such as flecainide and propafenone)
  - antipsychotics (such as chlorpromazine and haloperidol)
  - antidepressants (such as fluoxetine and amitriptyline)
  - opioids (such as methadone)
  - some antibiotics (such as erythromycin, clarithromycin and ciprofloxacin)

- antimalarials (such as quinone and chloroquine)
- antifungals (such as ketoconazole)
- kinase inhibitors (such as sunitinib)
- histone deacetylase inhibitors (such as vorinostat)
- beta-2 adrenoceptor agonists (such as salmeterol)

- Nitroglycerin, a drug used to improve blood flow. It may decrease your blood pressure and cause dizziness. You should lie down before and after taking nitroglycerin under your tongue.

**How to take KYNMOBI:**

- KYNMOBI is for sublingual (under your tongue) use only.
- KYNMOBI must be taken whole. Do NOT cut, chew or swallow KYNMOBI.
- Your healthcare professional may prescribe another medicine called an antiemetic (e.g., domperidone) to take while you are using KYNMOBI. Antiemetic medicines may help to decrease the symptoms of nausea and vomiting that can happen with KYNMOBI.
- **Do not take** KYNMOBI until:
  - you have read and understand these instructions.
  - you have reviewed the steps with your healthcare professional on how to take it.
- You may need help from a caregiver to take KYNMOBI during your OFF episodes.

**Usual dose:**

Your healthcare professional will determine the right dose for you. Take it exactly as your healthcare professional has told you to. The usual starting dose of KYNMOBI is 10 mg. Depending on how you respond to KYNMOBI your healthcare professional may increase your dose 5 mg at a time to a maximum of 30 mg.

Take 1 film per OFF episode. Do not take another dose of KYNMOBI sooner than 2 hours after the last dose. Most patients need to take KYNMOBI 2 times a day. Do not take more than 5 films per day.

Do not change your dose of KYNMOBI or use it more often than prescribed unless your healthcare professional has told you to.

**<u>Instructions for Use:</u>**

Each KYNMOBI soluble film comes in a sealed foil pouch (see Figure A)

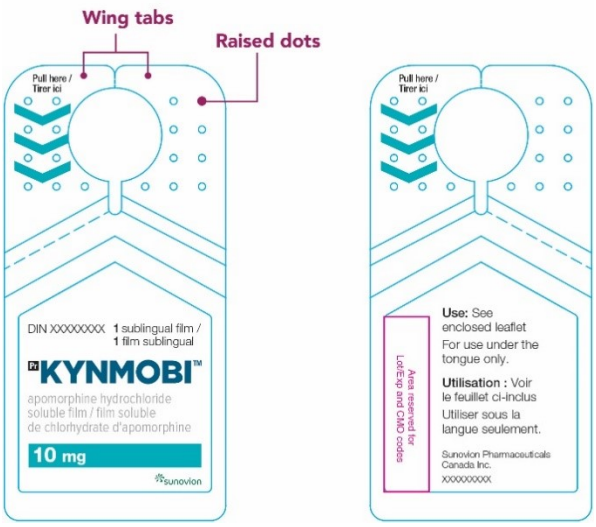


Figure A

**Step 1: Drink water and swallow excess water before taking the KYNMOBI film**. This helps the film dissolve more easily.

**Step 2: Open the KYNMOBI foil pouch.**

- Hold the wing tabs on the pouch between your thumb and finger of each hand. Make sure to place your fingers directly on the raised dots on each wing tab. Gently pull the tabs apart to open the pouch (see Figure B).

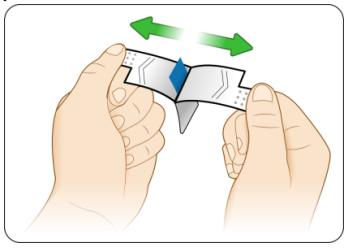


Figure B

**Step 3: Take the film out of the pouch.**

- Hold the film between your fingers by the outside edges and remove the entire film from the pouch (see Figure C).

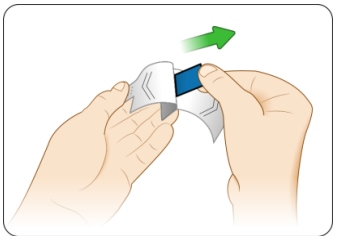


Figure C

**Step 4: Place the film on the underside of your tongue.**

- Place the film close to the base of your tongue, as far back as you can (see Figure D).
- Close your mouth.

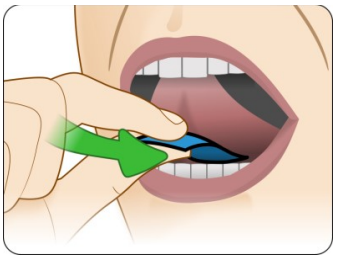


Figure D

**Step 5: Keep the film in place under your tongue until it has completely dissolved.**

- **Do not** chew or swallow the film.
- **Try not to** swallow your saliva.
- **Do not** talk while the film is dissolving because this can affect how well the medicine in KYNMOBI is absorbed (see Figure E).

Figure E

**Step 6: Visually check if the film completely dissolves, if possible.**

- You can use a mirror to check or ask someone to look under your tongue for you.
- It can take about 3 minutes for the film to dissolve.
- After the film completely dissolves, you may swallow.
- You may notice some leftover dye in your mouth after the film has dissolved.

**Overdose:**

If you think you, or a person you are caring for, have taken too much KYNMOBI, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

**Missed Dose:**

You should only use KYNMOBI during an OFF episode. If you are unable to take KYNMOBI during an OFF episode, you can take it at your next OFF episode.

**What are possible side effects from using KYNMOBI?**

These are not all the possible side effects you may have when taking KYNMOBI. If you experience any side effects not listed here, tell your healthcare professional.

Common side effects of KYNMOBI include:

- Nausea
- Vomiting
- Dizziness
- Dry mouth
- Fatigue
- Yawning
- Sleepiness
- Runny nose
- Increased sweating
- Headache
- Chills

| Serious side effects and what to do about them | | | |
|---|---|---|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| **VERY COMMON**<br>**Oral irritation:** redness, numbness, swelling, infection, ulceration, pain or dryness of mouth, lips or tongue | | X | |
| **COMMON**<br>**Dyskinesia:** severe uncontrolled movements, muscle twitching or unusual/abnormal movement of the face, tongue, or other parts of your body | | X | |
| Falls and injuries from falling | | X | |
| **Hallucinations or psychotic-like behavior:** seeing or hearing things that are not real, confusion, excessive suspicion, aggressive behavior, agitation, delusional beliefs and disorganized thinking | | X | |
| **Hypotension** (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up) | | X | |
| **Syncope:** fainting when standing up, temporary loss of consciousness | | X | |
| **UNCOMMON**<br>**Allergic reaction:** hives, itching, rash, swelling of the face, lips, mouth, tongue or throat, trouble breathing and/or swallowing, feeling sick to your stomach and throwing up | | X | |
| **RARE**<br>**Compulsive behavior:** inability to resist the impulse to perform an action that could be harmful such as gambling too much, increased sexual urges, uncontrollable urge to eat or spend money, or repeating meaningless actions | | X | |
| Excessive sleepiness or falling asleep suddenly, without warning, while doing normal activities | | X | |

| | | | |
|---|---|---|---|
| **Heart problems:** uneven (irregular) heart beat, palpitation, chest pain and/or discomfort, pain in jaw, shoulders, arm and/or back, shortness of breath, sweating, nausea or light-headedness | | X | |
| **Melanoma skin cancer:** changed patches of pigmented skin, including irritated or irregular moles, or moles in which you have noticed changes | | X | |
| **Neuroleptic Malignant Syndrome:** high fever, rapid or irregular heart beat, sweating, confusion, reduced consciousness and stiffness in your muscles | | X | |
| **Priapism:** long-lasting (greater than 4 hours in duration) and painful erection | | | X |
| **UNKNOWN**<br>**Hemolytic Anemia** (breakdown of red blood cells): pale skin, skin or eyes look yellow, dark coloured urine, feeling tired or weak, dizziness, fainting, rapid breathing, fever | | X | |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

Store KYNMOBI at room temperature (15° – 30°C). Keep KYNMOBI in the foil pouch, protected from light, until ready to use.

Keep out of reach and sight of children.

**If you want more information about KYNMOBI:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.sunovion.ca , or by calling 1-866-260-6291, or by visiting www.kynmobi.ca .

This leaflet was prepared by Sunovion Pharmaceuticals Canada Inc.

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