

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

Pr **KYNMOBI**<sup>TM</sup>

apomorphine hydrochloride

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

Antiparkinson Agent

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## RECENT MAJOR LABEL CHANGES

Not applicable

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## 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 KYNMOBI 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.

### 2 CONTRAINDICATIONS

Apomorphine hydrochloride is contraindicated in patients:

- Hypersensitive to apomorphine hydrochloride or to any ingredient (including sodium metabisulfite) in the formulation or component of the container (see **DOSAGE FORMS, 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 (apomorphine hydrochloride) should not take KYNMOBI again.
- Using concomitant drugs of the 5HT<sub>3</sub> antagonist class including antiemetics (e.g., ondansetron, granisetron, palonosetron) (see **DRUG INTERACTIONS**). There have been reports of profound hypotension and loss of consciousness when subcutaneous apomorphine was administered with ondansetron.
- With severe hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations**).
- With severe renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations**).

### 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

#### Serious Warnings and Precautions

##### 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.

### 4 DOSAGE AND ADMINISTRATION

#### 4.1 Dosing Considerations

- The initial dosing and administration instructions and titration should be conducted under medical supervision (especially in patients with a history of hypotension, cardiovascular disease or those who are currently using antihypertensive medication, and patients with renal and hepatic impairment).
- KYNMOBI (apomorphine hydrochloride) is for sublingual administration only. KYNMOBI must be administered whole. Do not cut, chew or swallow KYNMOBI.
- Pre-treatment with a concomitant antiemetic (e.g. domperidone) may be considered to minimize the risk of nausea and vomiting. The antiemetic can be started up to three days prior to the initial dose of KYNMOBI. 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 hydrochloride and drugs of the 5HT<sub>3</sub> antagonist class are contraindicated (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Gastrointestinal, and DRUG INTERACTIONS, Drug-Drug Interactions**).

## 4.2 Recommended Dose and Dosage Adjustment

### 4.2.1 Dosing Information

- The therapeutic dose range for KYNMOBI is 10 mg to 30 mg per dose, administered sublingually, as needed, for the acute, intermittent treatment of “OFF” episodes
- Doses 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. The total daily dose should not exceed 90 mg.
- Administer one film for one “OFF” episode. Do not repeat dosing even if the response is less than optimal.

### 4.2.2 Titration

The patient should be adequately instructed on how to use KYNMOBI to ensure proper administration and appropriate use (refer to the Patient Medication Information 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.

KYNMOBI must be titrated for optimal response and tolerability before starting the maintenance treatment. The recommended starting dose of KYNMOBI 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 KYNMOBI 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 **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 KYNMOBI un-aided.

If a single dose of KYNMOBI 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 KYNMOBI for a new “OFF” episode sooner than 2 hours after the last dose.

Treatment dose may require adjustment during the maintenance period, which should be

conducted under medical supervision. Treatment should be maintained with the lowest effective dose of KYNMOBI that provides 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.

Treatment should be discontinued when KYNMOBI is no longer effective or is associated with significant adverse effects. KYNMOBI 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. KYNMOBI 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.

### **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. KYNMOBI is not recommended in patients with moderate renal impairment unless the benefits outweigh potential risks. Use of KYNMOBI in patients with severe renal impairment is contraindicated (see **CONTRAINDICATIONS**).

#### **Patients with Hepatic Impairment**

No dose adjustment is required for patients with mild hepatic impairment. KYNMOBI is not recommended in patients with moderate hepatic impairment unless the benefits outweigh potential risks. Use of KYNMOBI in patients with severe hepatic impairment is contraindicated (see **CONTRAINDICATIONS**).

### **4.3 Administration**

KYNMOBI is indicated for sublingual administration only.

## **5 OVERDOSAGE**

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

For management of a suspected drug overdose, contact your regional poison control centre.
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## 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 10 mg apomorphine hydrochloride	Disodium EDTA Dihydrate, Emprove® (-)-Menthol Crystals, FD&C Blue #1 Granular (05603), glycerin (natural), Imwitor 491 glyceryl monostearate, maltodextrin M180, Natrosol 250G Pharm hydroxyethyl cellulose, Natrosol 250L Pharm hydroxyethyl cellulose, Nisso hydroxypropyl cellulose (HPC-SSL), pyridoxine hydrochloride, sodium hydroxide, sodium metabisulfite, sucralose, white ink
Sublingual	Soluble film 15 mg apomorphine hydrochloride	
Sublingual	Soluble film 20 mg apomorphine hydrochloride	
Sublingual	Soluble film 25 mg apomorphine hydrochloride	
Sublingual	Soluble film 30 mg apomorphine hydrochloride	

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 film contains the following inactive ingredients: ammonia, butyl alcohol, dehydrated alcohol, disodium EDTA dihydrate, FD&C Blue #1, glycerin (natural), glyceryl monostearate, hydroxyethyl cellulose, hydroxypropyl cellulose, isopropyl alcohol, maltodextrin, menthol crystals, potassium hydroxide, propylene glycol, pyridoxine hydrochloride, shellac, sodium hydroxide, sodium metabisulfite, sucralose and titanium dioxide. 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 the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

### General

#### **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.

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



Hypersensitivity adverse reactions may also occur during treatment with KYNMOBI (see **WARNINGS AND PRECAUTIONS, Hypersensitivity**).

### ***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 (see **ACTION AND 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.

## **Cardiovascular**

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

Dopamine agonists, including KYNMOBI, 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 KYNMOBI 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.

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 10 mmHg or more for standing minus supine/sitting diastolic blood pressure.

In pooled clinical studies, 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 and 2% during maintenance treatment experienced syncope.

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

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

### ***Nitroglycerin***

Caution is advised when using KYNMOBI in patients who are prescribed nitroglycerin. Patients taking KYNMOBI 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 **ACTION AND CLINICAL PHARMACOLOGY**). 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.

## **Connective Tissue**

### ***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 KYNMOBI, can cause these reactions is unknown.

## **Dependence**

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.

## **Gastrointestinal**

### ***Nausea and Vomiting***

KYNMOBI may cause nausea and vomiting when administered at recommended doses. Treatment with an antiemetic (e.g. domperidone) may be considered to minimize the risk of nausea or vomiting (see **DOSAGE AND ADMINISTRATION, Dosing Considerations**).

5HT<sub>3</sub> antagonists including antiemetics (for example, ondansetron, granisetron, palonosetron) are contraindicated (see **CONTRAINDICATIONS**).

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.

### **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, 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 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, KYNMOBI should be discontinued. The patients should not be rechallenged, as the reaction is likely to worsen (see **WARNINGS AND PRECAUTIONS, 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

### ***Somnolence***

During the titration phase of the controlled clinical study, somnolence was reported as an adverse reaction in 11% of patients treated with KYNMOBI. During the maintenance phase 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 and 9% during maintenance treatment experienced somnolence (see **ADVERSE REACTIONS**).

### ***Dyskinesias***

Apomorphine may cause dyskinesia or exacerbate pre-existing dyskinesia.

During the titration phase of the controlled clinical study, dyskinesia was reported as an adverse reaction in 1% of patients treated with KYNMOBI. During the maintenance phase 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 and 5% during maintenance treatment reported dyskinesia or worsening of dyskinesia. In the pooled clinical studies, 0% of KYNMOBI-treated patients during titration and 1% during maintenance 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. KYNMOBI 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 KYNMOBI 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 rat, 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 [ $\text{mg}/\text{m}^2$ ] 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 monkey at doses up to 1.5 mg/kg/day, a dose similar to the MRHD on a mg/m<sup>2</sup> basis. The clinical significance of the finding in rat has not been established but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (e.g., disk shedding) may be involved.

## **Psychiatric**

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

KYNMOBI 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 KYNMOBI (see **DRUG INTERACTIONS**).

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

During the maintenance phase 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.

In pooled clinical studies, 0.2% KYNMOBI-treated patients during titration and 4% during maintenance treatment 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, punting 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 KYNMOBI.

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

## **Sexual Health**

### ***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, there were less than 1% of KYNMOBI-treated male patients who reported priapism.

## **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 KYNMOBI 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 KYNMOBI in pregnant women. KYNMOBI 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/m<sup>2</sup> basis.

### **7.1.2 Breastfeeding**

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. KYNMOBI should not be used unless its potential benefits outweigh the risk and uncertainties.

### **7.1.3 Pediatrics**

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

### **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 KYNMOBI in patients with severe renal impairment is contraindicated (see **CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**).

### 7.1.6 Hepatic Impairment

Use of KYNMOBI in patients with severe hepatic impairment is contraindicated (see **CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**).

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

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 **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 and Maintenance 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) %
<b>Gastrointestinal disorders</b>			
Nausea	21	28	4
Oral/pharyngeal soft tissue swelling <sup>1</sup>	1	15	0
Oral/pharyngeal soft tissue pain and paraesthesia <sup>2</sup>	2	13	2
Oral ulceration and stomatitis <sup>3</sup>	2	7	0
Oral mucosal erythema	4	7	4
Vomiting	4	7	0
Dry mouth	1	6	0
<b>Nervous system disorders</b>			
Somnolence	11	13	2
Dizziness	11	9	0
Headache	8	6	0
<b>Respiratory, thoracic, and mediastinal disorders</b>			
Rhinorrhea	6	7	0
<b>General disorders and administration site conditions</b>			
Fatigue	3	7	0
<b>Injury, poisoning, and procedural complications</b>			
Fall	4	6	2
Laceration	1	6	0
<b>Skin and subcutaneous tissue disorders</b>			
Hyperhidrosis	4	6	4
<b>Immune system disorders</b>			
Hypersensitivity <sup>4</sup>	0	6	0

<sup>1</sup> Includes lip swelling, lip edema, oropharyngeal swelling, gingival edema, edema mouth, swollen tongue, and pharyngeal edema

<sup>2</sup> Includes throat irritation, glossodynia, oral pain, oral paresthesia, oropharyngeal pain, gingival pain, and oral hypoesthesia

<sup>3</sup> Includes lip ulceration, oral mucosal blistering, stomatitis, cheilitis, and tongue ulceration

<sup>4</sup> 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 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 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: 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. 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

## **9 DRUG INTERACTIONS**

### **9.1 Overview**

KYNMOBI is contraindicated with 5HT<sub>3</sub> antagonists (e.g., ondansetron, granisetron, palonosetron) (see **CONTRAINDICATIONS**).

### **9.2 Drug-Drug Interactions**

#### **Carbidopa/levodopa**

Levodopa pharmacokinetics were unchanged when subcutaneous apomorphine and levodopa were co-administered 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.

### **Apomorphine Sulfate**

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 KYNMOBI 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, the concomitant use of KYNMOBI with 5HT3 antagonists including antiemetics (for example, ondansetron, granisetron, palonosetron) is contraindicated (see **CONTRAINDICATIONS**).

### **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 **WARNINGS AND PRECAUTIONS, Cardiovascular**).

### **Nitroglycerin**

Caution is advised when using KYNMOBI in patients who are prescribed nitroglycerin. Patients taking KYNMOBI should lie down before and after taking sublingual nitroglycerin (see **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 KYNMOBI.

### **Other QTc-Prolonging Drugs**

Caution should be exercised when prescribing KYNMOBI concomitantly with drugs that prolong the QT/QTc interval (see **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; 5HT<sub>3</sub> 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 KYNMOBI 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 KYNMOBI 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 KYNMOBI. 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 KYNMOBI to interact with concomitant medications to cause a metabolism or transporter based drug-drug interaction is low.

### **COMT Interactions**

A pharmacokinetic interaction of subcutaneous 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.

## **9.3 Drug-Food Interactions**

Interactions with food have not been established.

## **9.4 Drug-Herb Interactions**

Interactions with herbal products have not been established.

## **9.5 Drug-Laboratory Test Interactions**

Interactions with laboratory tests have not been established.

## 9.6 Drug-Lifestyle 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 KYNMOBI.

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

## 10 ACTION AND CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

KYNMOBI is a non-ergoline dopamine agonist with high in vitro binding affinity for the dopamine D<sub>4</sub> receptor, and moderate affinity for the dopamine D<sub>2</sub>, D<sub>3</sub>, and D<sub>5</sub>, and adrenergic  $\alpha_{1D}$ ,  $\alpha_{2B}$ ,  $\alpha_{2C}$  receptors. The precise mechanism of action of KYNMOBI 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<sub>2</sub>-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 randomized crossover phase, 36 subjects received apomorphine at therapeutic doses in the 10 mg to 25 mg range, 3 subjects received a suprathreshold dose of 35 mg, and 1 subject received a suprathreshold 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 KYNMOBI (see **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 (T<sub>max</sub>) 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 KYNMOBI 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 KYNMOBI 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 KYNMOBI 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.

**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<sup>2</sup>), by 52% in moderate renal impairment ( $CL_{cr}$  10-40 mL/min/1.73 m<sup>2</sup>) and by 67% in severe renal impairment ( $CL_{cr}$  less than 10 mL/min/1.73 m<sup>2</sup>) (see **DOSAGE AND ADMINISTRATION**).

**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 **DOSAGE AND ADMINISTRATION**).

## 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

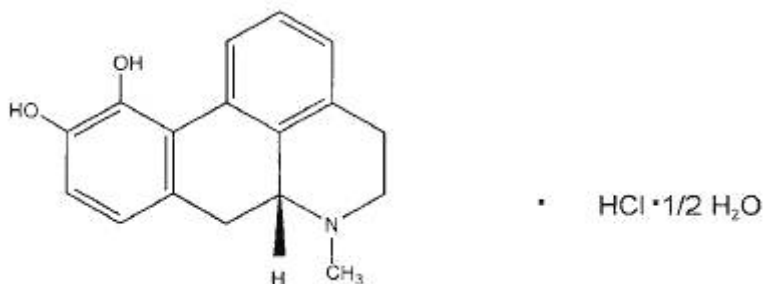
Proper name: Apomorphine hydrochloride

Chemical name: 6 $\beta$ -Aporphine-10,11-diol hydrochloride hemihydrate

Molecular formula: C<sub>17</sub>H<sub>17</sub>NO<sub>2</sub> · HCL · ½ H<sub>2</sub>O

Molecular mass: 312.79

Structural formula:



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 OR Placebo 12 weeks	N = 109 KYNMOBI: 54 Placebo: 55	62.7 years (43 – 79 years) 41.3% ≥ 65 years	62.4% males 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%).

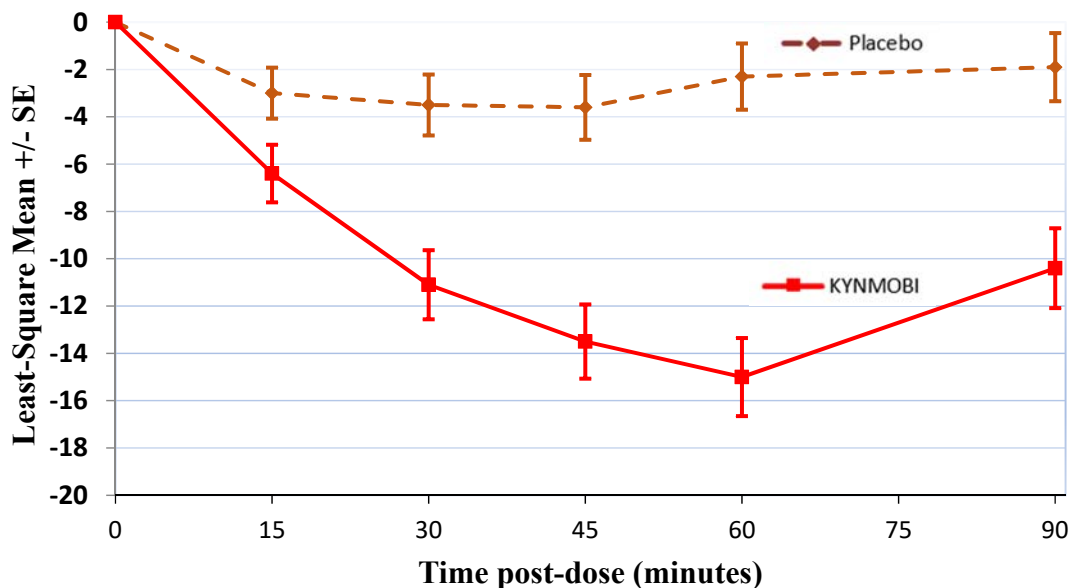
## 14.2 Study Results

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  $\pm$  14.38; KYNMOBI: 43.2 points  $\pm$  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 ( $\pm$  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 NON-CLINICAL TOXICOLOGY

### 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<sup>2</sup> 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<sup>2</sup> 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).

### Mutagenicity

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.

### 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> basis.

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**  
**PATIENT MEDICATION INFORMATION**

Pr**KYNMOBI**<sup>™</sup>  
**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**

**You can suddenly fall asleep without any warning while taking KYNMOBI. You should not:**

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

**You may put yourself and others at risk for serious injury or death.**

**If this happens to you, contact your doctor right away.**

**Falling asleep suddenly without warning has been reported in patients taking other similar drugs to treat Parkinson's disease.**

**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 doctor 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: ammonia, butyl alcohol, dehydrated alcohol, disodium EDTA dihydrate, FD&C Blue #1, glycerin (natural), glyceryl monostearate, hydroxyethyl cellulose, hydroxypropyl cellulose, isopropyl alcohol, maltodextrin, menthol crystals, potassium hydroxide, propylene glycol, pyridoxine hydrochloride, shellac, sodium hydroxide, sodium metabisulfite, sucralose 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 you:**

- 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 doctor 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.**

**The following may interact with KYNMOBI:**

- Other medicines used to treat Parkinson’s disease, including levodopa
- Drugs used to treat nausea or vomiting called 5HT3 antagonists such as ondansetron, granisetron and palonosetron
- 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 doctor 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 doctor will determine the right dose for you. Take it exactly as your doctor has told you to. The usual starting dose of KYNMOBI is 10 mg. Depending on how you respond to KYNMOBI your doctor 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 doctor has told you to.

**Instructions for Use:**

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

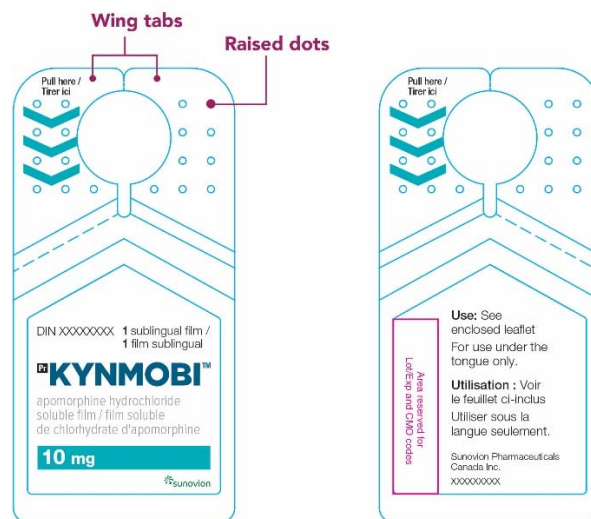


Figure A

**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).

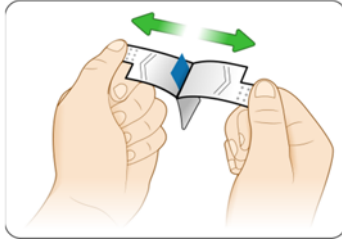


Figure B

**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).

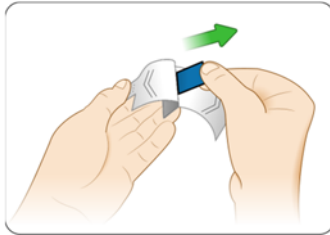


Figure C

**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.

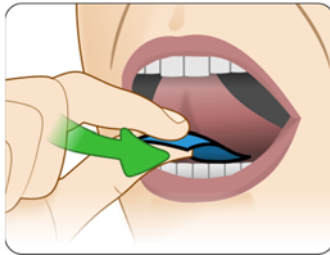


Figure D

**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 have taken too much KYNMOBI, contact your 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 feel when taking KYNMOBI. If you experience any side effects not listed here, contact your healthcare professional.

Common side effects of KYNMOBI include:

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

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>VERY COMMON</b> Oral irritation: redness, numbness, swelling, infection, ulceration, pain or dryness of mouth, lips or tongue		X	
<b>COMMON</b> Falls and injuries from falling		X	
Dyskinesia: severe uncontrolled movements		X	
Syncope: fainting when standing up		X	
Low blood pressure: dizziness, fainting, light-headedness when rising to a sitting or standing position.		X	



<b>UNCOMMON</b> 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	
Allergic reaction: hives, itching, rash, swelling of the face, lips, mouth, tongue or throat, trouble breathing and/or swallowing		X	
<b>RARE</b> 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	
Uneven (irregular) heart beat, palpitation, chest pain and/or discomfort, pain in jaw, shoulders, arm and/or back, shortness of breath, sweating, nausea or lightheadedness		X	
Neuroleptic Malignant Syndrome: high fever, confusion, altered states and stiffness in your muscles		X	
Skin cancer (melanoma): changed patches of pigmented skin, including irritated or irregular moles, or moles in which you have noticed changes		X	
Priapism: prolonged painful erection			X
Excessive sleepiness or falling asleep while doing normal activities		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, talk to 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://health-products.canada.ca/dpd-bdpp/index-eng.jsp>), the manufacturer's website [www.sunovion.ca](http://www.sunovion.ca), by calling 1-866-260-6291, or by visiting [www.kynmobi.ca](http://www.kynmobi.ca).

This leaflet was prepared by Sunovion Pharmaceuticals Canada Inc.

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