

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1 NAME OF THE MEDICINAL PRODUCT**

Treatment Initiation Pack

Kynmobi 10 mg sublingual film

Kynmobi 15 mg sublingual film

Kynmobi 20 mg sublingual film

Kynmobi 25 mg sublingual film

Kynmobi 30 mg sublingual film

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film contains 10 mg, 15 mg, 20 mg, 25 mg or 30 mg of apomorphine hydrochloride (equivalent to 8.8 mg, 13.2 mg, 17.6 mg, 22.0 mg, and 26.4 mg of apomorphine, respectively).

#### Excipient(s) with known effect

Each film of 10 mg, 15 mg, 20 mg, 25 mg and 30 mg contains 0.27 mg, 0.40 mg, 0.54 mg, 0.67 mg and 0.81 mg of metabisulphite, respectively, and contains less than 1 mmol of sodium (23 mg) per dose.

For the full list of excipients, see section 6.1.

### **3 PHARMACEUTICAL FORM**

Sublingual film

Kynmobi sublingual film is a blue to green rectangular film with a white printed number identifying the strength (e.g., “10” is 10 mg).

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Kynmobi is indicated for the intermittent treatment of “OFF” episodes in adult patients with Parkinson’s disease (PD) which are not sufficiently controlled by oral anti-Parkinson medication.

### 4.2 Posology and method of administration

#### Selection of patients suitable for Kynmobi

Patients selected for treatment with Kynmobi should be able to recognise the onset of their “OFF” symptoms.

If domperidone (an antiemetic) is considered medically warranted, then the lowest effective domperidone dose should be utilized and discontinued as soon as possible. Before the decision to initiate domperidone and apomorphine treatment, risk factors for QT interval prolongation in the individual patient should be carefully assessed to ensure that the benefit outweighs the risk (see section 4.5).

Kynmobi should be initiated in the controlled environment of a specialist clinic. The patient should be supervised by a trained healthcare professional experienced in the treatment of PD (eg. Neurologist).

#### Posology

##### *Titration*

The appropriate dose for each patient is established by incremental dosing schedules. The following schedule is recommended.

The initial dose of Kynmobi is 10 mg. Dose initiation should occur when the patient is having an “OFF” episode. If the patient tolerates the 10 mg dose, and responds adequately (satisfactory motor response within 30 minutes), the maintenance dose should be 10 mg. If the dose is tolerated but the response is insufficient, continue to titrate in 5 mg increments when the patient is having an “OFF” episode and assess response until an effective and tolerable dose is achieved up to a maximum of 30 mg per dose, up to five times a day. The minimal interval between doses is 2 hours, with no more than one dose of Kynmobi for an “OFF” episode.

Kynmobi is available as a treatment initiation pack, containing two sublingual films of each strength. The treatment initiation pack is usually used at the start of treatment to find an effective and tolerable dose. Depending on the patient response not all doses in this pack may be needed.

If an “ON” response is achieved, consider further up-titration as tolerated to achieve a better ‘ON’ response if clinically warranted.

##### *Maintenance*

Once the appropriate dose is determined Kynmobi may be taken, as needed, up to 30 mg up to five times a day. The minimal interval between doses is 2 hours. The total maximum daily dose is 150 mg.

The optimal dose of Kynmobi once established, remains relatively constant for each patient.

#### Special populations

##### *Elderly*

The elderly are well represented in the population of patients with PD and constitute a high proportion of those studied in clinical studies of Kynmobi. The management of elderly patients treated with Kynmobi has not differed from that of younger patients. There is a higher risk of postural hypotension in elderly patients, therefore particular caution should be exercised during the initiation of treatment.

##### *Renal impairment*

No dose adjustment is required for patients with mild or moderate renal impairment. There is no clinical experience in patients with severe renal impairment. The use of Kynmobi is not recommended in patients with severe and end-stage renal disease (ESRD) (CLcr <30 mL/min).

##### *Hepatic impairment*

There is no clinical experience in patients with hepatic impairment, therefore the use of Kynmobi is not recommended in these patients (see section 5.2.).

#### Paediatric population

There is no relevant use of Kynmobi in the paediatric population for the indication of Parkinson's disease and motor fluctuations.

#### Method of administration

For sublingual use.

The sublingual film should dissolve under the tongue. It must be administered whole, must not be cut, chewed, or swallowed.

### **4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Co-administration with 5HT<sub>3</sub> antagonists (e.g. granisetron, dolasetron, palonosetron and alosetron) (see section 4.5).
- Concomitant use with ondansetron (see section 4.5)

- Dementia;
- Psychotic disorder;
- Cankers or mouth sores
- Hepatic impairment
- Respiratory depression

#### **4.4 Special warnings and precautions for use**

Kynmobi should be given with caution to patients with pulmonary or cardiovascular disease and persons prone to nausea and vomiting.

##### *Syncope, hypotension or orthostatic hypotension*

Kynmobi may cause syncope, hypotension or orthostatic hypotension. Patients should be instructed to rise slowly after sitting or lying down after taking Kynmobi. Care should be exercised in patients with pre-existing postural hypotension. The hypotensive effects of Kynmobi may be increased by the concomitant use of antihypertensive medications, vasodilators (especially nitrates) and alcohol (see section 4.5).

##### *Cardiac symptoms and other related disorders*

The patient should be instructed to report possible cardiac symptoms including palpitations, syncope, or near-syncope. They should also report clinical changes that could lead to hypokalaemia, such as gastroenteritis or the initiation of diuretic therapy.

##### *QTc prolongation and potential for proarrhythmic effects*

Since apomorphine, especially at high doses, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for *torsades de pointes* arrhythmia.

Palpitations and syncope may signal the occurrence of an episode of *torsades de pointes*. The risks and benefits of Kynmobi treatment should be considered prior to initiating treatment with Kynmobi in patients with risk factors for prolonged QTc.

##### *Oropharyngeal adverse events*

Kynmobi may cause oral mucosal irritation, including erythema in the oral cavity (tongue, lips, gingiva), oral soft tissue swelling (lips, tongue, gingiva), and infrequently systemic hypersensitivity, including facial flushing, increased lacrimation, swelling of the face, or urticaria. It is not known whether these events are related to apomorphine, or any other excipient. Kynmobi rechallenge is not recommended after discontinuation as oral adverse reactions may recur and be more severe than the initial reaction.

### *Neuropsychiatric disorders*

Neuropsychiatric problems co-exist in many patients with advanced Parkinson's disease. There is evidence that for some patients, neuropsychiatric disturbances may be exacerbated by apomorphine. Special care should be exercised when apomorphine is used in these patients. Kynmobi should not be considered for patients with a major psychotic disorder unless the potential benefits outweigh the risks and uncertainties.

### *Sudden onset of sleep and somnolence*

Apomorphine has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution whilst driving or operating machines during treatment with apomorphine. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines (see section 4.7). Furthermore, a reduction of dose may be considered.

### *Impulse control disorders*

Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating, and compulsive eating can occur in patients treated with dopamine agonists including apomorphine. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

### *Dopamine dysregulation Syndrome (DDS)*

This is an addictive disorder resulting in excessive use of the medicinal product seen in some patients treated with apomorphine. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS.

### *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.

### *Neuroleptic malignant syndrome*

A symptom complex resembling neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, elevated serum creatine kinase, and autonomic instability) with no other obvious aetiology has been reported in association with rapid dose reduction, withdrawal of, or changes in antiparkinsonian therapy.

#### *Haemolytic anaemia and thrombocytopenia*

Haemolytic anaemia and thrombocytopenia have been reported in patients treated with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa, when given concomitantly with apomorphine.

#### *Others*

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.

#### *Excipients*

Kynmobi contains sodium metabisulphite, which may rarely cause severe allergic reactions and bronchospasm. This medicinal product contains less than 1 mmol sodium (23 mg) per film, i.e. essentially “sodium-free”.

### **4.5 Interaction with other medicinal products and other forms of interaction**

Concomitant use of 5HT<sub>3</sub> antagonists, including antiemetics, is contraindicated. There have been reports of profound hypotension and loss of consciousness when subcutaneous apomorphine was administered with a 5HT<sub>3</sub> antagonist (e.g. granisetron, dolasetron, palonosetron and alosetron) (see section 4.3).

Concomitant use of apomorphine with ondansetron may lead to severe hypotension and loss of consciousness and is therefore contraindicated (see section 4.3). Such effects might also occur with other 5-HT<sub>3</sub> antagonists.

Patients selected for treatment with Kynmobi are almost certain to be taking concomitant medications for their Parkinson's disease. In the initial stages of therapy, the patient should be monitored for unusual side-effects or signs of potentiation of effect.

Neuroleptic medicinal products may have an antagonistic effect if used with apomorphine. Certain medications used to treat psychosis may exacerbate the symptoms of PD and may decrease the effectiveness of Kynmobi. Special care should be exercised when apomorphine is used in these patients. There is a potential interaction between clozapine and apomorphine, however clozapine may also be used to reduce the symptoms of neuropsychiatric complications.

When apomorphine is used in combination with domperidone, risk factors in the individual patient should be carefully assessed. This should be done before treatment initiation, and during treatment. Important risk factors include serious underlying heart conditions such as congestive cardiac failure, severe hepatic impairment or significant electrolyte disturbance. Also, medication possibly affecting electrolyte balance, CYP3A4 metabolism or QT interval should be assessed. Monitoring for an effect on the QTc interval is advisable. An ECG should be performed prior to treatment with domperidone, during the treatment initiation phase or as clinically indicated thereafter.

The hypotensive effects of Kynmobi may be increased by the concomitant use of alcohol, antihypertensive medications, vasodilators (especially nitrates) and cardiac active medicinal products even when co-administered with domperidone (see Section 4.4.). Patients should avoid alcohol when using Kynmobi. Monitor blood pressure for hypotension and orthostatic hypotension in patients taking Kynmobi with concomitant antihypertensive medications and/or vasodilators.

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 at the maximum daily dosage is coadministered with drugs that depend on this enzyme for clearance.

The possible effects of apomorphine on the plasma concentrations of other medicinal products have not been studied. Therefore, caution is advised when combining apomorphine with other medicinal products, especially those with a narrow therapeutic range.

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy

There are no or limited amount of data from the use of apomorphine in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Kynmobi is not recommended during pregnancy and in women of childbearing potential not using contraception.

##### Breast-feeding

It is unknown whether apomorphine /metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Kynmobi therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

##### Fertility

Apomorphine did not affect fertility in rats (see section 5.3).

#### **4.7 Effects on ability to drive and use machines**

Kynmobi has moderate influence on the ability to drive and use machines.

Apomorphine may cause dizziness, symptomatic orthostatism, and somnolence. Therefore, caution should be exercised when driving or using machines. Patients being treated with apomorphine and presenting with somnolence and/or sudden sleep

episodes must be informed to refrain from driving or engaging in activities (e.g. operating machines) where impaired alertness may put themselves or others at risk of serious injury or death until such recurrent episodes and somnolence have resolved (see sections 4.4 and 4.8).

## 4.8 Undesirable effects

### Summary of the safety profile

The most common adverse reactions reported in pooled analyses for two phase II and two phase III clinical studies were nausea (20.5%) during titration phase, and nausea (22.0%), somnolence (8.5%) and dizziness (5.9%) during maintenance phase. Oropharyngeal adverse events (swelling, oedema, pain, irritation, ulceration) were also commonly observed in the patients treated with Kynmobi.

### Tabulated summary of adverse reactions

Adverse reactions are presented by system organ class and frequency in Table 1 below. Frequency categories are defined as follows: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), unknown (cannot be estimated from the available data).

*Table 1: Adverse Drug Reactions Based Upon Pooled Data from phase II and III studies*

|                                           | <b>Very Common</b> | <b>Common</b>    | <b>Uncommon</b>                                                                     | <b>Rare</b> | <b>Unknown</b>                                                                       |
|-------------------------------------------|--------------------|------------------|-------------------------------------------------------------------------------------|-------------|--------------------------------------------------------------------------------------|
| <b>Infections and infestations</b>        |                    | Oral candidiasis | Gingivitis                                                                          |             |                                                                                      |
| <b>Immune system disorders</b>            |                    |                  | Hypersensitivity                                                                    |             |                                                                                      |
| <b>Metabolism and nutrition disorders</b> |                    |                  | Decreased appetite                                                                  |             |                                                                                      |
| <b>Psychiatric disorders</b>              |                    | Hallucination    | Anxiety<br>Confusional state<br>Obsessive-compulsive disorder<br>Psychotic disorder |             | Impulse control disorders:<br>Gambling disorder<br>Libido increased<br>Hypersexualit |

|                                                        |                                                                                                  |                                                                                                                                                                       |                                                                                                                                   |  |                                                        |
|--------------------------------------------------------|--------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|--|--------------------------------------------------------|
|                                                        |                                                                                                  |                                                                                                                                                                       | Dopamine dysregulation syndrome<br>Agitation                                                                                      |  | y<br>Compulsive shopping<br>Binge eating<br>Aggression |
| <b>Nervous system disorders</b>                        | Somnolence                                                                                       | Dizziness<br>Dyskinesia<br>Headache<br>Syncope                                                                                                                        | Drooling<br>Sedation<br>Sudden onset of sleep                                                                                     |  |                                                        |
| <b>Eye disorders</b>                                   |                                                                                                  | Vision blurred                                                                                                                                                        | Lacrimation increased                                                                                                             |  |                                                        |
| <b>Cardiac disorders</b>                               |                                                                                                  |                                                                                                                                                                       | Cardiac arrest<br>Atrial fibrillation                                                                                             |  |                                                        |
| <b>Vascular disorders</b>                              |                                                                                                  | Orthostatic hypotension<br>Hypotension<br>Hot flush<br>Hypertension<br>Flushing                                                                                       | Pallor                                                                                                                            |  |                                                        |
| <b>Respiratory, thoracic and mediastinal disorders</b> | Yawning                                                                                          | Rhinorrhoea<br>Dyspnoea                                                                                                                                               | Nasal congestion                                                                                                                  |  |                                                        |
| <b>Gastrointestinal disorders</b>                      | Nausea<br>Oral soft tissue signs and symptoms*<br>Stomatitis and ulceration<br>Tongue conditions | Vomiting<br>Oral soft tissue swelling and oedema<br>Oral dryness and saliva altered<br>Oral soft tissue disorder<br>Retching<br>Gingival disorder, signs and symptoms | Angular cheilitis<br>Constipation<br>Dyspepsia<br>Eructation<br>Dysphagia<br>Tooth discoloration<br>Dental caries<br>Tongue polyp |  |                                                        |
| <b>Skin and subcutaneous tissue</b>                    |                                                                                                  | Rash<br>Hyperhidrosis                                                                                                                                                 |                                                                                                                                   |  |                                                        |

|                                                             |  |                                                       |                                                                                |              |  |
|-------------------------------------------------------------|--|-------------------------------------------------------|--------------------------------------------------------------------------------|--------------|--|
| <b>disorders</b>                                            |  | Cold sweat                                            |                                                                                |              |  |
| <b>Reproductive system and breast disorders</b>             |  |                                                       | Spontaneous penile erection                                                    |              |  |
| <b>General disorders and administration site conditions</b> |  | Fatigue<br>Feeling abnormal<br>Feeling cold<br>Chills | Malaise<br>Asthenia<br>Feeling drunk<br>Oedema peripheral                      |              |  |
| <b>Investigations</b>                                       |  |                                                       | Heart rate decreased<br>Vitamin B6 increased<br>Electrocardiogram QT prolonged |              |  |
| <b>Injury, poisoning, and procedural complications</b>      |  | Fall                                                  |                                                                                |              |  |
| <b>Blood and lymphatic system disorders</b>                 |  |                                                       | Haemolytic anaemia and thrombocytopenia                                        | Eosinophilia |  |
| <b>Investigations</b>                                       |  |                                                       | Positive coombs' test                                                          |              |  |

#### Oropharyngeal Adverse Events (\*)

As Kynmobi is administered sublingually, irritation, erythema, oedema, ulceration, pain, para/dysesthesias of oral cavity, teeth colour change, caries, changes in salivary gland secretion were observed in clinical studies. Oral soft tissue sign and symptoms\* commonly observed in patients treated with Kynmobi, included oral mucosal erythema, hypoaesthesia oral, oral discomfort, oral mucosal blistering, and uncommonly oral contusion, lip exfoliation, oral dysaesthesia, oral hyperaesthesia, oral mucosal discolouration and oral mucosal exfoliation.

These events were mild to moderate in severity. For most subjects, events were tolerated or resolved either spontaneously or soon after discontinuation of treatment. Kynmobi rechallenge is not recommended after discontinuation as oral adverse reactions may recur and be more severe than the initial reaction.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions

via Yellow Card Scheme Website: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

## **4.9 Overdose**

There is little clinical experience of overdose with apomorphine by the sublingual route of administration. Symptoms of overdose may be treated empirically as suggested below:

- excessive emesis may be treated with domperidone
- respiratory depression may be treated with naloxone
- hypotension: appropriate measures should be taken, e.g. raising the foot of the bed
- bradycardia may be treated with atropine

# **5 PHARMACOLOGICAL PROPERTIES**

## **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Dopamine agonists, ATC code: N04BC07

### Mechanism of action

Apomorphine is a direct stimulant of dopamine receptors and while possessing both D1 and D2 receptor agonist properties does not share transport or metabolic pathways with levodopa.

Although in intact experimental animals, administration of apomorphine suppresses the rate of firing of nigro-striatal cells and in low dose has been found to produce a reduction in locomotor activity (thought to represent pre-synaptic inhibition of endogenous dopamine release) its actions on parkinsonian motor disability are likely to be mediated at post-synaptic receptor sites. This biphasic effect is also seen in humans.

### Clinical Efficacy and Safety

The efficacy and safety of Kynmobi (apomorphine sublingual) in the intermittent treatment of “OFF” episodes in adult patients with Parkinson’s disease (PD) has been demonstrated in two Phase III studies, one double-blind, placebo-controlled (Study 1) and one open-label, randomized, crossover, active-comparator (subcutaneous apomorphine) trial utilising a single-blinded rater (Study 2). These studies were similar in design in that each had a titration phase in which subjects were titrated to an effective and tolerable dose, ranging from 10 mg to 35 mg of Kynmobi (Study 1),

and from 10 mg to 30 mg (Study 2). Titration phase was followed by a maintenance phase of 12 weeks (Study 1) or 4 weeks (Study 2). Clinical and safety experience of subcutaneous apomorphine hydrochloride in Parkinson's disease was also considered to support the indication of Kynmobi.

In Study 1, a total of 109 subjects were randomized in the Maintenance Treatment Phase (54 Kynmobi and 55 placebo). The mean age of subjects was 62.7 years (range 43 to 79 years). The mean time since diagnosis of PD was 9.0 years (range 2 to 22 years), and the mean time since onset of motor fluctuations was 4.61 years (range 0.5 to 22 years). At study entry, subjects typically experienced a mean of 3.9 "OFF" episodes daily. Subjects had disease severity stages 1 to 3 (modified Hoehn and Yahr) at ON, with majority in stage 2 (72.5%). All subjects in this study received concomitant levodopa/DDCI at baseline with a median dose levodopa of 950 mg per day. 56% of subjects were using a concomitant dopamine agonist, 42% monoamine oxidase B inhibitors, 22% amantadine derivatives, and 9.2% other dopaminergic agents (including COMT inhibitors).

The primary endpoint in Study 1, mean change from pre-dose in the MDS-UPDRS Part III score at 30 minutes after dosing at Week 12, was statistically significant in favour of Kynmobi versus placebo (LS mean difference: -7.6; 95% CI: -11.5, -3.7;  $P = 0.0002$ ) (Table 2). The percentage of subjects achieving a subject-rated full ON response within 30 minutes at Week 12 was statistically superior with Kynmobi vs placebo in the clinic ( $P=0.0426$ ; key secondary endpoint).

*Table 2: Change from Pre-dose in the MDS-UPDRS Part III Score at 30 Minutes Post-dose at Week 12 of Maintenance Treatment Phase (mITT Population) (Study 1)*

| Visit   | Statistic <sup>a)</sup>                     | Placebo<br>(N = 55) | Kynmobi<br>(N = 54) |
|---------|---------------------------------------------|---------------------|---------------------|
| Week 12 | LS Mean (SE)                                | -3.5 (1.29)         | -11.1 (1.46)        |
|         | 95% CI                                      | 6.1, -0.9           | -14.0, -8.2         |
|         | LS Mean Difference (Kynmobi – Placebo) (SE) |                     | -7.6 (1.96)         |
|         | 95% CI                                      |                     | -11.5, -3.7         |
|         | <i>P</i> value                              |                     | 0.0002              |

Abbreviations: CI = confidence interval; LS = least squares; MDS-UPDRS Part III= Movement Disorders Society Unified Parkinson's Disease Rating Scale Part III Motor Examination; mITT = modified Intent-to-Treat; MMRM = mixed model for repeated measures; SE = standard error.

Note: Baseline Visit refers to last titration visit at which the dose assigned in the Maintenance Treatment Phase is given up through TV6.

<sup>a)</sup> Statistics are from a MMRM including the observed change from pre-dose MDS-UPDRS Part III score values after 30 minutes at MV4 (Week 12) as the response values. The model includes treatment group (Kynmobi or placebo), visit (MV4, and the interaction between the treatment group and visit as fixed factors, and the change from pre-dose in MDS-UPDRS Part III score after 30 minutes at Baseline visit as a covariate. An unstructured covariance matrix is used to model the

correlation among repeated measurements and the denominator degrees of freedom are computed using the Kenward-Roger method.

In Study 2, a total of 74 subjects entered into the Maintenance Treatment Phase with 37 subjects randomized to 4 weeks of treatment with Kynmobi followed by 4 weeks of treatment with subcutaneous apomorphine, and 37 subjects randomized to 4 weeks of treatment with subcutaneous apomorphine followed by 4 weeks of treatment with Kynmobi. The mean age of subjects was 64.3 years (range 44 to 79 years). The mean time since diagnosis of PD was 9.8 years (range 2 to 23 years), and the mean time since onset of motor fluctuations was 3.72 years (range 0.5 to 13 years). At study entry, subjects typically experienced a mean of 4.1 "OFF" episodes daily. Most subjects had an "ON" State Modified Hoehn and Yahr of 2 (44.6%) or 2.5 (20.3%). All subjects in this study received concomitant levodopa/DDCI at baseline with a median levodopa dose of 687.5 mg per day. 85.1% of subjects were using a concomitant dopamine agonist, 48.6% monoamine oxidase B inhibitors, 20.3% amantadine derivatives, and 24.3% other dopaminergic agents (including COMT inhibitors).

In Study 2, Kynmobi demonstrated comparable therapeutic efficacy to subcutaneous apomorphine, with numerically similar LS mean changes (LS mean change: -13.55; 95% CI: -16.39, -10.70 for Kynmobi and LS mean change: -13.78; 95% CI: -16.65, -10.90 for subcutaneous apomorphine) in MDS-UPDRS Part III scores from predose to 90 minutes postdose at Week 4 (primary endpoint evaluated after 4 weeks in each crossover period).

## 5.2 Pharmacokinetic properties

### Absorption

Following sublingual administration of 15 mg of apomorphine, the time to maximum concentration ( $t_{max}$ ) 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 following a single sublingual administration of Kynmobi in patients with PD.

### Distribution

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

### Biotransformation

The main site of apomorphine metabolism is the liver and the major metabolic pathways for sublingual apomorphine are sulfation by multiple sulfotransferase (SULT) enzymes; glucuronidation by multiple glycosyltransferase (UGT) enzymes; N-demethylation catalyzed by multiple enzymes, including CYP2B6, CYP2C8, and CYP3A4/5; followed by conjugation. Metabolism of sublingual apomorphine results in three major inactive metabolites: apomorphine sulphate, apomorphine glucuronide, and norapomorphine glucuronide.

### Elimination

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).

### Pharmacokinetics in special patient groups:

The apparent clearance of apomorphine does not appear to be influenced by age, gender, race, weight, duration of PD, levodopa dose, or duration of therapy.

#### *Hepatic impairment*

Studies with Kynmobi in patients with hepatic impairment have not been conducted.

In a study with subcutaneous apomorphine comparing patients with moderate hepatic impairment (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. These changes are not expected to be clinically significant for patients with mild or moderate hepatic impairment.

#### *Renal impairment*

Clinical studies of Kynmobi only included patients with mild and moderate renal impairment (as determined by estimated creatine clearance). The population pharmacokinetics analysis suggested that there were no differences in apomorphine exposure after administration of Kynmobi in patients with mild and moderate renal impairment as compared to patients with normal renal function ( $CL_{cr}$  of  $\geq 90$  mL/min).

In a study with subcutaneous apomorphine comparing patients with moderate renal impairment (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. Since the  $C_{max}$  and  $AUC_{0-\infty}$  of apomorphine following the sublingual administration are lower as compared to the subcutaneous route of administration and the Kynmobi dose is titrated individually, these changes are not expected to be clinically significant for patients with mild or moderate renal impairment.

## **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, oral local tolerance and carcinogenic potential.

In vitro genotoxicity studies demonstrated mutagenic and clastogenic effects, most likely due to products formed by oxidation of apomorphine. However, apomorphine was not genotoxic in the in vivo studies performed.

Reproductive toxicity has not been evaluated by the oral route. Subcutaneous apomorphine did not impact on fertility or early embryonic development and was not teratogenic in rats, but increased the incidence of malformations of the heart and/or

great vessels in pregnant rabbits at clinically relevant doses, which were associated with maternal toxicity. Subcutaneous apomorphine administration throughout gestation and lactation in rats resulted in offspring mortality, associated with maternal toxicity with no effects on development or reproductive performance in the surviving offspring.

#### Environmental Risk Assessment (ERA)

Environmental risk assessment has shown that apomorphine hydrochloride may pose a risk for the aquatic environment.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

disodium edetate (E385)

FD&C Blue #1 (E133)

Glycerol (E422)

glyceryl monostearate (E471)

hydroxyethyl cellulose 250 G and 250 L (E1525)

hydroxypropyl cellulose (E463)

maltodextrin

levomenthol

Pyridoxine hydrochloride (for pH-adjustment)

sodium hydroxide (E524) (for pH-adjustment)

sodium metabisulfite (E223)

sucralose (E955)

white ink (Shellac (E904), Dehydrated alcohol (E1510), Isopropyl alcohol, Butyl alcohol, Propylene glycol (E1520), Strong ammonia solution (E527), Purified water, Potassium hydroxide (E525), titanium dioxide (E171))

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

30 months

### **6.4 Special precautions for storage**

Do not store above 25 °C. Store in the sachet in order to protect from light and moisture.

### **6.5 Nature and contents of container**

Sealed foil sachet (coated PET (polyethylene terephthalate), LDPE, Alu, High Performance Component, peelable coex film) containing one sublingual film.

The treatment initiation pack containing 10 sublingual films with 2 sublingual films of 10 mg, 15 mg, 20 mg, 25 mg, 30 mg each.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal**

This medicinal product may pose a risk to the environment (See section 5.3). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7 MARKETING AUTHORISATION HOLDER**

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PL 21566/0015

**9      DATE OF FIRST AUTHORISATION/RENEWAL OF THE  
AUTHORISATION**

Date of first authorisation: 01 June 2023

**10     DATE OF REVISION OF THE TEXT**

18/03/2024