# **Semaglutide 1mg Transmucosal Buccal Film 1mg**

Summary of Product Characteristics Updated 03-04-2024 | Limited.

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

**1. Name of the medicinal product**

Semaglutide 1mg Transmucosal Buccal Film

**2. Qualitative and quantitative composition**

**Semaglutide 1mg Transmucosal Buccal Film**

Contains 1mg of semaglutide\*. Each dose contains 1mg of semaglutide.

One Transmucosal Buccal Film contains 1 mg of semaglutide.

\*human glucagon-like peptide-1 (GLP-1) analogue produced in *Saccharomyces cerevisiae* cells by recombinant DNA technology.

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For the complete list of excipients, see section 6.1.

**3. Pharmaceutical form**

**Transmucosal Buccal Film.**

The semaglutide has been formulated into a transmucosal buccal film with mucoadhesive properties that allow it to adhere to buccal mucosa upon contact. It rapidly dissolves after attaching to the buccal mucosa, facilitating absorption into the bloodstream. The buccal administration facilitates immediate absorption into the rich vascular bed supplying buccal mucosa and avoids first-pass metabolism and any enzymatic degradation in the stomach. Thus, the buccal route of administration increases absorption and reduces any gastrointestinal adverse effects associated with taking tablets orally.

The traditional route of administration for semaglutide for weight loss is via subcutaneous injection. However, the revolutionary transmucosal buccal film has provided an alternative method to deliver the semaglutide, which is both practical and convenient. This method of drug delivery particularity will suit that cohort of needle-phobic patients.

The APC Labs Semaglutide Transmucosal Film is compounded as a green film and is packaged in a strip of ten in a crystal PET transparent blister.

**4. Clinical particulars**

**4.1 Therapeutic indications**

**Adults**

Semaglutide 1mg Transmucosal Buccal Film is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of

• ≥ 30 kg/m2 (obesity), or

• ≥ 27 kg/m2 to <30 kg/m2 (overweight) in the presence of at least one weight-related comorbidity.

**4.2 Posology and method of administration**

**Posology**

**Adults**

The maintenance dose of licensed semaglutide is 2.4mg weekly and is reached by titrating doses over weeks. The APC Labs Transmucosal Semaglutide Film delivers 1mg buccally. An equivalent maintenance dose could be 2mg weekly or 1mg transmucosal film administered twice weekly. Again, to reduce the likelihood of gastrointestinal symptoms, the dose should be escalated over four weeks to a maintenance dose of 2mg once weekly. In case of significant gastrointestinal symptoms, consider delaying dose escalation or lowering to the previous dose until symptoms have improved. The dose should be tailored to the response and weight loss.

Suppose patients have been unable to lose at least 5% of their initial body weight after six months of treatment. In that case, a decision is required on whether to continue treatment, considering the individual patient's benefit/risk profile (see section 5.1).

**Table 2 Dose escalation schedule**

Week 1-4: Semaglutide 1mg weekly

Maintenance dose: Semaglutide 1mg twice weekly

***Missed dose***

If a dose is forgotten, it should be taken as soon as remembered and within five days of the missed dose. If more than five days have elapsed, skip the missed dose and resume the regular dosing schedule on the next scheduled day. Patients should then continue with their once-weekly dosing regimen. If multiple doses are missed, it may be advisable to consider reducing the starting dose when restarting treatment.

**Special populations**

***Patients with type 2 diabetes***

Using semaglutide in conjunction with other GLP-1 receptor agonists is not advised. When initiating semaglutide treatment, reducing the dosage of concurrently administered insulin or insulin secretagogues (such as sulfonylureas) is recommended to mitigate the risk of hypoglycaemia.

***Elderly patients (≥ 65 years old)***

There is no need for dosage adjustment based on age. However, limited therapeutic data are available for patients aged 75 years and older who use the licensed semaglutide preparations.

***Patients with renal impairment***

No dosage adjustments are needed for patients with mild, moderate, or severe renal impairment. However, there is limited experience with the utilisation of semaglutide in patients with severe renal impairment. Semaglutide is not advised for individuals with end-stage renal disease (refer to section 5.2).

***Patients with hepatic impairment***

No dose adjustment is required for patients with hepatic impairment. Experience with the use of semaglutide in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with semaglutide (see section 5.2).

**Method of administration**

Semaglutide 1mg Transmucosal Buccal Film is administered once or twice weekly at any time of the day, with or without meals. The Transmucosal Buccal film is placed on the inner side of the cheek and allowed to dissolve. It should not be swallowed.

If necessary, the day of weekly administration can be changed as long as the time between two doses is at least three days (>72 hours). After selecting a new dosing day, once-weekly dosing should be continued (\*the dose can be tailored to the response).

Patients should read the instructions for use included in the package leaflet carefully before administering the medicinal product.

For further information on administration, see section 6.6.

**4.3 Contraindications**

Hypersensitivity to the active substance or any excipients listed in section 6.1.

**Warnings:**

Semaglutide injection may potentially elevate the risk of developing tumours in the thyroid gland, including medullary thyroid carcinoma (MTC), a form of thyroid cancer. Laboratory studies involving animals administered semaglutide revealed tumour formation, though it remains uncertain whether this medication poses a similar risk in humans. Patients should be screened for a history of MTC or Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

**4.4 Special warnings and precautions for use**

**Gastrointestinal effects**

The utilisation of GLP-1 receptor agonists may be linked to gastrointestinal adverse reactions, potentially resulting in dehydration, which in rare instances may contribute to a decline in renal function. Patients should be informed about the potential risk of dehydration associated with gastrointestinal side effects and advised to take precautions to prevent fluid depletion.

**Acute pancreatitis**

Acute pancreatitis has been noted in association with using GLP-1 receptor agonists. Patients should be educated about the typical symptoms of acute pancreatitis. If pancreatitis is suspected, discontinuation of semaglutide is recommended; if confirmed, semaglutide should not be resumed. Caution is advised in patients with a history of pancreatitis.

Elevations in pancreatic enzymes alone, without other signs and symptoms of acute pancreatitis, do not indicate the condition.

**For patients with diabetes**

Semaglutide must not be used as a substitute for insulin in patients with diabetes.

**Hypoglycaemia in patients with diabetes**

Insulin and sulfonylureas are recognised for their potential to induce hypoglycaemia. Individuals receiving semaglutide alongside a sulfonylurea or insulin may face an elevated risk of hypoglycaemia. This risk can be mitigated by reducing the sulfonylurea or insulin dosage upon initiating treatment with a GLP-1 receptor agonist. It's important to note that the introduction of semaglutide 2.4 mg in patients treated with insulin has not been assessed.

**Diabetic retinopathy in patients with type 2 diabetes**

In individuals with diabetic retinopathy undergoing treatment with insulin and semaglutide, a heightened risk of diabetic retinopathy complications has been noted. While rapid enhancement in glucose regulation has been linked to the temporary worsening of diabetic retinopathy, other mechanisms cannot be discounted. Close monitoring and adherence to clinical guidelines are recommended for patients with diabetic retinopathy using semaglutide. However, there is no available data on the use of semaglutide 2.4 mg in patients with type 2 diabetes exhibiting uncontrolled or potentially unstable diabetic retinopathy.

**Populations not studied**

No experience exists in patients with congestive heart failure New York Heart Association (NYHA) class IV. There is limited experience in patients aged 75 years or more.

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

Like other GLP-1 receptor agonists, semaglutide may slow gastric emptying and potentially affect the absorption of concurrently administered oral medications. However, no clinically significant impact on gastric emptying rate was noted with semaglutide 2.4 mg. In clinical pharmacology trials investigating the influence of semaglutide 1.0 mg on the absorption of concomitant oral medications at a steady state, no clinically relevant drug interactions with semaglutide were observed based on the evaluated medications. Consequently, no dosage adjustment is necessary when co-administering with semaglutide.

**Oral contraceptives**

Semaglutide is not expected to reduce the efficacy of oral contraceptives. Clinical studies have shown that semaglutide does not significantly alter the overall exposure of ethinylestradiol and levonorgestrel when co-administered with an oral contraceptive combination product (containing 0.03 mg ethinylestradiol/0.15 mg levonorgestrel). Specifically, exposure to ethinylestradiol remained unaffected, while a 20% increase in levonorgestrel exposure at steady state was observed. There were no changes in Cmax for either compound.

**Atorvastatin**

Following a single dose of atorvastatin (40 mg), semaglutide did not affect the overall exposure to atorvastatin. However, the maximum concentration (Cmax) of atorvastatin decreased by 38%, which was deemed not clinically relevant.

**Digoxin**

Semaglutide did not alter the overall exposure or maximum concentration (Cmax) of digoxin after a single digoxin dose (0.5 mg).

**Metformin**

Semaglutide did not affect the overall exposure or maximum concentration (Cmax) of metformin after administering a dose of 500 mg twice daily for 3.5 days.

**Warfarin**

Semaglutide did not alter the overall exposure or maximum concentration (Cmax) of both R- and S-warfarin after a single dose of warfarin (25 mg). Furthermore, the pharmacodynamic effects of warfarin, as measured by the international normalised ratio (INR), were not clinically significantly affected.

**Paediatric population**

Interaction studies have only been performed in adults.

**4.6 Fertility, pregnancy and lactation**

**Women of childbearing potential**

Women of childbearing potential are recommended to use contraception when treated with semaglutide.

**Pregnancy**

Animal studies have indicated reproductive toxicity (refer to section 5.3). Data regarding the use of semaglutide in pregnant women are limited. Hence, semaglutide is not recommended for use during pregnancy. If a patient plans to conceive or becomes pregnant, discontinuation of semaglutide is advised. Semaglutide should be stopped at least two months before planned pregnancy due to its prolonged half-life (refer to section 5.2).

**Breast-feeding**

Semaglutide was detected in the milk of lactating rats. While the potential risk to breastfed infants cannot be ruled out, semaglutide is not recommended for use during breastfeeding.

**Fertility**

The effect of semaglutide on fertility in humans is unknown. Semaglutide did not affect male fertility in rats. In female rats, an increase in oestrous length and a slight reduction in number of ovulations were observed at doses associated with maternal body weight loss.

**Important Safety Information**

MHRA/CHM advice: GLP-1 receptor agonists: reports of diabetic ketoacidosis when concomitant insulin was rapidly reduced or discontinued (June 2019)

Serious and life-threatening cases of diabetic ketoacidosis have been reported in patients with type 2 diabetes mellitus on a combination of insulin and the glucagon-like peptide-1 (GLP-1) receptor agonist exenatide, liraglutide, or dulaglutide, particularly after discontinuation or rapid dose reduction of concomitant insulin.

The MHRA has not currently received any UK reports of diabetic ketoacidosis with the GLP-1 receptor agonists lixisenatide and semaglutide, but this risk cannot be excluded. Healthcare professionals are advised that any insulin dose reduction should be done stepwise with careful blood glucose self-monitoring, mainly when GLP-1 receptor agonist therapy is initiated. Patients should be informed of the risk factors for and signs and symptoms of diabetic ketoacidosis and advised to seek immediate medical attention if these develop.

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

Semaglutide has minimal to no effect on the capacity to operate machinery or drive. Nevertheless, dizziness, particularly during the dose escalation phase, may occur. If dizziness arises, caution should be exercised when driving or operating machinery.

**Patients with type 2 diabetes**

If semaglutide is utilised alongside a sulfonylurea or insulin, patients should be counselled to take precautions to prevent hypoglycaemia when driving or operating machinery (refer to section 4.4).

**4.8 Undesirable effects**

**Summary of the safety profile of licensed semaglutide**

Across four phase 3a trials, 2,650 adult patients were treated with semaglutide 2.4 mg over 68 weeks. Consistent with other GLP-1 receptor agonists, gastrointestinal disorders such as nausea, diarrhoea, constipation, and vomiting were the most commonly reported adverse reactions.

**Tabulated list of adverse reactions with Semaglutide in Licensed Medicines**

Table 3 presents adverse reactions observed in phase 3a clinical trials among adults. The frequencies are derived from a pooled analysis of the phase 3a trials. Adverse reactions associated with semaglutide 2.4 mg are categorised by system organ class and frequency, with frequency categories defined as: Very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000).

**Table 3 Adverse reactions from controlled phase 3 trials in adults**

| **MedDRA system organ class** | **Very common** | **Common** | **Uncommon** | **Rare** |
| --- | --- | --- | --- | --- |
| Immune system disorders |  |  |  | Anaphylactic reaction |
| Metabolism and nutrition disorders |  | Hypoglycaemia in patients with type 2 diabetes |  |  |
| Nervous system disorders | Headache | Dizziness |  |  |
| Eye disorders |  | Diabetic retinopathy in patients with type 2 diabetes |  |  |
| Cardiac disorders |  |  | Increased heart rate,c |  |
| Gastrointestinal disorders | Vomiting,b  Diarrhoea,b  Constipation,b  Nausea,b  Abdominal pain, c | Gastritis, c  Gastroesophageal reflux disease  Dyspepsia  Eructationb  Flatulence  Abdominal distensionb | Acute pancreatitis  Delayed gastric emptying |  |
| Hepatobiliary disorders |  | Cholelithiasis |  |  |
| Skin and subcutaneous tissue disorders |  | Hair loss |  | Angioedema |
| General disorders and administration site conditions | Fatigueb,c | Injection site reactionsc |  |  |
| Investigations |  |  | Increased amylase  Increased lipase |  |

a)See the description of selected adverse reactions below

b)Mainly seen in the dose-escalation period

c) Grouped preferred terms

**Description of selected adverse reactions**

***Gastrointestinal adverse reactions***

During dose escalation, the events were most frequently reported. Over 68 weeks, nausea was observed in 43.9% of patients receiving semaglutide 2.4 mg (16.1% for placebo), diarrhoea in 29.7% (15.9% for placebo), and vomiting in 24.5% (6.3% for placebo). Most of these events were of mild to moderate severity and short duration. Constipation occurred in 24.2% of patients treated with semaglutide 2.4 mg (11.1% for placebo) and was generally mild to moderate in severity but of longer duration. Gastrointestinal events led to permanent discontinuation of treatment in 4.3% of patients.

***Acute pancreatitis***

In phase 3a clinical trials, the frequency of adjudication-confirmed acute pancreatitis reported was 0.2% for semaglutide 2.4 mg and less than 0.1% for placebo, respectively.

***Acute gallstone disease/Cholelithiasis***

Cholelithiasis occurred in 1.6% of patients treated with semaglutide 2.4 mg, and cholecystitis resulted in 0.6% of these patients.

***Hair loss***

Hair loss occurred in 2.5% of patients treated with semaglutide 2.4 mg and in 1.0% of patients treated with placebo. The events were primarily mild in severity, and most patients recovered while continuing treatment. Hair loss was reported more frequently in patients experiencing more significant weight loss (≥ 20%).

***Increased heart rate***

During the phase 3a trials, patients treated with semaglutide 2.4 mg exhibited a mean increase of 3 beats per minute (bpm) from a baseline mean of 72 bpm. The proportions of patients experiencing a maximum increase from baseline of ≥ 20 bpm/min at any timepoint during the treatment period were 26.0% in the semaglutide 2.4 mg group compared to 15.6% in the placebo group.

***Immunogenicity***

As is typical with medicinal products containing proteins or peptides, patients may generate antibodies following semaglutide treatment. However, the percentage of patients testing positive for anti-semaglutide antibodies at any time post-baseline was low (2.9%), and none of the patients developed anti-semaglutide neutralising antibodies or anti-semaglutide antibodies with endogenous GLP-1 neutralising effect by the end of the trial.

***Hypoglycaemia in patients with type 2 diabetes***

In STEP 2, clinically significant hypoglycaemia was noted in 6.2% (0.1 events/patient-year) of patients receiving semaglutide 2.4 mg, compared to 2.5% (0.03 events/patient-year) of patients receiving placebo. One episode (0.2% of subjects, 0.002 events/patient-year) was categorised as severe. The risk of hypoglycaemia was elevated when semaglutide 2.4 mg was used concomitantly with a sulfonylurea.

***Diabetic retinopathy in patients with type 2 diabetes***

In STEP 2, new onset or deterioration of diabetic retinopathy was observed in 4.0% of patients treated with semaglutide 2.4 mg, compared to 2.7% of patients receiving placebo.

**Paediatric population**

In a clinical trial involving adolescents aged 12 to under 18 years with obesity or overweight and at least one weight-related comorbidity, a total of 133 patients received semaglutide over 68 weeks.

Overall, the frequency, type, and severity of adverse reactions in adolescents were similar to those observed in adults. Cholelithiasis was reported in 3.8% of patients treated with Semaglutide 1mg Transmucosal Buccal Film, compared to 0% of patients treated with a placebo. Additionally, no effects on growth or pubertal development were observed after 68 weeks of treatment.

**Reporting of suspected adverse reactions**

It is vital to report any suspected adverse reactions following the authorisation of the medicinal product. This facilitates ongoing monitoring of the product's benefit-to-risk ratio. Healthcare professionals are encouraged to report any suspected adverse reactions through the Yellow Card Scheme.

**Great Britain**

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

**4.9 Overdose**

An overdose of semaglutide may result in gastrointestinal disorders that could potentially lead to dehydration. In case of overdose, patients should be monitored for clinical signs, and appropriate supportive treatment should be administered as necessary.

**5. Pharmacological properties**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Drugs used in diabetes, Glucagon-like peptide-1 (GLP-1) analogues, ATC code: A10BJ06.

**Mechanism of action**

Semaglutide, a GLP-1 analogue, shares 94% sequence homology with human GLP-1. As a GLP-1 receptor agonist, semaglutide selectively binds to and activates the GLP-1 receptor, also targeted by native GLP-1.

GLP-1 is a natural regulator of appetite and calorie intake, with its receptor distributed across various brain regions involved in appetite control. Semaglutide exerts direct effects on brain areas responsible for the homeostatic regulation of food intake, such as the hypothalamus and brainstem, as well as an indirect impact on areas governing hedonic food intake, including the septum, thalamus, and amygdala.

In clinical trials, semaglutide has demonstrated the ability to lower blood glucose levels in a glucose-dependent manner by promoting insulin secretion and reducing glucagon secretion when blood glucose levels are elevated. Additionally, its mechanism of action involves a slight delay in gastric emptying during the early postprandial phase. Notably, semaglutide attenuates insulin secretion during hypoglycaemia while preserving glucagon secretion.

**Pharmacodynamic effects**

***Appetite, energy intake and food choice***

In a phase 1 trial, after 20 weeks of dosing, energy intake during an ad libitum meal was 35% lower with semaglutide 2.4 mg compared to placebo. This reduction was corroborated by enhancements in control of eating, increased feelings of fullness, greater satiety, decreased hunger, reduced food cravings (especially for dairy and savoury foods), diminished desire for sweet foods, and a relative decrease in preference for high-fat foods.

Food cravings were further evaluated in STEP 5 using the Control of Eating Questionnaire (CoEQ). At week 104, the estimated treatment difference significantly favoured semaglutide in controlling cravings for savoury foods, while no discernible effect was observed for sweet food cravings.

**5.2 Pharmacokinetic properties**

Semaglutide offers a prolonged half-life of approximately one week, unlike native GLP-1, allowing for convenient once-weekly administration when given by subcutaneous injection This extended duration is primarily attributed to albumin binding, which reduces renal clearance and shields the compound from metabolic breakdown. Additionally, semaglutide is fortified against degradation by the DPP-4 enzyme. Semaglutide is mainly distributed within the plasma volume, with a plasma protein binding of >99% and is extensively metabolised before excretion via urine and faeces.

**5.3 Preclinical safety data of licensed semaglutide**

Preclinical data from standard safety pharmacology, repeat-dose toxicity, and genotoxicity studies do not indicate any specific hazards for humans.

Non-lethal thyroid C-cell tumours observed in rodents are a known class effect for GLP-1 receptor agonists. In 2-year carcinogenicity studies involving rats and mice, liraglutide-induced thyroid C-cell tumours at exposures relevant to clinical settings. However, no other treatment-related tumours were observed. The occurrence of these tumours in rodents is attributed to a GLP-1 receptor-mediated mechanism, which is non-genotoxic and specific, and rodents are particularly sensitive to it. Although the relevance for humans is deemed low, it cannot be entirely ruled out.

In fertility studies conducted in rats, semaglutide did not impact mating performance or male fertility. In female rats, an increase in oestrous cycle length and a slight reduction in corpora lutea (ovulation) were observed at doses associated with maternal body weight loss. Preclinical data reveal no special hazards for humans based on conventional safety pharmacology studies, repeat-dose toxicity or genotoxicity.

In embryo-foetal development studies conducted in rats, semaglutide resulted in embryotoxicity at exposures below clinically relevant levels. Notably, semaglutide led to significant reductions in maternal body weight, as well as decreased embryonic survival and growth. Additionally, major skeletal and visceral malformations were observed in the foetuses, affecting structures such as long bones, ribs, vertebrae, tail, blood vessels, and brain ventricles. Mechanistic assessments indicated that this embryotoxicity involved impairment of nutrient supply to the embryo via the rat yolk sac, mediated by the GLP-1 receptor. However, this mechanism is unlikely to be relevant to humans due to differences in yolk sac anatomy and GLP-1 receptor expression between species, particularly non-human primates. Nonetheless, the direct effect of semaglutide on the foetus cannot be ruled out.

In developmental toxicity studies involving rabbits and cynomolgus monkeys, increased pregnancy loss and a slightly elevated incidence of foetal abnormalities were noted at clinically relevant exposures. These findings coincided with marked maternal body weight loss, reaching up to 16%. Whether these effects are linked to decreased maternal food consumption as a direct effect of GLP-1 is uncertain. Postnatal growth and development evaluations in cynomolgus monkeys revealed that infants were slightly smaller at birth but regained average size during lactation.

In juvenile rats, semaglutide led to delayed sexual maturation in both males and females. However, these delays did not affect fertility or reproductive capacity in either sex or impair the females' ability to sustain pregnancy.

**6. Pharmaceutical particulars**

**6.1 List of excipients**

* Nova film Base
* Sucralose
* Mango flavour
* Passion Fruit flavour
* Silica
* Food Colour
* Bitterness reducing agent
* Glycerin

**6.2 Shelf life**

180 days from the date of compounding

In-use shelf life: 180 days from the day of compounding

**6.4 Special precautions for storage**

Store at room temperature in the original blister and foil bag at room temperature. Please protect it from light.

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