PROFESSIONAL INFORMATION FOR

GILIPTRA

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

GILIPTRA 6 mg/mL solution for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains liraglutide 18 mg in 3 mL.

Preservative: Phenol 0,55 % *w/v*

Sugar free.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pens.

Clear colourless solution free from visible particles.

Solution is Isotonic and pH = 8,15.

Osmolality ranges between 250 and 320 mOsm / kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GILIPTRA is indicated as an adjunct to diet and exercise to achieve glycaemic control in patients with type 2 diabetes mellitus.

GILIPTRA is indicated for once-daily administration:

- as monotherapy,
- combination therapy with one or more oral antidiabetic medicines (metformin, sulphonylureas or a thiazolidinedione) when previous therapy does not achieve adequate glycaemic control,
- combination therapy with insulin in patients not achieving adequate glycaemic control with GILIPTRA and metformin.

4.2 Posology and method of administration

Posology

Monotherapy

To reduce gastro-intestinal adverse effects for all patients, GILIPTRA should be initiated with a dose of 0,6 mg for at least one week, after which the dose may be increased to 1,2 mg. Based on clinical response and after at least one week the dose can be increased to 1,8 mg to achieve maximum efficacy. Daily doses higher than 1,8 mg are not recommended.

Combination therapy

GILIPTRA can be used in combination with other glucose lowering agents and no dose adjustments are required for metformin, thiazolidinedione and SGLT2i therapy.

When GILIPTRA is added to a sulphonylurea or insulin, a reduction in the dose of sulphonylurea or insulin should be considered to reduce the risk of hypoglycaemia (see s**ection 4.4**).

Self-monitoring of blood glucose is not needed in order to adjust the dose of GILIPTRA. However, when initiating treatment with GILIPTRA in combination with a sulphonylurea or insulin, blood glucose self-monitoring may become necessary to adjust the dose of the sulphonylurea or insulin.

Incompatibilities

Substances added to GILIPTRA may cause degradation of liraglutide. GILIPTRA must not be mixed with other medicinal products, e.g. infusion fluids.

Special populations

Elderly population:

No dosage adjustment is required based on age and gender.

Obesity:

Population pharmacokinetic analysis suggests that body mass index (BMI) has no significant effect on the pharmacokinetics of liraglutide.

Hepatic impairment

No dose adjustment is required for patients with hepatic impairment **(see section 4.4)**.

Renal impairment

No dose adjustment is required for patients with mild or moderate or severe renal impairment. There is no therapeutic experience in patients with end-stage renal disease and GILIPTRA is therefore not recommended for use in these patients (see **section 4.4**).

Paediatric population

GILIPTRA has not been studied in paediatric patients below 18 years of age **(**see **section 4.4**).

Method of administration

GILIPTRA must not be administered intravenously or intramuscularly.

GILIPTRA is administered once daily at any time, independent of meals, and can be injected subcutaneously in the abdomen, in the thigh or in the upper arm. Injection sites should always

be rotated within the same region in order to reduce the risk of cutaneous amyloidosis (see **section 4.8**). The injection site and timing can be changed without dose adjustment.

4.3 Contraindications

- Patients with known hypersensitivity to liraglutide or to any of the excipients in GILIPTRA (see **section 6.1**).
- A history of previous pancreatitis.
- Type 1 diabetes mellitus.
- Pregnancy and lactation (see **section 4.6**).

4.4 Special warnings and precautions for use

- GILIPTRA should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- GILIPTRA should not be administered intravenously or intramuscularly.
- GILIPTRA is not a substitute for insulin.
- Safety and efficacy of GILIPTRA in patients below 18 years of age has not been established.
- Patients above 70 years may experience more gastrointestinal effects when treated with GILIPTRA.
- Patients with mild and moderate renal impairment (creatinine clearance 60 to 90 mL/min and 30 to 59 mL/min, respectively) may experience more gastrointestinal effects when treated with GILIPTRA.
- There is no therapeutic experience in patients with end-stage renal disease and GILIPTRA is therefore not recommended for use in these patients.

- There is no therapeutic experience in patients with patients with congestive heart failure New York Heart Association (NYHA) class IV and GILIPTRA is therefore not recommended for use in these patients.
- There is limited experience in patients with inflammatory bowel disease and diabetic gastroparesis and GILIPTRA is therefore not recommended for use in these patients. The use of GILIPTRA is associated with gastrointestinal adverse reactions, including nausea, vomiting and diarrhoea.
- *Hypoglycaemia*:

  Patients receiving liraglutide in combination with a sulphonylurea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by a reduction in the dose of sulphonylurea or insulin.
- *Immunogenicity:*

  Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients may develop anti-liraglutide antibodies following treatment with GILIPTRA. On average, 8,6 % of patients developed antibodies. Antibody formation has not been associated with reduced efficacy of GILIPTRA.
- *Injection site reactions:*

  Injection site reaction has been reported in approximately 2 % of subjects receiving liraglutide in long-term (26 weeks or longer) controlled trials. These reactions have usually been mild and did not lead to discontinuation of GILIPTRA.
- *Acute pancreatitis*:

  Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, liraglutide should be discontinued; Once acute pancreatitis is confirmed,

liraglutide or any other GLP-1 receptor agonist should never again be restarted. Caution should be exercised in patients with a history of pancreatitis.

- *Thyroid disease*:

  Thyroid adverse events, such as goitre, have been reported in clinical trials and in particular in patients with pre-existing thyroid disease. Liraglutide should therefore be used with caution in these patients.

- *Allergic reactions:*

  Allergic reactions including urticaria, rash and pruritus have been reported from marketed use of liraglutide. Cases of anaphylactic reactions with additional symptoms such as hypotension, palpitations, dyspnoea, oedema have been reported with marketed use of liraglutide (see **section 4.3**).

- *Dehydration:*

  Signs and symptoms of dehydration, including renal impairment and acute renal failure, have been reported in patients treated with liraglutide. Patients treated with GILIPTRA should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Excipients

GILIPTRA contains less than 1 mmol sodium (23 mg) per dose, therefore the medicinal product is essentially 'sodium-free'. (see **section 6.1)**

4.5 Interaction with other medicines and other forms of interaction

In vitro assessment of interaction studies

Liraglutide has shown a low potential involvement in pharmacokinetic interactions with other active substances related to cytochrome P450 (CYP) and plasma protein binding.

In vivo assessment of interaction studies

Interaction has been investigated using paracetamol, digoxin, lisinopril, griseofulvin and atorvastatin representing various degrees of solubility and permeability properties. In addition, the effect of liraglutide on the absorption of ethinyloestradiol and levonorgestrel administered in an oral combination contraceptive medicine has been investigated (see table below).

Product	**Dose**	**C_{max}**	**Median t_{max}**	**Comments**
Paracetamol	Single dose of 1000 mg	Decreased by 31 %	Delayed up to 15 min	No dose adjustment for concomitant use of paracetamol is required
Atorvastatin	Single dose of 40 mg	Decreased by 38 %	Delayed from 1 h to 3 h	No dose adjustment of atorvastatin is required when given with GILIPTRA
Griseofulvin	Single dose of 500 mg	Increased by 37 %	Did not change	Dose adjustments of griseofulvin and other compounds with low solubility and high permeability are not required
Digoxin	Single dose of 1 mg	Decreased by 31 %	Delayed from 1 h to 1,5 h	No adjustment of digoxin dose is required
Oral Contraception:	Single dose		Delayed up to 1,5 h for both compounds	The contraceptive effect is anticipated to be unaffected when co-administered with GILIPTRA
Ethinyloestradiol		Decreased by 12 %		
Levonorgestrel		Decreased by 13 %		

The minor delay of gastric emptying caused by liraglutide did not affect the absorption of orally administered medicines to any clinically relevant degree and therefore no dose adjustment is required. Few patients treated with liraglutide reported at least one episode of severe diarrhoea. Diarrhoea may affect the absorption of concomitant oral medicines.

Warfarin and other coumarin derivatives:

No interaction study has been performed. A clinically relevant interaction with active substances with poor solubility or with narrow therapeutic index such as warfarin cannot be excluded. Upon initiation of liraglutide treatment in patients on warfarin or other coumarin derivatives, more frequent monitoring of INR (International Normalised Ratio) is recommended.

Insulin

No pharmacokinetic or pharmacodynamic interactions were observed between liraglutide and insulin detemir when administering a single dose of insulin detemir 0,5 U/kg with liraglutide 1,8 mg at steady state in patients with type 2 diabetes.

4.6 Fertility, pregnancy, and lactation

Pregnancy

GILIPTRA is contraindicated during pregnancy and lactation.

There are no adequate data for use of GILIPTRA in pregnant women. Liraglutide crossed the placental barrier in rabbits. Studies in animals have shown reproductive toxicity and GILIPTRA should therefore not be used during pregnancy. The use of insulin is recommended. If a patient wishes to become pregnant, or pregnancy occurs, treatment with GILIPTRA should be discontinued.

Breastfeeding

It is not known whether liraglutide is excreted in human milk. In lactating rats, up to 3 % of the maternal dose was present in breast milk. Women on treatment with GILIPTRA should not breastfeed.

Fertility

Apart from a slight decrease in the number of live implants, animal studies did not indicate harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. GILIPTRA may affect the ability to drive or use machines. Patients should be advised to ensure that they are aware of the effect of GILIPTRA on their abilities beforehand and to take precautions to avoid hypoglycaemia while driving and using machines, in particular when GILIPTRA is used in combination with a sulphonylurea or insulin (see **section 4.8**).

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse events during clinical trials were gastrointestinal adverse events: nausea and diarrhoea (reported by > 10 % of patients) and vomiting, dyspepsia, upper abdominal pain, constipation, gastritis, flatulence, abdominal distension, gastro-oesophageal reflux disease and eructation (reported by ≥ 1 % and ≤ 10 % of patients).

Headache and upper respiratory tract infections were common. Furthermore, hypoglycaemia was common and very common especially when GILIPTRA is used in combination with sulphonylurea. Major hypoglycaemia may occur uncommonly and has only been observed when combined with a sulphonylurea.

Severe hypoglycaemia may occur uncommonly and has only been observed when combined with a sulphonylurea.

Table 1: Tabulated summary of adverse reactions

Body system/ adverse reaction terms	**Frequency of occurrence**		
Reactions	***Frequent***	***Less Frequent***	***Frequency unknown***

Body system/ adverse reaction terms	**Frequency of occurrence**		
Reactions	***Frequent***	***Less Frequent***	***Frequency unknown***
Infections and infestations	Upper respiratory tract infection.	Bronchitis, gastroenteritis, osteomyelitis.	-
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)		Papillary thyroid cancer, prostate cancer, breast cancer.	-
Blood and the lymphatic system disorders		Thrombocytopenia.	-
Immune system disorders		Anaphylactic reaction.	-
Metabolism and nutrition disorders	Hypoglycaemia Anorexia Decreased appetite	Dehydration.	-
Nervous system disorders	Headache.	Cerebrovascular accident, syncope.	-
Eye disorders		Cataract.	-

Body system/ adverse reaction terms	**Frequency of occurrence**		
Reactions	***Frequent***	***Less Frequent***	***Frequency unknown***
Cardiac disorders	Increased heart rate*.	Angina pectoris, acute myocardial infarction, coronary artery disease, atrial fibrillation, congestive cardiac failure, supraventricular tachycardia.	-
Gastro-intestinal disorders	Nausea, diarrhoea, vomiting, dyspepsia, abdominal pain upper, constipation, gastritis, flatulence, abdominal distension, gastro-oesophageal reflux disease,	Appendicitis with perforation, inguinal hernia, pancreatitis (Including necrotising pancreatitis).	-

Body system/ adverse reaction terms	**Frequency of occurrence**		
Reactions	***Frequent***	***Less Frequent***	***Frequency unknown***
	eructation.		
Hepatobiliary disorders		Cholelithiasis, cholecystitis.	-
Skin and subcutaneous tissue disorders	Rash.	Urticaria, pruritus.	Cutaneous amyloidosis†
Musculoskeletal, connective tissue and bone disorders		Intervertebral disc protrusion, osteoarthritis.	-
General disorders and administration site conditions	Fatigue, injection site reactions.	Chest pain, malaise.	-
Renal and urinary disorders		Renal failure acute *, renal impairment *.	-
Investigations		Increased lipase, increased amylase.	-
Injury, poisoning and procedural		Fall.	-

Body system/ adverse reaction terms	**Frequency of occurrence**		
Reactions	***Frequent***	***Less Frequent***	***Frequency unknown***
complications			

**Spontaneous reports*

† ADR from post marketing sources

Description of selected adverse reactions

Hypoglycaemia

Most episodes of confirmed hypoglycaemia in clinical trials were minor. No episodes of severe hypoglycaemia were observed in the trial with liraglutide used as monotherapy. Severe hypoglycaemia may occur uncommonly and has primarily been observed when liraglutide is combined with a sulphonylurea (0,02 events/patient year). Very few episodes (0,001 events/ subject year) were observed with administration of liraglutide in combination with a non-sulphonylurea.

As reported in trials, severe hypoglycaemic episodes were reported at a lower rate with liraglutide vs placebo (1,0 vs 1,5 events per 100 patient years of exposure; estimated rate ratio 0,69 [0,51 to 0,93]) **(**see **section 5.1).**

For patients treated with premix insulin at baseline and at least for the following 26 weeks, the rate of severe hypoglycaemia for both liraglutide and placebo was 2.2 events per 100 patient years of exposure.

Cholelithiasis and cholecystitis

Few cases of cholelithiasis (0,4 %) and cholecystitis (0,1 %) have been reported during long-term, controlled phase 3a clinical trials with liraglutide. As reported in trials, the frequency of cholelithiasis and cholecystitis was 1,5 % and 1,1 % for liraglutide and 1,1 % and 0,7 % for placebo, respectively.

Pancreatitis

Few cases of acute pancreatitis (< 0,2 %) have been reported during long-term, controlled phase 3 clinical trials with liraglutide. Pancreatitis was also reported from marketed use. As reported in trials, the frequency of acute pancreatitis confirmed by adjudication was 0,4 % for liraglutide and 0,5 % for placebo, respectively.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website, or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

With overdose, the patients reported severe nausea, vomiting and diarrhoea and severe hypoglycaemia. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. The patient should be observed for clinical signs of dehydration and blood glucose should be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 21.13 Other hormones

Pharmacotherapeutic group: Drugs used in diabetes, glucagon-like peptide-1 (GLP-1) analogues.

ATC code: A10BJ02

Mechanism of action

Liraglutide is a human Glucagon-Like Peptide-1 (GLP-1) analogue with 97 % homology to human GLP-1 that binds to and activates the GLP-1 receptor. The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from the pancreatic beta cells. Unlike native GLP-1, liraglutide has a pharmacokinetic and pharmacodynamic profile in humans, suitable for once daily administration.

Following subcutaneous administration, the protracted action profile is based on three mechanisms: self-association, which results in slow absorption, and binding to albumin and enzymatic stability towards the DPP-IV and NEP enzymes resulting in a long plasma half-life.

Liraglutide action is mediated via a specific interaction with GLP-1 receptors, leading to an increase in cAMP. Liraglutide stimulates insulin secretion in a glucose-dependent manner and improves beta-cell function. Simultaneously, liraglutide lowers inappropriately high glucagon secretion, also in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated, and glucagon secretion is inhibited. Conversely, during hypoglycaemia liraglutide diminishes insulin secretion and does not impair glucagon secretion. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying.

Liraglutide reduces body weight and body fat mass through mechanisms involving reduced hunger and lowered energy intake.

GLP-1 is a physiological regulator of appetite and calorie intake, and GLP-1 receptor (GLP-R) is present in several areas of the brain involved in appetite regulation.

In animal studies, peripheral administration of liraglutide led to uptake in specific brain regions including the hypothalamus, where liraglutide, via specific activation of the GLP-1 receptor increased satiety and decreased hunger signals, thereby leading to lower body weight.

Liraglutide has been shown *in vitro* to be a potent agent for specific stimulation of beta cell proliferation and prevention of both cytokine and free fatty acid induced beta-cell death (apoptosis). *In vivo*, liraglutide increases insulin biosynthesis, and beta-cell mass in diabetic animal models. When glucose is fully normalised, liraglutide does not increase beta-cell mass.

Pharmacodynamic effects

Liraglutide has 24-hour duration of action and improves glycaemic control by lowering fasting and postprandial blood glucose in patients with type 2 diabetes mellitus. The difference between liraglutide 1,8 mg/1,2 mg and placebo in reduction of mean fasting glucose was found to be 3,90 mmol/L (70 mg/dL)/3,33 mmol/L (60 mg/dL). Following a standard meal, the difference in mean 2-hour postprandial glucose concentration was 6,02 mmol/L (108 mg/dL)/5,63 mmol/L (101 mg/dL). In addition, liraglutide decreased postprandial glucose excursion (incremental postprandial glucose) on average by 1,1 mmol/L (20 mg/dL)/1,08 mmol/L (19 mg/dL).

5.2 Pharmacokinetic properties

Absorption

The absorption of liraglutide following subcutaneous administration is slow, reaching maximum concentration 8 to 12 hours post dosing. Estimated maximum liraglutide concentration was 9,4 nmol/L for a subcutaneous single dose of liraglutide 0,6 mg. At 1,8 mg liraglutide, the average steady state concentration of liraglutide ($AUC_{\tau/24}$) reached approximately 34 nmol/L. Liraglutide exposure increased proportionally with dose. The intra-subject coefficient of variation for

liraglutide AUC was 11 % following single dose administration. Liraglutide can be administered subcutaneously in the abdomen, thigh, or upper arm. Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55 %.

Distribution

The apparent volume of distribution after subcutaneous administration is 11 to 17 L. The mean volume of distribution after intravenous administration of liraglutide is 0,07 L/kg. Liraglutide is extensively bound to plasma protein (> 98 %).

Biotransformation

During 24 hour following administration of a single [3H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Two minor plasma metabolites were detected (≤ 9 % and ≥ 5 % of total plasma radioactivity exposure). Liraglutide is endogenously metabolised in a similar manner to large proteins without a specific organ as major route of elimination.

Elimination

Following a [3H]-liraglutide dose, intact liraglutide was not detected in urine or faeces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or faeces (6 % and 5 %, respectively). The urine and faeces radioactivity was mainly excreted during the first 6 to 8 days, and corresponded to three minor metabolites, respectively.
The mean clearance following s.c. administration of a single dose liraglutide is approximately 1,2 L/h with an elimination half-life of approximately 13 hours.

Renal impairment

The pharmacokinetics of liraglutide was evaluated in subjects with varying degrees of renal impairment in a single-dose trial. Subjects with mild (estimated creatinine clearance 50 to 80 mL/min) to severe (estimated creatinine clearance < 30 mL/min) renal impairment and subjects with end stage renal disease requiring dialysis were included in the trial. Renal impairment did not have any clinically relevant effect on the pharmacokinetics of liraglutide.

Paediatric population

Liraglutide has not been studied in paediatric patients below 18 years of age (see **section 4.4**).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients:

Disodium phosphate dihydrate,

Hydrochloric acid (for pH adjustment),

Phenol,

Propylene glycol, (E 1520)

Sodium hydroxide (for pH adjustment),

Water for injection.

6.2 Incompatibilities

Substances added to GILIPTRA may cause degradation of liraglutide. In the absence of compatibility studies, these medicines must not be mixed with other medicines.

6.3 Shelf life

24 months.

After first use: 30 days

6.4 Special precautions for storage

Before opening: Store in a refrigerator between 2 °C and 8 °C. Do not store in the freezer or directly adjacent to the refrigerator cooling element.

Do not freeze GILIPTRA and do not use GILIPTRA if it has been frozen.

After first use:

- You can keep the pen for 1 month when stored at a temperature below 30˚C or in a refrigerator between 2 °C and 8 °C, away from the freezer compartment. Do not freeze.
- GILIPTRA should be protected from excessive heat and sunlight.
- Always remove the injection needle after each injection and store the GILIPTRA pen without an injection needle attached. This prevents contamination, infection and leakage. It also ensures that the dosing is accurate.
- Recap the pen to protect from light.
- Keep out of reach of children**.**
- For shelf life after first opening of the medicine, see **section 6.3**.

6.5 Nature and contents of container

GILIPTRA is a sterile, aqueous, clear, colourless or almost colourless solution filled in a 3 mL glass cartridge and assembled into a single-patient use, disposable multi-dose pen-injector. Each pen-injector contains 3 mL of drug product at a concentration of 6 mg/mL. The delivered dose of each injection is 0,6 mg, 1,2 mg or 1,8 mg per dose depending on the setting of the multi-dose pen injector. Pack sizes of 2 or 3 pre-filled pens-injector in one carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

GILIPTRA should not be used if it does not appear clear and colourless or almost colourless. GILIPTRA should not be used if it has been frozen.

GILIPTRA can be administered with needles up to a length of 8 mm and as thin as 32G. The pen can be used with NovoFine™ or BD UltraFine™ disposable needles.

Needles are not included.

The patient should be advised to discard the injection needle in accordance with local requirements after each injection and store the pen without an injection needle attached. This prevents contamination, infection and leakage. It also ensures that the dosage is accurate.

Any unused medicinal product or waste material should be disposed in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9, Parc du Cap,

Mispel Street,

Belville, 7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER

58/21.13/0001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 21 January 2025

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

VP