**Professional Information for Sogroya®**

## SCHEDULING STATUS

S4

## 1. NAME OF THE MEDICINE

Sogroya® 5 mg/1,5 mL solution for injection in pre-filled pen

Sogroya ® 10 mg/1,5 mL solution for injection in pre-filled pen

Sogroya ® 15 mg/1,5 mL solution for injection in pre-filled pen

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Sogroya 5 mg/1,5 mL solution for injection in pre-filled pen**

One mL of solution contains 3,3 mg of somapacitan*

Each pre-filled pen contains 5 mg of somapacitan in 1,5 mL solution.

**Sogroya 10 mg/1,5 mL solution for injection in pre-filled pen**

One mL of solution contains 6,7 mg of somapacitan*

Each pre-filled pen contains 10 mg of somapacitan in 1,5 mL solution.

**Sogroya 15 mg/1,5 mL solution for injection in pre-filled pen**

One mL of solution contains 10 mg of somapacitan*

Each pre-filled pen contains 15 mg of somapacitan in 1,5 mL solution.

*Produced by recombinant DNA technology in *Escherichia coli* followed by attachment of an albumin binding moiety.

Contains sugar (66 mg mannitol per 1,5 mL solution).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection.

Clear to slightly opalescent, colourless to slightly yellow liquid, essentially free from visible particles.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Sogroya is indicated for the replacement of endogenous growth hormone (GH) in paediatric patients with growth failure due to growth hormone deficiency (GHD).

Sogroya is indicated for the replacement of endogenous growth hormone in adults with growth hormone deficiency (AGHD).

### 4.2 Posology and method of administration

Somapacitan treatment should be initiated and monitored by health care professionals who are appropriately qualified and experienced in the diagnosis and management of patients with the condition for which Sogroya is indicated (e.g. endocrinologists).

**Posology**

**Table 1: Dose recommendation**

| **Paediatric GHD** | **Recommended dose** |
|---|---|
| Treatment-naïve patients and patients switching from other growth hormone products | 0,16 mg/kg/week |
| **Adult GHD** | **Recommended starting dose** |
| Naïve patients<br>Adults (18 to less than 60 years)<br>Women on oral oestrogen therapy (irrespective of age) | <br>1,5 mg/week<br>2 mg/week |

| | |
|---|---|
| Elderly (60 years or older) | 1 mg/week |
| Patients switching from daily GH medicines<br>Adults (18 to less than 60 years)<br>Women on oral oestrogen therapy (irrespective of age)<br>Elderly (60 years or older) | <br><br>2 mg/week<br>4 mg/week<br><br>1,5 mg/week |

***Paediatric GHD***

Individualise and adjust the dosage based on response.

When GHD persists after growth completion, growth hormone treatment should be continued to achieve full somatic adult development including lean body mass and bone mineral accrual (for guidance on dosing see recommended dose for adults (Table 1).

***Adult GHD***

*Dose titration*

The somapacitan dose must be individually adjusted for each patient. It is recommended to increase the dose gradually with 2 – 4 weeks intervals in steps from 0,5 mg to 1,5 mg based on the patients' clinical response and experience of adverse reactions up to a dose of 8 mg somapacitan per week.

Serum insulin like growth factor-I (IGF-I) levels (drawn 3-4 days after dosing) can be used as guidance for the dose titration. Dose titration should be individualised and the IGF-I standard deviation score (SDS) target should aim for the upper half of the normal range not exceeding 2 SDS. See Treatment evaluation below and section 5.1.

*Treatment evaluation*

Using IGF-I SDS as a biomarker for dose titration, the aim is to reach IGF-I SDS levels within the age-adjusted upper reference range (IGF-I SDS upper reference range: 0 and +2) within 12 months of titration.

During somapacitan maintenance treatment, evaluation of efficacy and safety should be considered at approximately 6- to 12-month intervals and may be assessed by evaluating biochemistry (IGF-I-, glucose-, and lipid levels), body composition, and body mass index.

*Maintenance dose*

Maintenance dose varies from person to person and between male and female patients. The average somapacitan maintenance dose observed in the phase 3 clinical trials was 2,4 mg/week.

***Switching from other growth hormone products***

Switching a patient from another type or brand of growth hormone should be done by health care professional who has experience in diagnosis and management in growth hormone deficiency.

Patients switching from a weekly human growth hormone to once-weekly somapacitan are recommended to continue their once weekly dosing schedule.

Patients switching from daily human growth hormone to once-weekly somapacitan should choose the preferred day for the weekly dose and take the final dose of daily treatment the day before (or at least 8 hours before) taking the first dose of once-weekly somapacitan. Patients should follow the instructions for the dose presented in Table 1.

***Flexibility in dosing time***

The day of weekly injection can be changed as long as the time between two doses is at least 4 days (96 hours). After selecting a new dosing day, the once weekly dosing should be continued.

On occasions when administration at the scheduled dosing day is not possible, once-weekly Sogroya can be taken up to 2 days before or 3 days after the scheduled weekly dosing day as long as the time between two doses is at least 4 days (96 hours). Once-weekly dosing for the next dose could be resumed at the regularly scheduled dosing day.

**Special populations**

***Elderly (60 years of age or older)***

Generally, lower doses of Sogroya may be necessary in older patients. For further information, see section 5.2.

***Gender***

Adults: Women may require higher doses than men, with men showing an increasing IGF-1 sensitivity over time. This means that there is a risk that women, especially those on oral oestrogen replacement are undertreated while men are overtreated. In women using oral oestrogen replacement, it should be considered to change the route of oestrogen administration (e.g. transdermal, vaginal). See sections 4.4 and 5.2.

***Race and ethnicity***

No dose adjustment is required based on race. Ethnicity (Hispanic or Latino 4,5 % (15 subjects received somapacitan)) was not investigated due to small sample size in the development programme.

***Patients with renal impairment***

Adults: No adjustment of the starting dose is required for patients with renal impairment. Patients with renal impairment may need lower doses of somapacitan but since the dose of somapacitan is individually adjusted according to the need of each patient, no further dose adjustment is required (see section 5.2). Sogroya is not recommended in patients with severe hepatic impairment. Sogroya has not been studied in paediatric patients with renal impairment.

***Patients with hepatic impairment***

Adults: No adjustment of the starting dose is required for patients with hepatic impairment. Patients with moderate hepatic impairment may need higher doses of somapacitan but since the dose of somapacitan is individually adjusted according to the need of each patient, no further dose adjustment is required (see section 5.2). Sogroya is not recommended in patients with severe hepatic impairment.

Sogroya has not been studied in paediatric patients with hepatic impairment.

**Method of administration**

Subcutaneous injection.

Sogroya is to be administered once weekly at any time of the day.

Sogroya is to be injected subcutaneously in the abdomen, thighs, buttocks or upper arms.

The injection site should be rotated every week.

For further information on administration, see section 6.6.

The Sogroya 5 mg/1,5 mL (3,3 mg/mL) pen delivers doses from 0,025 mg to 2 mg in increments of 0,025 mg (0,0075 mL).

The Sogroya 10 mg/1,5 mL (6,67 mg/mL) pen delivers doses from 0,05 mg to 4 mg in increments of 0,05 mg (0,0075 mL).

The Sogroya 15 mg/1,5 mL (10 mg/mL) pen delivers doses from 0,10 mg to 8 mg in increments of 0,1 mg (0,01 mL).

**Missed dose**

Patients who miss a dose are advised to inject once-weekly Sogroya upon discovery as soon as possible, within 3 days after the missed dose, and then resume their usual once-weekly dosing schedule. If more than 3 days have passed, the dose should be skipped and the next dose should

be administered on the regularly scheduled day. If two or more doses have been missed, the dose should be resumed on the regularly scheduled day.

## 4.3 Contraindications

Known hypersensitivity to somapacitan or to any of the excipients listed in section 6.1.

Sogroya must not be used when there is any evidence of activity of a tumour. Intracranial tumours must be inactive and antitumour therapy must be completed prior to starting somapacitan therapy. Treatment should be discontinued if there is evidence of tumour growth.

Sogroya should not be used for longitudinal growth promotion in children with closed epiphyses.

(Adults) Patients with acute critical illness suffering from complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar conditions should not be treated with Sogroya.

Active proliferative or severe non-proliferative diabetic retinopathy.

## 4.4 Special warnings and precautions for use

### Traceability

In order to improve the traceability of biological medicines, the name and the batch number of the administered product should be clearly recorded.

### Adrenocortical insufficiency

Patients receiving growth hormone therapy who have or are at risk for pituitary hormone deficiency(s) may experience reduced serum cortisol levels and/or unmasking of central (secondary) hypoadrenalism. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of growth hormone treatment. Monitor patients for reduced serum cortisol levels and/or need for glucocorticoid dose increases in those with known hypoadrenalism.

### Thyroid function

Growth hormone increases the extrathyroidal conversion of T4 to T3 and may as such unmask

incipient hypothyroidism. As hypothyroidism interferes with the response to growth hormone therapy, patients should have their thyroid function tested regularly, and should receive replacement therapy with thyroid hormone when indicated.

**Glucose metabolism impairment**

Treatment with growth hormone may decrease insulin sensitivity, particularly at higher doses in susceptible patients, and consequently hyperglycaemia may occur in subjects with inadequate insulin secretory capacity. As a result, previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during growth hormone treatment. Therefore, glucose levels should be monitored periodically in all patients treated with growth hormone, especially in those with risk factors for diabetes mellitus, such as obesity, or a family history of diabetes mellitus. Patients with pre-existing type 1 or type 2 diabetes mellitus or impaired glucose tolerance should be monitored closely during growth hormone therapy (see section 4.5). The doses of antihyperglycaemic medicines (i.e. insulin or oral agents) may require adjustment when growth hormone therapy is instituted in these patients.

**Neoplasms**

There is no evidence for increased risk of new primary cancers in adults, treated with growth hormone.

In patients in complete remission from malignant disease or pituitary tumour, growth hormone therapy has not been associated with an increased relapse rate.

Patients who have achieved complete remission of malignant disease or pituitary tumour should be followed closely for relapse after commencement of growth hormone therapy. Growth hormone treatment should be interrupted in case of any development or reoccurrence of malignant disease.

An overall slight increase in second neoplasms has been observed in childhood cancer survivors treated with growth hormone, with the most frequent being intracranial tumours. The dominant risk factor for second neoplasms seems to be prior exposure to radiation.

**Benign intracranial hypertension**

In the event of severe or recurrent headache, visual symptoms, nausea, and/or vomiting, a fundoscopy for papilloedema is recommended. If papilloedema is confirmed, a diagnosis of benign intracranial hypertension should be considered and if appropriate the growth hormone treatment should be discontinued. At present there is insufficient evidence to guide clinical decision making in patients with resolved intracranial hypertension. If growth hormone treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.

**Lipohypertrophy**

When Sogroya is administered at the same site over a long period of time, lipohypertrophy may occur. The injection site should be rotated to reduce the risk, see sections 4.2 and 4.8.

**Adults**

***Oral oestrogen replacement***

Oral oestrogen influences the IGF-I response to growth hormone including somapacitan.
Women taking any form of oral oestrogen replacement should consider changing the route of oestrogen administration (e.g. transdermal-, vaginal hormone products). If a woman on oral oestrogen replacement is starting Sogroya therapy, higher starting doses and a longer titration period may be required (see section 4.2).
If a woman using Sogroya begins oral oestrogen replacement, the dose of somapacitan may need to be increased to maintain the serum IGF-I levels within the normal age-appropriate range. Conversely, if a woman on Sogroya discontinues oral oestrogen replacement, the dose of somapacitan may need to be reduced to avoid excess of somapacitan and/or undesirable effects, see sections 4.2 and 4.5.

**Long term treatment**

Growth hormone deficiency is a lifelong disease and needs to be treated accordingly.

**Laboratory Tests**

Serum levels of inorganic phosphorus and alkaline phosphatase may increase after Sogroya therapy.

Serum levels of parathyroid hormone may increase with somatropin treatment.

**Sodium**

This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially sodium-free.

## 4.5 Interaction with other medicines and other forms of interaction

**Cytochrome P450 metabolised medicines**

Data from an interaction study performed in growth hormone deficient adults suggests that growth hormone administration may increase the clearance of medicines known to be metabolised by cytochrome P450 isoenzymes. The clearance of medicines metabolised by cytochrome P450 (e.g. sex steroids, corticosteroids, anticonvulsants and ciclosporin) may be especially increased resulting in lower plasma levels of these medicines. The clinical significance of this is unknown.

**Glucocorticoids**

Growth hormone decreases the conversion of cortisone to cortisol and may unmask previously undiscovered central hypoadrenalism or render low glucocorticoid replacement doses ineffective, see section 4.4.

**Antihyperglycaemic medicines**

Antihyperglycaemic treatment including insulin may require dose adjustment in case of Sogroya co-administration since somapacitan may decrease insulin sensitivity, see sections 4.4 and 4.8.

**Other**

The metabolic effects of somapacitan can also be influenced by concomitant therapy with other hormones, e.g. testosterone and thyroid hormones, see section 4.4.

**Adults**

***Oral oestrogen replacement***

In women on oral oestrogen replacement, a higher dose of Sogroya may be required to achieve the treatment goal.

## 4.6 Fertility, pregnancy and lactation

**Pregnancy**

There are no data from the use of somapacitan in pregnant women. Studies in animal have shown reproductive toxicity, see section 5.3.

Sogroya is not recommended during pregnancy and in women of childbearing potential not using contraception.

**Breastfeeding**

It is unknown whether somapacitan/metabolites are excreted in human milk.

Available pharmacodynamic/toxicological data in animals have shown excretion of somapacitan in milk, see section 5.3.

A risk to the breastfed newborns/infants cannot be excluded.

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

**Fertility**

There is no clinical experience with somapacitan use and its potential effect on fertility. No adverse effects were observed on male and female fertility in rats, see section 5.3.

## 4.7 Effects on ability to drive and use machines

Sogroya has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

**Paediatric GHD**

***Summary of safety profile***

In paediatric patients, the adverse drug reactions (ADRs) are (in decreasing order) headache (12 %), hypothyroidism (5%), injection site reactions (5 %), peripheral oedema (3 %), arthralgia (2 %), hyperglycaemia (2 %), fatigue (2 %), and adrenocortical insufficiency (1,5 %).
In general, the ADRs are non-serious, of mild severity and generally transient.

***Tabulated list of adverse reactions***

The ADRs listed below are based on the safety data from one ongoing pivotal phase 3 trial (52 weeks) in paediatric patients with GHD and adverse reactions from somapacitan treatment. The frequencies of the ADRs have been calculated based on the frequencies in the pivotal phase 3 trial.

The ADRs are listed by MedDRA system organ class and frequency category 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 2: Adverse reactions from phase 3 clinical trial (GHD)**

| **MedDRA system organ class** | **Very common** | **Common** |
|---|---|---|
| Endocrine disorders | | Hypothyroidism<br>Adrenocortical insufficiency |
| Metabolism and nutrition disorders | | Hyperglycaemia |
| Nervous system disorders | Headache | |
| Musculoskeletal and connective tissue disorders | | Arthralgia |
| General disorders and | | Peripheral oedema |

| | | |
|---|---|---|
| administration site conditions | | Injection site reactions<br>Fatigue |

***Description of selected adverse reactions***

- Headache was very commonly observed (12 %). Almost all of the cases were of mild severity, and the majority of the cases recovered.
- Peripheral oedema was commonly observed (3 %). All cases were of mild severity, and all cases recovered.
- Hypothyroidism was commonly observed (5 %). Almost all of the cases were of mild severity, and the hypothyroidism did not recover spontaneously. Refer to section 4.4.
- Injection site reactions were commonly observed (5 %). All cases were of mild severity, and the majority of cases recovered after short durations. The injection site reactions were injection site bruising (1,5 %), injection site pain (1,5 %), injection site haematoma (1,5 %) and injection site swelling (0,8 %).

**Adult GHD**

***Summary of safety profile***

The commonly reported and serious adverse reactions after treatment with somapacitan are headache (12 %), peripheral oedema (4 %) and adrenocortical insufficiency (3 %).

***Tabulated list of adverse reactions***

The adverse reactions listed below are based on the compiled safety data from three completed phase 3 trials in patients with AGHD. The frequencies of the ADRs have been calculated based on a pool of the phase 3a trials.

The adverse reactions are listed by MedDRA system organ class and frequency category 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**

| **MedDRA system organ class** | **Very common** | **Common** | **Uncommon** |
|---|---|---|---|
| Endocrine disorders | | Adrenocortical insufficiency<br>Hypothyroidism | |
| Metabolism and nutrition disorders | | Hyperglycaemia* | |
| Nervous system disorders | Headache | Paraesthesia | Carpal tunnel syndrome |
| Skin and subcutaneous tissue disorders | | Rash*<br>Urticaria* | Lipohypertrophy*<br>Pruritus* |
| Musculoskeletal and connective tissue disorders | | Arthralgia<br>Myalgia<br>Muscle stiffness* | Joint stiffness |
| General disorders and administration site conditions | | Peripheral oedema<br>Fatigue<br>Asthenia<br>Injection site reactions* | |

*In general, these adverse reactions were non-serious, mild or moderate severity and transient.

***Description of selected adverse reactions***

- Headache was very commonly observed (12 %). Almost half of the cases were of mild severity

and almost all the cases were transient and recovered.

- Fatigue and asthenia (weakness) was commonly observed (6% and 3 %, respectively). The majority of cases were of mild severity and the majority of cases recovered.
- Peripheral oedema was commonly observed (4 %). All cases were of mild, or moderate severity and the majority of cases recovered. Growth hormone deficient patients are characterised by extracellular volume deficit. When treatment with growth hormone products is initiated, this deficit is corrected and with peripheral oedema and a slight weight increase may occur. This is usually dose-dependent and transient.
- Adrenocortical insufficiency was commonly observed (3 %). All cases were of mild, or moderate severity and the majority of the cases recovered. Refer to section 4.4.
- Hyperglycaemia was commonly observed (1 %). All cases were of mild severity and all the cases were transient and recovered., refer to section 4.4.
- Lipohypertrophy at the injection site was uncommonly observed (0,4 %). In the single case observed, the adverse event was of mild severity, non-serious, transient and recovered after change of the injection site.

***Other special populations***

*Renal impairment*

Sogroya was well tolerated in subjects with renal impairment.

*Hepatic impairment*

Sogroya was well tolerated in subjects with hepatic impairment.

*Elderly*

Sogroya was well tolerated in the elderly (60 years of age or older).

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of Sogroya is important. It allows continued monitoring of the benefit/risk balance of Sogroya. Health care providers are asked to

report any suspected adverse reactions via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

### 4.9 Overdose

There is limited clinical experience with overdose of Sogroya.

## 5. PHARMACOLOGICAL PROPERTIES

**Category and class:** A 21.10 Trophic hormones

**Pharmacotherapeutic group:** Pituitary and hypothalamic hormones and analogues, somatropin and somatropin agonists, ATC code: H01AC07.

### 5.1 Pharmacodynamic properties

**Mechanism of action**

The mechanism of action of somapacitan is either directly via the GH-receptor and/or indirectly via IGF-I produced in tissues throughout the body, but predominantly by the liver.

When growth hormone deficiency is treated with somapacitan a normalisation of body composition (i.e., decreased body fat mass, increased lean body mass) and of metabolic action is achieved.

Somapacitan distributes to the hypertrophic zone and primary spongiosa in the epiphysis of proximal tibia of GH-deficient hypophysectomised rats. Distribution of somapacitan to peripheral tissues is comparable to GH.

Somapacitan stimulates skeletal growth in paediatric patients with GHD as a result of effects on the growth plates (epiphyses) of bones.

**Pharmacodynamic data**

***IGF-I***

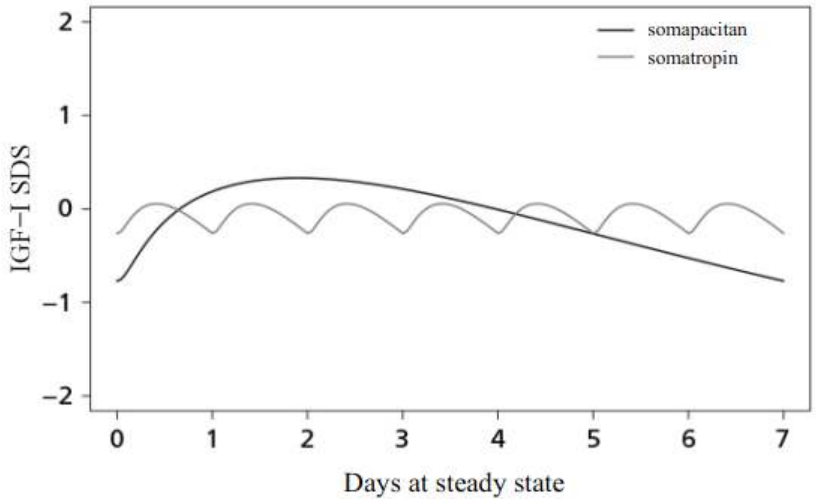
IGF-I is a generally accepted biomarker for efficacy in GHD.

A dose-dependent IGF-I response is induced following somapacitan administration. Steady state IGF-I was reached after 1-2 weekly doses with limited cumulative IGF-I concentrations.

The IGF-I levels (peak to trough) fluctuated during the week. The IGF-I response is maximal after 2 to 4 days. Compared with daily GH treatment, the IGF-I profile of somapacitan differs, see Figure 1.

In paediatric GHD patients somapacitan produces a dose linear IGF-I response, with a change of 0.02 mg/kg on average resulting in a change in IGF-I standard deviation score (SDS) of 0.32.

**Figure 1: Model-derived IGF-I profiles during steady state of somapacitan and somatropin (based on data from AGHD)**




***Cardiac electrophysiology (QTc)***

The potential effect of somapacitan in adults on cardiac repolarisation was assessed based on ECGs collected at around the time of $C_{max}$ for somapacitan at therapeutic doses in the pivotal phase 3 trial REAL 1. There was no correlation/association between the change from baseline in QTcF and the somapacitan concentration. The results of the overall interpretation of ECGs and the evaluation of adverse events related to cardiac safety did not indicate any safety signals.

**Clinical efficacy and safety**

***Paediatric GHD***

*REAL 4 (phase 3)*

The efficacy and safety of once weekly Sogroya (5 mg/1,5 mL, 10 mg/1,5 mL and 15 mg/1,5 mL) was evaluated in a 52 weeks randomised, multi-centre, open-label, active-controlled, parallel-group phase 3 trial (REAL 4) in 200 treatment-naïve, pre-pubertal paediatric patients with GHD. Patients were randomised to 0,16 mg/kg/week once weekly Sogroya (N=132) or 0,034 mg/kg/day daily somatropin (N=68).

At baseline, the 200 patients had a mean age of 6,4 years (range: 2,5 to 11). 25,5 % patients were female and 74,5 % were male. 37 % of patients were Asian, 0,5 % were Black or African American, 57 % were Caucasian, and 5,5 % were categorised as 'other' or not reported.

Treatment with once weekly Sogroya for 52 weeks resulted in an annualised height velocity of 11,2 cm/year. Patients treated with daily somatropin achieved an annualised height velocity of 11,7 cm/year after 52 weeks of treatment (Table 4).

**Table 4: Growth results at Week 52 in paediatric patients with GHD**

| | Once weekly Sogroya (N=132) | Daily somatropin (N=68) | Estimate of treatment difference (95 % CI) (Sogroya minus somatropin) |
|---|---|---|---|
| Annualised Height Velocity (cm/year) | 11,2 | 11,7 | -0,5 [-1,1; 0,2] |

Height SDS (change from baseline) was 1,25 in the once weekly Sogroya arm and 1,30 in the daily

somatropin arm at Week 52 (Table 5). The IGF-I SDS change from baseline at week 52 was highly similar in the two arms with values of 2,36 for once weekly Sogroya and 2,33 for daily somatropin Mean IGF-I SDS was also similar between Sogroya and daily somatropin at week 52.

**Table 5: Height SDS and IGF-I SDS in paediatric patients with GHD – 52 weeks treatment**

| | Once weekly Sogroya (N=132) | Daily somatropin (N=68) | Estimate of treatment difference (95 % CI) (Sogroya minus somatropin) |
|---|---|---|---|
| Height SDS, baseline[a] | -2,99 | -3,47 | |
| Height SDS, change from baseline | 1,25 | 1,30 | 0,05 [-0,18; 0,08] |
| IGF-I SDS, baseline[a] | -2,03 | -2,33 | |
| IGF-I SDS, week 52[a] | 0,28 | 0,10 | |
| IGF-I SDS level change from baseline | 2,36 | 2,33 | 0,03 [-0,30; 0,36] |

[a] Observed mean

The vast majority of paediatric patients (97 %) in the trial achieved an average IGF-I SDS level within normal range (-2 to +2) after 52 weeks of treatment with once weekly Sogroya (Table 6). Low number of patients had average IGF-I SDS above +2 (2,3 %) and no patients had average IGF-I SDS above +3.

**Table 6: Average IGF-I SDS values after 52 weeks of treatment of paediatric patients with GHD with once weekly Sogroya**

| IGF-I SDS category | Week 52 Average (N=132) |
|---|---|
| <-2 | 0,8 % |
| -2 to 0 | 21,2 % |
| 0 to +2 | 75,8 % |
| +2 to +3 | 2,3 % |
| >+3 | 0 |

*REAL 3 (phase 2)*

A total of 59 GH treatment-naïve GH-deficient paediatric patients completed a 26-week main period and a 26-week extension in a 4-arm parallel group trial with once weekly Sogroya at dose levels of 0,04, 0,08 and 0,16 mg/kg/week and active control arm of 0,034 mg/kg/day daily somatropin.

The patients continued in a 104-week open-label safety extension parallel arms with Sogroya 0,16 mg/kg/week and daily somatropin 0,034 mg/kg/day. All patients were afterwards transferred to once weekly Sogroya 0,16 mg/kg/week in a 208-week long-term safety extension.

Treatment with once weekly Sogroya 0,16 mg/kg/week led to continuous treatment benefits up to at least 4 years.

Height SDS was -1,06 (change from baseline: +2,85) in 38 patients.

Height outcome obtained at week 208 in patients switching from 0,034 mg/kg/day daily somatropin to 0,16 mg/kg/week once weekly Sogroya at week 156 indicated that treatment benefits with daily GH treatment are maintained after switching to once weekly Sogroya.

Mean IGF-I SDS remained within the normal range for all groups.

*IGF-I SDS sampling after injection*

Blood samples may be taken on any day of the week following injections of somapacitan. Sampling 2 days after the injection closely approximates the expected maximum IGF-I value, whereas the average IGF-I concentration over the weekly dosing interval is most closely approximated with a sample taken 4 days after injection.

Based on clinical trial data in paediatric GHD patients, a guidance for calculating average IGF-I SDS based on blood sampling after injection is provided in Table 7.

**Table 7: Formula for calculating approximate average IGF-I SDS over the weekly dosing interval in paediatric subjects based on blood sampling after injection**

| **Interval**<br>**Days (hours) after dose** | **Measured IGF-I SDS adjustment to approximate average IGF-I SDS** |
|---|---|
| 1 day after dose (25 – 48 hours) | IGF-I SDS – 0,8 |
| 2 days after dose (49 – 72 hours) | IGF-I SDS – 1,0 |
| 3 days after dose (73 – 96 hours) | IGF-I SDS – 0,5 |
| 4 days after dose (97 – 120 hours) | No adjustment* |
| 5 days after dose (121 – 144 hours) | IGF-I SDS + 0,7 |
| 6 days after dose (145 – 168 hours) | IGF-I SDS + 1,1 |

* No adjustment based on the result of IGF-I SDS + 0,1, which is considered of negligible clinical relevance

***Clinical safety***

The safety profile of somapacitan was similar to the well-known safety profile of somatropin, section 4.8. No new safety issues were identified. No local tolerability issues were identified.

***Immunogenicity***

A low number of patients tested positive for somapacitan binding antibodies at any time during treatment. None of these antibodies were neutralising and there was no clinical impact.

***Patient Reported Outcomes***

*REAL 4*

Paediatric patients treated with once weekly Sogroya reported a lower treatment burden as measured using the GHD-CTB[1] at week 52 compared to patients treated with daily somatropin.

Caregivers of paediatric patients treated with once weekly Sogroya reported lower treatment burden as measured using the GHD-PTB[2] at week 52 compared to patients treated with daily somatropin.

**Table 8: Results of GHD-CTB and GHD-PTB in REAL 4 at 52 weeks**

| | Result at Week 52 (Sogroya) | Result at Week 52 (somatropin) | ETD* (Sogroya – somatropin) [95 % CI] |
|---|---|---|---|
| GHD-CTB | | | |
| Physical | 11,6 | 14,5 | -2,9 [-6,8; 1,0] |
| Emotional well-being | 15,5 | 19,1 | -3,5 [-9,5; 2,4] |
| Interference | 5,2 | 6,4 | -1,3 [-3,9; 1,3] |
| Overall score | 10,7 | 13,1 | -2,4 [-5,7; 0,9] |
| GHD-PTB | | | |
| Emotional well-being | 12,4 | 17,7 | -5,3 [-10,0; -0,7] |
| Interference | 4,9 | 11,6 | -6,7 [-11,6; -1,9] |
| Overall score | 8,7 | 14,7 | -6,0 [-10,0; -2,1] |

[1] GHD-CTB (Growth Hormone Deficiency – Child Treatment Burden)

[2] GHD-PTB (Growth Hormone Deficiency – Parent Treatment Burden)

* Lower scores indicate improvement

ETD (estimated treatment difference)

*REAL 3*

82 % of caregivers of paediatric patients who switched from daily somatropin preferred once weekly Sogroya using the PPQ (Patient Preference Questionnaire).
89 % of those who preferred once weekly Sogroya, indicated that they would be more adherent to therapy than daily somatropin.

***Adult GHD***

Improvement in body composition with an increase in lean body mass parameters and reduction of adipose tissue parameters are an integral part of the treatment of AGHD.

The efficacy and safety of once weekly Sogroya 10 mg/1,5 mL were evaluated in three randomised controlled phase 3 clinical trials in adult patients with confirmed growth hormone deficiency. Of these, one trial (REAL 1) assessed changes in truncal fat percentage (%) as the primary endpoint, while the two other trials (REAL 2 and REAL JP) evaluated safety of somapacitan as the primary objective. REAL JP was conducted in Japanese patients only.

The trials included in total 454 randomised adult patients with growth hormone deficiency (333 treated with Sogroya).

Adult GHD patients treated with Sogroya demonstrated a decrease in truncal fat percentage (%), visceral adipose tissue, truncal fat mass, total fat mass and android fat mass that is accompanied by an increase in truncal lean body mass, lean body mass and appendicular skeletal muscle mass.

A dose up to 8 mg per week has been used in the phase 3 clinical trials.

*REAL 1*

In a 34-week, double-blinded, placebo-controlled study, treatment naïve adult patients with GHD were randomised (2:1:2) and exposed to once-weekly Sogroya 10 mg/1,5 mL (N=120) or to placebo (N=60) or to daily somatropin for a 34-week treatment period (main phase of the trial).

A total of 272 AGHD patients who completed the 34-week main phase continued on a 53-week open-label extension period. Subject on placebo were switched to Sogroya and patients on somatropin were re-randomised (1:1) to either Sogroya or somatropin.

Patients had a mean age of 45,1 years with the majority of patients in the age group from 23 to 64 years, 51,7 % were females, and 69,7 % had adult onset GHD. The mean BMI was 27,4 kg/$m^2$. There were 66,7 % White, 28,7 % Asian and 2,3 % Black or African American. For ethnicity, 4,5 % patients were Hispanic or Latino.

Treatment with Sogroya demonstrated superiority compared to placebo with a statistically significant reduction in truncal fat % after 34 weeks (see Table 9).

**Table 9: Results at 34 weeks in REAL 1**

| **Change from baseline at 34 weeks[a]** | **Somapacitan** | **Somatropin** | **Placebo** | **Difference Somapacitan-placebo [95 % CI] p-value** |
|---|---|---|---|---|
| Number of subjects in FAS (N) | 120 | 119 | 61 | |
| Truncal fat % Primary | -1,06 | -2,23 | 0,47 | -1,53 [-2,68; -0,38] 0,0090[b] |

| | | | | |
|---|---|---|---|---|
| analysis of primary endpoint | | | | |
| Visceral adipose tissue ($cm^2$) | -10 | -9 | 3 | -14 [-21; -7] 0,0001[c] |
| Appendicular skeletal muscle mass (ASMM) (g) | 558 | 462 | -121 | 679 [340; 1,019] 0,0001[c] |
| Lean body mass (g) | 1,394 | 1,345 | 250 | 1144 [459; 1,829] 0,0011[c] |
| IGF-I SDS level | 2,40 | 2,37 | -0,01 | 2,40 [2,09;2,72] |

**Abbreviations:** N = Number of subjects in FAS, CI = Confidence interval, DM Diabetes Mellitus. Changes in truncal fat % from baseline to the 34 week's measurements was analysed using an analysis of covariance model with treatment, GHD onset type, sex, region, DM and sex by region by DM interaction as factors and baseline as a covariate incorporating a multiple imputation technique where missing week 34 values were imputed based on data from the placebo group. ASMM=Appendicular skeletal muscle mass. Estimated change from baseline to the 34 week's measurements was analysed using an analysis of covariance model with treatment, GHD onset type, sex, region, DM and sex by region by DM interaction as factors and baseline as a covariate incorporating a multiple imputation technique where missing week 34 values were imputed based on data from the placebo group.

[a] Body composition parameters based on dual-energy X-ray absorptiometry (DXA) scanning.

[b] The primary analysis was a comparison of changes from baseline for somapacitan and placebo in truncal fat %. Changes in truncal fat % from baseline to the 34 week's measurements was analysed using an analysis of covariance model with treatment, GHD onset type, sex, region, DM

and sex by region by DM interaction as factors and baseline as a covariate incorporating a multiple imputation technique where missing week 34 values were imputed based on data from the placebo group.

[c] p for treatment difference unadjusted for multiplicity.

Improvements of abnormal body composition manifestations in adults with GHD were observed for Sogroya compared to placebo, see Table 9.

Sogroya induced reductions pertaining to abdominal adipose tissue (visceral adipose tissue mass, truncal fat mass and android fat mass) were observed at 34 weeks for Sogroya compared to placebo with statistically significant reductions in visceral adipose tissue (VAT). Visceral fat reduction is an important indicator of metabolic risk, in particular risk of cardiovascular disease. Across the lean body composition parameters (appendicular skeletal muscle mass and lean body mass) statistically significant increases from baseline were observed at 34 weeks with Sogroya® compared to placebo, see Table 9.

The observed clinical effects for the extension treatment phase (Table 10) are presented below.

**Table 10: Results at 87 weeks in REAL 1**

| **Change from baseline at 87 weeks[a]** | **somapacitan/ somapacitan** | **somatropin/ somatropin** | **placebo /somapacitan** | **somatropin/ somapacitan** | **Difference somapacitan/ somapacitan vs somatropin/ somatropin [95 % CI]** |
|---|---|---|---|---|---|
| Number of subjects (N) | 114 | 52 | 54 | 51 | |

| | | | | | |
|---|---|---|---|---|---|
| Truncal fat % | -1,52 | -2,67 | -2,28 | -1,35 | 1,15 [-0,10; 2,40] |
| Visceral adipose tissue ($cm^2$) | -6,64 | -6,85 | -10,21 | -8,77 | 0,22 [-10; 10] |
| Appendicular skeletal muscle mass (g) | 546,11 | 449,09 | 411,05 | 575,80 | 97,02 [-362; 556] |
| Lean body mass (g) | 1 739,05 | 1 305,73 | 1 660,56 | 1 707,82 | 433,32 [-404; 1271] |

[a] Body composition parameters are based on DXA scanning

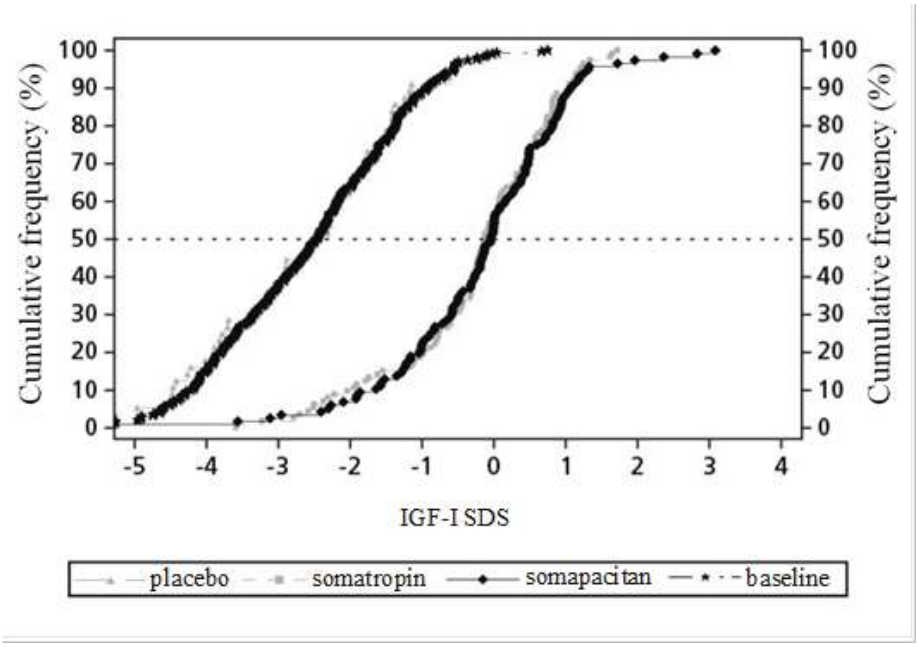
*IGF-I SDS*

REAL 1

After 34 weeks Sogroya normalised the mean IGF-I SDS from a baseline value below -2 to a value within the reference range (-2 to +2) in treatment naïve AGHD patients, see Figure 2 and Table 5. Statistically significant differences in change from baseline to week 34 in IGF-I SDS were observed between somapacitan and placebo.

Mean IGF-I SDS levels at 34 and 87 weeks for Sogroya were comparable to somatropin. The distribution of IGF-I SDS levels at the end of trial was similar between Sogroya and somatropin. The mean IGF-I SDS values were maintained within the reference range for up to 87 weeks.

**Figure 2: IGF-I SDS – empirical distribution at week 34 compared to baseline**




REAL 2 and REAL JP

In previously GH treated AGHD patients, the mean IGF-I SDS levels were similar for Sogroya and somatropin and maintained throughout the trials (REAL 2 and REAL JP) in both treatment groups. Both at baseline and at end-of-treatment the mean IGF-I SDS were within the reference range.

*Glucose metabolism*

Sogroya did not show changes in mean fasting glucose and $HbA_{1c}$. GH related effect on mean fasting insulin level comparable to the effect of somatropin was seen. Mean fasting insulin level remained within the normal ranges and no new cases of diabetes mellitus were reported in the phase 3 trials for Sogroya.

*Body weight*

No clinically relevant changes from baseline in mean body weight were observed following multiple-dose exposure of somapacitan in AGHD patients in any of the phase 3 trials. Similar mean values were observed for somapacitan and somatropin.

*Immunogenicity*

Data from clinical trials conducted in adults with somapacitan indicate no immunogenicity. No anti-

somapacitan antibodies were detected in any of the trials.

## 5.2 Pharmacokinetic properties:

Somapacitan has pharmacokinetic properties compatible with once weekly administration. The reversible binding to endogenous albumin delays elimination of somapacitan and thereby prolongs the in vivo half-life and duration of action.

The pharmacokinetics (PK) of somapacitan following subcutaneous administration have been investigated at dose levels from 0,02 to 0,16 mg/kg/week in paediatric population, at dose levels from 0,01 to 0,32 mg/kg in healthy adults, and in doses up to 0,12 mg/kg in adults with GHD. Overall, somapacitan displays non-linear pharmacokinetics.

In the clinically relevant dose range of somapacitan in adults with GHD, somapacitan pharmacokinetics are approximately linear.

### Absorption

In adult and paediatric patients with GHD median $t_{max}$ ranged from 4 to 24 hours at doses from 0,02 mg/kg/week to 0,16 mg/kg/week. Steady state exposure was achieved following 1 – 2 weekly administration.

Absolute bioavailability of somapacitan in human has not been investigated.

### Distribution

Somapacitan is extensively bound (> 99 %) to plasma proteins and is expected to be distributed like albumin. Based on population PK analyses, the estimated volume of distribution (V/F) was 1,7 L in paediatric GHD patients and 14,6 L in adults.

### Biotransformation

Somapacitan is extensively metabolised by proteolytic degradation and cleavage of the linker sequence between the peptide and albumin binder.

Somapacitan was extensively metabolised before excretion and no intact somapacitan was found neither in urine, which was the main excretion route (81 %), nor in faeces where 13 % of

somapacitan related material was found, indicating full biotransformation before excretion.

**Elimination**

Following a single dose of 0,16 mg/kg/week the terminal half-life was 34 hours in paediatric GHD patients.

The terminal half-life was estimated with geometric means ranging from approximately 2 to 3 days at steady state in GHD patients (doses: 0,02 to 0,12 mg/kg).

Somapacitan will be present in circulation for approximately 2 weeks after the last dose.

Little to no accumulation (mean accumulation ratio: 1 – 2) of somapacitan following multiple dosing has been observed.

**Special populations**

It is recommended that the dose is adjusted based on the clinical response and the patient's experience of adverse events. No additional dosing considerations of somapacitan is needed based on race (Japanese, Asian non-Japanese vs White), body weight, renal or hepatic impairment. For starting dose and dose adjustment information, refer to section 4.2.

***Paediatric GHD patients***

Based on population pharmacokinetic analysis gender, race and body weight do not have a clinically meaningful effect on the pharmacokinetics following weight-based dosing.

***Adult GHD patients***

*Age*

Subjects older than 60 years have higher exposure (29 %) than younger subjects at the same somapacitan dose. A lower starting dose for subjects above 60 years is described in section 4.2.

*Gender*

Female subjects and in particular female subjects on oral oestrogen, have lower exposure (53 % for females on oral oestrogen and 30 % for females not on oral oestrogen) than male subjects at

the same somapacitan dose. A higher starting dose for females on oral oestrogen is described in section 4.2.

*Race*

There was no difference in somapacitan exposure and IGF-I response between Japanese and white subjects. Despite a higher exposure in Asian non-Japanese compared to white at the same somapacitan dose, white, Japanese and Asian non-Japanese needed the same doses to reach similar IGF-I levels. Therefore, there is no dose adjustment recommendation based on race.

*Ethnicity*

Ethnicity (Hispanic or Latino 4,5% (15 subjects received somapacitan)) was not investigated due to small sample size in the development programme.

*Body weight*

Despite a higher exposure in subjects with low body weight as compared to subjects with high body weight at the same somapacitan dose, subjects needed the same doses to reach similar IGF-I levels across the body weight range 35 kg to 150 kg. Therefore, there is no dose adjustment recommendation based on body weight.

*Renal impairment*

A somapacitan dose of 0,08 mg/kg at steady state resulted in higher exposures in subjects with renal impairment, most pronounced in subjects with severe renal impairment and in subjects requiring haemodialysis, where $AUC_{0\text{-}168h}$ ratios to normal renal function were 1,75 and 1,63, respectively. In general, somapacitan exposure tended to increase with decreasing GFR.
Higher IGF-$I_{AUC0\text{-}168h}$ levels were observed in subjects with moderate and severe renal impairment and subjects requiring haemodialysis, with ratios to normal renal function of 1,35, 1,40 and 1,24 respectively.
Due to the modest increase observed in IGF-I combined with the low recommended starting doses and the individual dose titration of somapacitan, there is no dose adjustment recommendation in

patients with renal impairment.

*Hepatic impairment*

A somapacitan dose of 0,08 mg/kg at steady state resulted in higher exposure in subjects with moderate hepatic impairment with ratios to normal hepatic function of 4,69 for $AUC_{0\text{-}168h}$ and 3,52 for $C_{max}$.

Lower somapacitan stimulated IGF-I levels were observed in subjects with mild and moderate hepatic impairment compared to subjects with normal hepatic function (ratio to normal was 0,85 for mild and 0,75 for moderate).

Due to the modest decrease observed in IGF-I combined with the individual dose titration of somapacitan, there is no dose adjustment recommendation in patients with hepatic impairment.

## 5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity or pre- and postnatal development.

No genotoxic potential was identified in the *in vitro* or *in vivo* studies conducted with somapacitan.

No carcinogenicity studies have been performed with somapacitan.

No adverse effects were observed on male and female fertility in rats at a dose resulting in exposure at least 29 times greater than the expected maximum clinical exposure at 8 mg/week in adults. However, irregular female oestrus cycle was seen at all doses treated.

Such findings in rats are known to resolve after birth. No evidence of foetal harm was identified when pregnant rats and rabbits were administered subcutaneous somapacitan during organogenesis at doses leading to exposures well above expected exposure at the maximum clinical dose of 8 mg/week (at least 18-fold). At high doses leading to exposure at least 250-fold above the expected maximum clinical exposure at 8 mg/week, short/bent/thickened long bones were found in pups from female rats receiving and should be regarded as minor malformations, not permanent abnormalities.

No juvenile toxicity studies have been performed, since no target tissue with specific concern for paediatric patients has been identified in the toxicity studies.

In lactating rats, somapacitan related material was secreted into milk but to a lower level than observed in plasma (up to 50% of level in plasma).

The local reactions seen in both the rat and Cynomolgus monkey after subcutaneous administration and in the rabbit after intramuscular, intravenous and intra-arterial injection were considered mild and acceptable for clinical administration.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Histidine

Mannitol

Poloxamer 188

Phenol

Water for injections

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment).

### 6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

### 6.3 Shelf life

24 months.

***After first opening***

6 weeks. Store in a refrigerator (2 °C – 8 °C).

Do not freeze. Keep away from the freezing element.

Keep Sogroya in the outer carton with the pen cap on to protect from light.

***Before and after first opening***

If refrigeration is not possible (e.g. during travelling), Sogroya may be kept temporarily at temperatures up to 30 °C for up to a total of 72 hours (3 days).

Return Sogroya to the refrigerator again after storage at this temperature.

If stored out of refrigeration and then returned to refrigeration, the total combined time out of refrigeration should not exceed 3 days, monitor this carefully.

The Sogroya pen should be discarded, if it has been kept up to 30 °C for more than 72 hours (3 days) or for any period of time kept above 30 °C.

### 6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Do not freeze. Keep away from the freezing element.

Keep Sogroya in the outer carton with the pen cap on to protect from light.

For storage conditions after first opening of this medicine, see section 6.3.

### 6.5 Nature and contents of container

The primary packaging for Sogroya is a 1,5 mL glass cartridge (Type I colourless glass) with a plunger made of chlorobutyl rubber and a stopper made of bromobutyl/isoprene rubber sealed with an aluminium cap.

The cartridge is contained in a multidose disposable pen made of polypropylene, polyacetal, polycarbonate and acrylonitrile butadiene styrene and in addition two metal springs. The cartridge is permanently sealed in a pen-injector.

The dose button and cap on the pen-injector is colour–coded according to strength:

Sogroya 5 mg/1,5 mL is coloured teal.

Sogroya 10 mg/1,5 mL is coloured yellow.

Sogroya 15 mg/1,5 mL is coloured rubine red.

Pack sizes: a carton containing 1 pre-filled pen or a multipack of 5 (5 packs of 1) pre-filled pens.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

The pen is for use by one person only.

Sogroya should not be used if the solution does not appear clear to slightly opalescent, colourless to slightly yellow and free from visible particles.

Sogroya must not be used if it has been frozen.

The cartridge must not be taken out of the pre-filled pen and refilled.

A new needle must always be attached before use. Needles must not be re-used. The injection needle should be removed after each injection and the pen should be stored without a needle attached. This may prevent blocked needles, contamination, infection, leakage of solution and inaccurate dosing.

In the event of blocked needles, patients must follow the instructions described in the instructions for use accompanying the patient information leaflet.

Needles are not included. Sogroya pre-filled pen is designed to be used with disposable needles of a length between 4 mm and 8 mm and a gauge between 30G and 32G.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Novo Nordisk (Pty) Ltd

150 Rivonia Road

10 Marion Street Office Park

Building C1

Sandton, Johannesburg

2196

## 8. REGISTRATION NUMBERS

Sogroya® 5 mg/1,5 mL: 57/21.10/0738

Sogroya® 10 mg/1,5 mL: 57/21.10/0739

Sogroya® 15 mg/1,5 mL: 57/21.10/0740

## 9. DATE OF FIRST AUTHORISATION

08 October 2024

## 10. DATE OF REVISION OF THE TEXT

08 October 2024