Australian Government
Department of Health
Therapeutic Goods Administration

# Australian Public Assessment Report for Sogroya

## Active ingredients: Somapacitan

## Sponsor: Novo Nordisk Pharmaceuticals Pty Ltd

**August 2022**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

# About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

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# List of abbreviations

| Abbreviation | Meaning |
|---|---|
| ACM | Advisory Committee on Medicines |
| AGHD | Adults with growth hormone deficiency |
| ARTG | Australian Register of Therapeutic Goods |
| ASA | Australia specific annex |
| AUC | Area under the concentration versus time curve |
| BMI | Body mass index |
| $C_{max}$ | Maximum concentration |
| CMI | Consumer Medicines Information |
| COR-B | Comparable overseas regulators B |
| DLP | Data lock point |
| EMA | European Medicines Agency (European Union) |
| EU | European Union |
| FDA | Food and Drug Administration (United States of America) |
| GH | Growth hormone |
| GHRH | Growth hormone-releasing hormone |
| IGF-1 | Insulin-like growth factor 1 |
| PD | Pharmacodynamic(s) |
| PK | Pharmacokinetic(s) |
| PI | Product Information |
| popPK | Population pharmacokinetic(s) |
| PSUR | Periodic Safety Update Reports |
| PV | Pharmacovigilance |
| RMP | Risk management plan |
| TGA | Therapeutic Goods Administration |
| $T_{max}$ | Time of maximum concentration |

| Abbreviation | Meaning |
|---|---|
| US(A) | United States (of America) |

# Product submission

## Submission details

| | |
|---|---|
| *Type of submission:* | New biological entity |
| *Product name:* | Sogroya |
| *Active ingredient:* | Somapacitan |
| *Decision:* | Approved |
| *Date of decision:* | 14 February 2022 |
| *Date of entry onto ARTG:* | 21 February 2022 |
| *ARTG number:* | 363895 |
| ▼ *Black Triangle Scheme:* | Yes<br>This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia [for new medicines |
| *Sponsor's name and address:* | Novo Nordisk Pharmaceuticals Pty Ltd<br>Level 10, 118 Mount Street<br>North Sydney, NSW, 2060 |
| *Dose form:* | Solution for injection |
| *Strength:* | 6.7 mg/mL (10 mg/1.5 mL) |
| *Container:* | Pre-filled pen (cartridge) |
| *Pack sizes:* | 1 and 5 |
| *Approved therapeutic use:* | *Sogroya is indicated for the replacement of endogenous growth hormone (GH) in adults with growth hormone deficiency (AGHD).* |
| *Route of administration:* | Subcutaneous |
| *Dosage:* | Somapacitan should be initiated and monitored by physicians who are appropriately qualified and experienced in the diagnosis and management of adult patients with growth hormone deficiency (for example, endocrinologists).<br>Dosage is based on multiple factors, including the age of the patient and whether the patient has been switched from daily growth hormone medicinal products.<br>The somapacitan dose must be individually adjusted for each patient. |

| | |
|---|---|
| | For further information regarding dosage, refer to the Product Information. |
| *Pregnancy category:* | B1<br>Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.<br>Studies in animals have not shown evidence of an increased occurrence of fetal damage.<br>The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory. |

## Product background

This AusPAR describes the submission by Novo Nordisk Pharmaceuticals Pty Ltd (the sponsor) to register Sogroya (somapacitan) 6.7 mg/mL, solution for injection for the following proposed indication:

> *For the once-weekly replacement of endogenous growth hormone (GH) in adults with growth hormone deficiency (AGHD). Sogroya is for subcutaneous injection once a week.*

Somapacitan is a growth hormone analogue indicated to treat adults with growth hormone deficiency. This human growth hormone analogue differs from endogenous growth hormone by the creation of an albumin binding site and prolonging the effect so that it requires weekly dosing rather than daily.

Structurally, somapacitan is a long acting growth hormone derivative with a single substitution in the peptide backbone, with leucine substituted by cysteine to which an albumin-binding moiety has been attached. The albumin-binding moiety consists of a 16-carbon chain fatty acid moiety and a hydrophilic spacer attached to the protein by chemical conjugation. Noncovalent reversible binding to endogenous albumin delays the elimination of somapacitan and therefore prolongs the *in vivo* half-life.

Somapacitan binds to the growth hormone receptor and the mechanism of action is either directly via binding to the growth hormone receptor or indirectly via IGF-1 (insulin-like growth factor one).

The proposed indication is adults with growth hormone deficiency. This is a rare condition. It may occur in associated with genetic or structural central nervous system disease, or in association with acquired conditions such as trauma, tumours, surgery or infiltration from other diseases.

Adults with growth hormone deficiency experience a difference range of symptoms and signs than children. These include lethargy, fatigue, increased adiposity, reduced muscle strength, depression and poor concentration.

There are number of somatropin products available on the Australian Register of Therapeutic Goods (ARTG) for use in growth hormone deficiency.[1] These products are given by subcutaneous injection 6 to 7 days each week.

The main advantage of Sogroya over other growth hormone products is that it is administered once per week.

This submission was submitted through the TGA's Comparable Overseas Regulator B (COR-B) process, using evaluation reports from European Medicines Agency (EMA). The full dossier was submitted to the TGA.

## Regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

At the time the TGA considered this submission, a similar submission had been approved in European Union (EU) on 31 March 2021, in United States of America (USA) on 28 August 2020 and in Japan on 22 January 2021. A similar submission was submitted to Switzerland on 7 October 2019 and subsequently withdrawn on 28 January 2021.[2]

The following table summarises these submissions and provides the indications where approved.

**Table 1: International regulatory status**

| Region | Submission date | Status | Approved indications |
|---|---|---|---|
| European Union<br>Rapporteur: Netherlands<br>Co-rapporteur: France | 16 September 2019 | Approved on 31 March 2021 | *Sogroya is indicated for the replacement of endogenous growth hormone (GH) in adults with growth hormone deficiency (AGHD).* |
| United States of America | 28 August 2019 | Approved on 28 August 2020 | *Sogroya is indicated for the replacement of endogenous growth hormone (GH) in adults with growth hormone deficiency (GHD).* |
| Switzerland | 7 October 2019 | Withdrawn on 28 January 2021;[2] | Not applicable. |

[1] Fact sheet: Human growth hormone (somatropin) products approved by the Therapeutic Goods Administration and on the Pharmaceutical Benefits Scheme/ Department of Health and Aged Care, April 2022. Available at: https://www.health.gov.au/resources/publications/human-growth-hormone-somatropin-approved-by-the-therapeutic-goods-administration-and-on-the-pharmaceutical-benefits-scheme

[2] Novo Nordisk withdrew the application in Switzerland on 28 January 2021, due to the remaining requirement for clinical data to be made available prior to a possible approval, rather than post-marketing as was agreed by the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) in Europe.

| Region | Submission date | Status | Approved indications |
|---|---|---|---|
| Japan | 27 February 2020 | Approved on 22 January 2021 | *Adult growth hormone deficiency (only severe case)* |

### Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

## Registration timeline

The following table captures the key steps and dates for this submission.

**Table 2: Timeline for Submission PM-2021-01699-1-5**

Standard pathway

| Description | Date |
|---|---|
| Submission dossier accepted and first round evaluation commenced | 1 June 2021 |
| First round evaluation completed | 25 August 2021 |
| Sponsor provides responses on questions raised in first round evaluation | 25 October 2021 |
| Second round evaluation completed | 26 November 2021 |
| Delegate's Overall benefit-risk assessment | 14 January 2022 |
| Sponsor's pre-Advisory Committee response | Not applicable |
| Advisory Committee meeting | Not applicable |
| Registration decision (Outcome) | 14 February 2022 |
| Completion of administrative activities and registration on the ARTG | 21 February 2022 |
| Number of working days from submission dossier acceptance to registration decision* | 133 |

*The COR-B process has a 175 working day evaluation and decision timeframe.

# Submission overview and risk/benefit assessment

This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

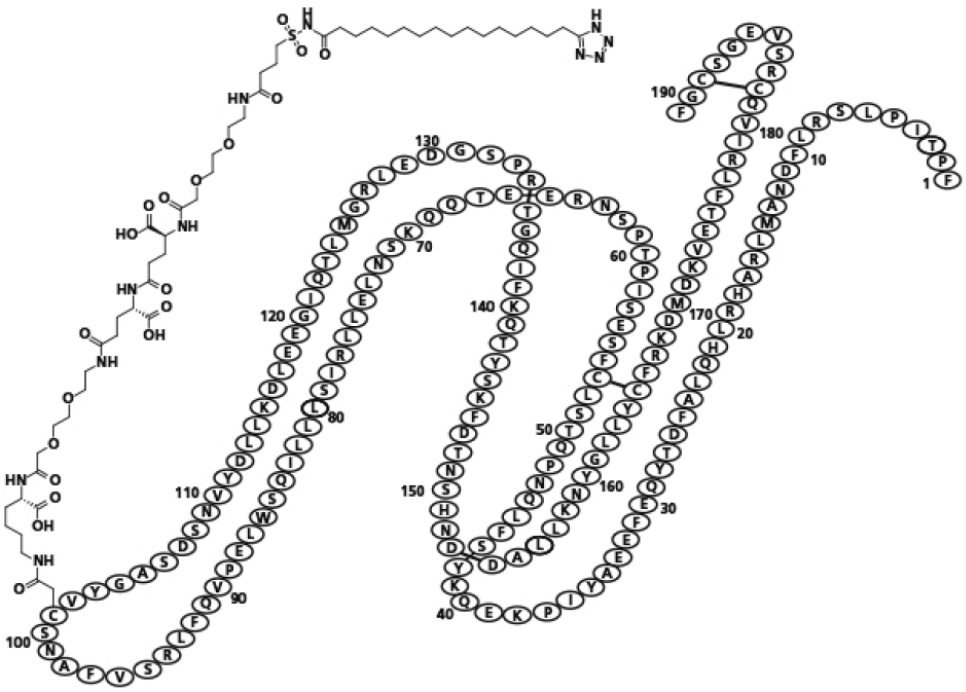
## Quality

Sogroya (somapacitan) solution for subcutaneous injection is presented as a single patient use pre-filled pen. Each pre-filled pen contains 10 mg in a deliverable volume of 1.5 mL. One mL of solution contains 6.7 mg of somapacitan.

The pen injector delivers doses from 0.05 mg to 4 mg in increments of 0.05 mg (0.075 mL). Excipients in product are mannitol, poloxamer, histidine, phenol, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment) and water for injection. The structural formula of sompacitan is shown in Figure 1.

Sogroya (somapacitan) solution is a sterile, clear to slightly opalescent, colourless to slightly yellow liquid, essentially free from visible particles.

**Figure 1: Structural formula of somapacitan**



Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Following evaluation, the recommended storage condition is 24 months when stored at 2 to 8°C.

In use stability data have also been submitted. The recommended shelf life and storage conditions for the opened product include an in use period of 6 weeks at 2 to 8°C including 72 hours (3 days) at or below 30°C.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the product information (PI), labels, consumer medicines information and the Australian Register of Therapeutic Goods (ARTG).

## Nonclinical

The submitted nonclinical dossier was of high quality with no major deficiencies. The scope of the nonclinical program was in accordance with the relevant TGA adopted guideline on the nonclinical evaluation of biotechnology-derived pharmaceuticals.[3] All pivotal safety related studies were Good Laboratory Practice compliant.

Somapacitan binds to the growth hormone receptor (with a third the potency of human growth hormones), human prolactin receptor (with 8-fold lower potency than human growth hormones and 25-fold lower potency than human prolactin). Somapacitan has a single substitution in the amino acid backbone which an albumin binding moiety has been attached, and was found to bind human serum albumin, while human growth hormones did not. Somapacitan activated growth hormone receptor (to a similar degree as human growth hormones) in primary rat hepatocytes and a human hepatoma cell line, and induced phosphorylation of signal transducer and activator of transcription 5 *in vitro*. In hypophysectomised Sprague Dawley rats, somapacitan decreased body weight-normalised body fat mass, and increased body weight gain, plasma insulin-like growth factor 1 (IGF-1) levels, lean body mass and bone mineral content of the tibia bone (without changing bone mineral density). Somapacitan increased IGF-1 plasma levels in cynomolgus monkeys and Göttingen minipigs. Similar pharmacological effects were also apparent in the toxicity studies conducted in (intact) rats and monkeys. These effects support the proposed indication.

No clinically relevant competitive interaction was found when somapacitan was screened against a broad panel of transmembrane and soluble receptors, ion channels and transporters. Possible interactions have been documented between human growth hormone and antihyperglycemic treatment, glucocorticoid therapy, sex hormones and thyroid hormones.

Safety pharmacology studies do not indicate clinically relevant effects of somapacitan on central nervous system cardiovascular or respiratory function.

The bioavailability of somapacitan after subcutaneous administration was 36% in minipig, 39% in rat and 69% in monkey-based studies, and the time after administration of somapacitan when time of maximum concentration is reached ($T_{max}$) ranged from 8 hours in rat-based studies to 24 hours in monkeys. Terminal half-life was between 4 and 17 hours via the subcutaneously route, whereas in patients it was 2 to 3 days, which is why nonclinical studies used more frequent dosing (usually twice per week) than that recommended clinically (once weekly). Anti-drug antibodies against somapacitan were detected in 33 to 46% of the rats and in two monkeys at the end of the 13- and 26-week studies, but no significant impact was observed on exposure levels. No clear gender differences in exposure were observed**.** Somapacitan was highly protein bound (> 99%) in nonclinical species and humans. Following a single subcutaneously administration, somapacitan was absorbed slowly, and distributed widely, with only low levels of radioactivity observed in the central nervous system. Placental transfer and secretion in milk was observed for somapacitan. Metabolites are formed via proteolysis of the peptide backbone of somapacitan. All human metabolites were found in rat and monkey plasma. Elimination of somapacitan was slow, with urine being the primary route of excretion in rats, monkeys and humans, followed by faecal excretion. Somapacitan was highly metabolised and excreted in the bile in rats. The rats and monkeys were found to be appropriate models for the study of somapacitan.

[3] ICH S6 (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals. CPMP/ICH/302/95.

Somapacitan inhibited the activities of cytochrome P450 enzymes;[4] CYP1A, CYP2B, CYP2C, CYP3A and CYP2E in rats, and weakly enhanced CYP1A activity in monkeys. The induction of CYP450 enzymes has been documented for recombinant human growth hormone (somatropin).

Somapacitan had a low order of acute oral toxicity in rats and monkeys.

Repeat-dose toxicity studies by the subcutaneous route were conducted in rats and monkeys (twice weekly administration for up to 26 weeks). Maximum exposures (area under the concentration versus time curve (AUC)) were high in both rat and monkey studies. Treatment related histopathological changes were observed at the subcutaneous injection site (local inflammatory reactions) in both laboratory animal species, and further changes recognised as exaggerated pharmacological effects involved increased IGF-1 levels, slight anaemia, feminisation, lactation and mammary changes in rats and in monkeys. In rats, increases in body weight gain and food consumption were also observed. The studies established that somapacitan has a similar toxicological profile to other human growth hormone products in the market.

Somapacitan was not found to be genotoxic in the reverse mutation test, chromosome aberration test and the *in vivo* micronucleus test. Additionally, somapacitan is not considered to pose a genotoxic hazard given its protein nature. No carcinogenicity studies were conducted with somapacitan, and proliferative changes observed in the repeat-dose toxicity studies (especially in the mammary gland) are considered to be due to the exaggerated pharmacology of somapacitan. Analysis of hepatocytes in monkeys showed no proliferative effects *in vivo*. The carcinogenic risk of somapacitan is expected to be comparable to that of recombinant human growth hormones (somatropin).

Male and female fertility indices were unaffected by somapacitan in rats, although treatment did cause irregular oestrous cycles, and low numbers of copulation plugs and sperm count estimates from vaginal smears. In rats, findings observed at very high relative exposures (277-fold at the no observed adverse effect level) included slightly increases in mean fetal weights and an increased incidence of variations (short-, bent-, and/or thickened long bones). In pregnant rabbits, the relative exposures at the no observed adverse effect level for malformations/embryo-fetal lethality and for maternal toxicity/fetal growth were 111 and 12.4, respectively. Since embryofetal development was unaffected at very high multiples of the clinical exposure, assignment to Pregnancy Category B1 is supported.[5]

Acceptable local tolerance with subcutaneous injection was shown for somapacitan in the general repeat dose toxicity studies, with monkeys displaying limited inflammatory tissue reaction after subcutaneous administration of somapacitan at the same strength (6.7 mg/mL) as that proposed for patients. In a dedicated local toxicity study in rabbits

[4] **Cytochrome P450 (CYP) enzymes:** CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds.
Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

[5] Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

using a higher strength (10 mg/mL), only mild inflammatory changes were observed at the injection sites.

There are no nonclinical objections to the registration of somapacitan for the proposed indication.

## Clinical

### Summary of clinical studies

The clinical dossier consisted of eight clinical trials: five clinical pharmacology studies and three Phase III clinical studies.

**Table 3: Summary of clinical studies**

| Study | Study design | Subjects | Dose |
|---|---|---|---|
| **Study 3915a**<br>4 week duration | Phase I: Safety, tolerability, PK and PD study<br>Randomised, single and multiple dose escalating, double blind, placebo controlled | 105 healthy subjects<br>22 to 45 years | Single dose cohorts 0.01, 0.04, 0.08, 0.16 and 0.32 mg/kg or placebo<br>Multiple dose cohorts: 0.02, 0.08, 0.16 and 0.24 mg/kg or placebo |
| **Study 4237**<br>5 week duration | Absorption, metabolism and excretion<br>Single dose open labelled | 7 subjects | 6 mg |
| **Study 4297** | PK/PD and safety of somapacitan in subjects with renal impairment. Multiple dose, open labelled<br>6 week duration | 44 subjects<br>28 to 74 years | Somapacitan once weekly, 0.08 mg/kg |
| **Study 4298** | PK/PD and safety study subjects with hepatic impairment. Multiple dose, open labelled.<br>6 weeks duration | 34 subjects<br>37 to 69 years | Somapacitan once weekly, 0.08 mg/kg |
| **Study 3947** | Safety, tolerability, PK/PD randomised multiple dose, dose escalation, active control | 34 AGHD patients | Somapacitan subcutaneously once weekly for 4 weeks 0.02, 0.04, 0.08 and 0.2 mg/kg in 12 patients<br>Somapacitan daily |

| Study | Study design | Subjects | Dose |
|---|---|---|---|
| **Study 4054a** | Phase III, efficacy and safety<br>Randomised, parallel group, placebo and active controlled (somatropin)<br>34 weeks with 52 week open label extension | 300 treatment naïve AGHD patients | Somapacitan dose depends on age and IGF-1<br>Somatropin dose depends on age and IGF-1 |
| **Study 4043a** | Phase III, safety:<br>Randomised, open label, parallel group<br>26 weeks duration | 92 previously treated GH patients | Somapacitan dose depends on age and IGF-1<br>Somatropin dose depends on age and IGF-1 |
| **Study 4244a** | Phase III, safety and efficacy | 62 previously treated growth hormone patients from Japan | Somapacitan dose depends on age and IGF-1<br>Somatropin dose depends on age and IGF-1 |

Abbreviations: AGHD = adult growth hormone deficiency; GH = growth hormone; IGF-1 = insulin-like growth factor-1 PK = pharmacokinetics; PD = pharmacodynamics.

## Pharmacology

### *Pharmacokinetics*

After subcutaneous administration, time of maximum concentration ($T_{max}$) was obtained after 8 to 20 hours.

A more than dose proportional increase in AUC and maximum concentration ($C_{max}$) was observed over the dose range of 0.01 to 0.32 mg/kg (about 0.7 to 25 mg/week). This may suggest saturable elimination mechanisms. At doses in the more clinically relevant range, that is below 0.08 mg/kg (about 6 to 7 mg/week) linear pharmacokinetics are observed for AUC. After the first dose, the somapacitan dose is titrated based upon the clinical response, so possible non-linear pharmacokinetics are less relevant. No unexpected accumulation is observed after applying the recommended dose scheme. Steady state was estimated to be reached after 1 to 2 doses, with a low accumulation ratio (< 2). A high inter-subject variability is observed in adult growth hormone deficiency (AGHD) patients at steady state, ranging from about 62 to 102% for area under the concentration versus time curve from time zero to 168 hours ($AUC_{0\text{-}168h}$) and from 113 to 201% in $C_{max}$. Population pharmacokinetics (popPK) simulations confirmed the moderate to high inter-subject variability (estimated 64%). The covariates body weight, sex and oral estrogen use, race and age, which were included in the popPK modelling, explained 78% of the observed inter-subject variability.

Somapacitan is highly bound to albumin (> 99%) and slowly release from albumin. The popPK model (incorporating rate limiting absorption) estimated a volume of distribution of 14.6 L, which would be in line with the volume of distribution of albumin (13.6 L).

After injection, somapacitan is considered metabolised by proteolytic cleavages of the peptide backbone and sequential degradation of the linker sequence. This resulted in three main plasma metabolites (named P1, M1 and M1B) and two main urine metabolites (named M4 and M5). Intact somapacitan accounted for 59% of the total exposure of somapacitan related material in plasma, and metabolite P1 accounted for 21% and

metabolites M1 and M1B accounted for 12%. The remaining plasma metabolites accounted for < 10% of the total AUC exposure.

After administration of [3H]-somapacitan, 94% of the administered dose was recovered 28 days after dosing, of which 80.9% was excreted in urine, 12.9% was excreted in faeces, and 0.19% was excreted in expired air. No intact somapacitan was recovered in urine and faeces.

In the pharmacokinetics model, body weight had an impact on exposure with exposure being higher in a subject with a low body weight of 45 kg (3.12-fold) and lower in a heavy subject weighing 115 kg (-39%) as compared to the reference subject weighing 85 kg. However, it appeared that dosing steps in mg resulted in similar IGF-1 levels after titration in all body weight groups, indicating that normalisation to body weight is not required to reach IGF-1 target level.

Adult growth hormone deficiency patients in the transition age (18 to 22 years) received higher doses but obtained lower IGF-1 levels after titration than older AGHD patients. This could indicate that AGHD patients in the transition age may need higher doses than AGHD patients outside the transition age and is in accordance with the fact that endogenous growth hormone secretion and IGF-1 levels are much higher in healthy subjects in this age group as compared to older subjects. Female subject using no estrogens has a 30% lower exposure compared to male subjects, while females subjects on estrogens had a 53% lower exposure. The IGF-1 response was lower in females compared to males and lowest in females on oral estrogen for similar doses of somapacitan. Females and especially females on oral estrogen may thus require higher doses of somapacitan to reach a similar IGF-1 target range as compared to males.

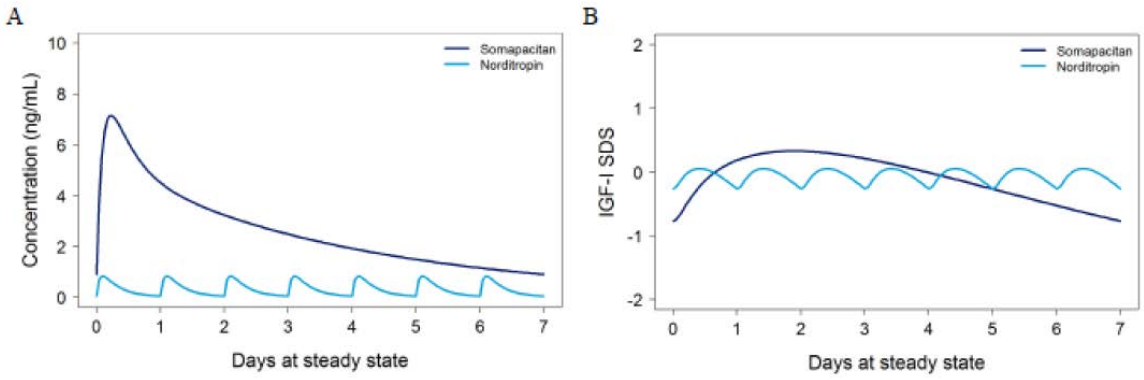
Somapacitan levels were higher in patients with renal impairment. This is in line with published data indicating decreased clearance of growth hormones due to renal impairment. IGF-1 levels were also increase. In hepatic impairment, there was higher somapacitan exposure but lower IGF-1.

### *Pharmacodynamics*

In the clinical studies patient had higher blood concentrations to somapacitan compared to Norditropin;[6] this is because somapacitan has a lower receptor binding affinity and higher doses are required to get the same IGF-1 result (see Figure 2). As expected from the longer duration of action, there was a higher and smoother profile for IGF-1 with somapacitan, compared to the more pulsatile secretion from Norditropin (see Figure 3).

[6] Norditropin (somatropin), biosynthetic human growth hormone of recombinant DNA origin.

**Figure 2: Geometric means of human growth hormones or somapacitan and insulin-like growth factor-1**



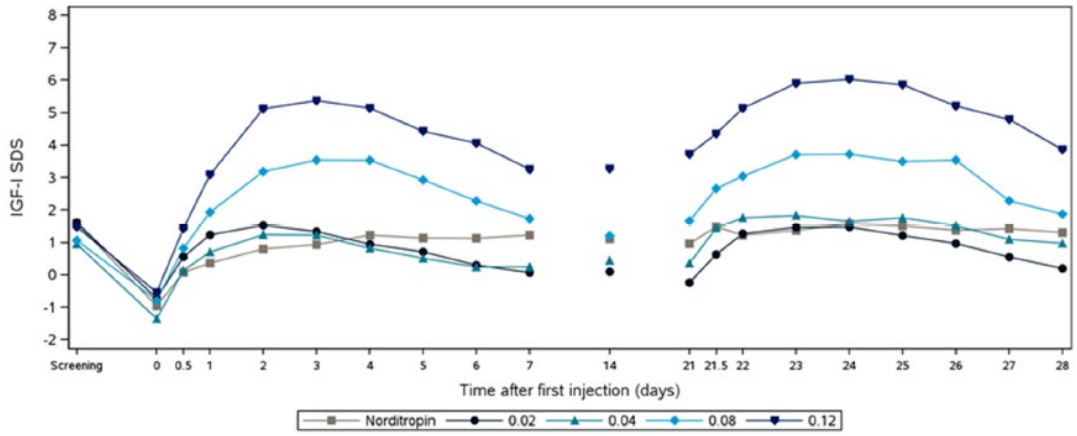

Abbreviations: IGF-1 SDS = insulin-like growth factor 1 standard deviation score.

Notes: line are geometric means of hGH or somapacitan concentration (panel A) and means of IGF-1 SDS (panel B) of individual predictions in the fixed dose periods after titration as observed in Phase III for somapacitan (average dose 2.4 mg weekly) and Norditropin (average dose 0.3 mg daily).

Data from Studies 4054, 4043 and 4244.

All dose levels produced an increased IGF-1 above Baseline, with higher IGF-1 levels for increasing dose.

**Figure 3: IGF-1 SDS levels after different dose levels of somatropin**




Abbreviations: IGF-1 SDS = insulin-like growth factor 1 standard deviation score

Somatropin and somapacitan produced very similar levels of IGF-1 (an indirect effect of these medications).

Somatropin and somapacitan exerted different effects on fat cells. In Study 4054, the observed direct effects were lower for somapacitan than they were for somatropin. This may be due to a number of factors, including differences in the study population, insufficient exposure to somapacitan and a lower affinity to adipose tissue for somapacitan as compared to somatropin due to the albumin binding moiety in somapacitan.

## Efficacy

### *Study 4054*

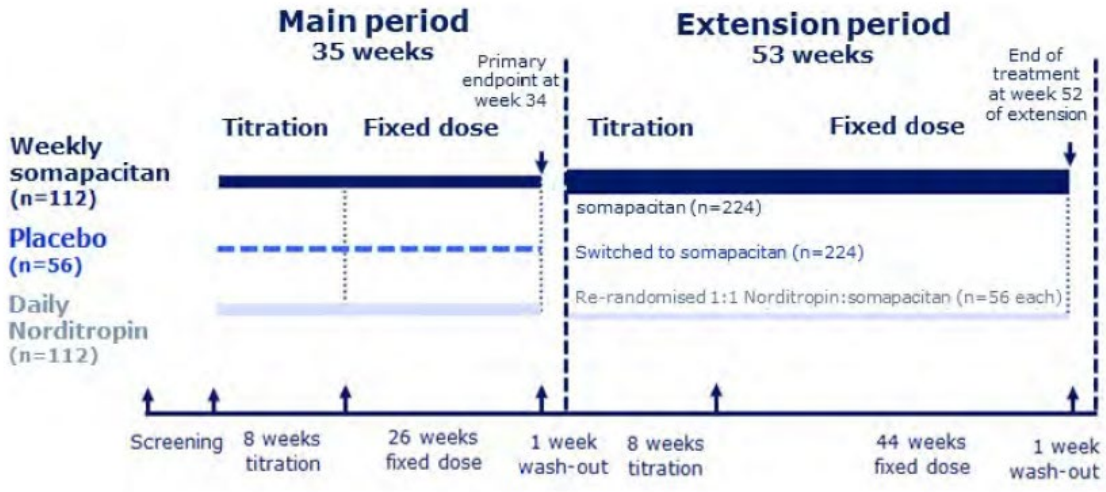
Study 4054 was a Phase III, multi-centre, multinational, randomised, parallel group, placebo-controlled (double blind) and active controlled study (Norditropin).

The treatment period was for 35 weeks, including 8 weeks dose titration, 24 weeks fixed dose. There as a one week washout between this and the extension study.

Patients were growth hormone naïve or had no exposure to growth hormone or growth hormone secretagogues for at least 180 days prior to randomisation. There was a third active treated arm where patients received Norditropin.

The study was followed by a 53 week open label extension study.

**Figure 4: Study 4054 trial design**




The trial consisted of the following periods: a 2-week screening period; a 35-week randomised, double-blind main period consisting of an 8-week titration period, and a 26-week fixed-dose treatment period and a one week washout period; a 53-week open-label extension period consisting of an 8-week titration period and a 44-week fixed-dose treatment period and a one week washout period.

Hence, the patients were treated for 34 weeks in the main period and 52 weeks in the extension period, thus for a total of 86 weeks.

The washout periods were set to one week to confirm antibody response. However, as the half-life of daily growth hormone (GH) is short, it is considered acceptable in real life to have 1-day washout only.

Patients were randomised in a 2:2:1 ratio to receive somapacitan, Norditropin or placebo during the main period. All patients who completed the 35-week main period, and who did not discontinue treatment in the main period, were offered to continue in the 53-week extension period:

Somapacitan treated patients continued their once-weekly treatment

Placebo patients were switched to somapacitan treatment

Norditropin treated patients were re-randomised 1:1 to somapacitan or Norditropin.

*Study populations*

- Age: 23 to 79 years.
- Confirmed diagnosis of AGHD. This was defined as either:
  - a peak growth hormone level of < 3 ng/ml using insulin tolerance test or glucagon test; or
  - peak growth hormone < 3 ng/ml using growth hormone-releasing hormone (GHRH) and arginine according to body mass index (BMI); or
  - three or more pituitary hormone deficiencies and IGF-1 standard deviation score less than -2.0.

- Growth hormone treatment naïve or no exposure to growth hormone or growth hormone secretagogues for at least 180 days prior to randomisation with a registered or investigational growth hormone or growth hormone secretagogue.
- If applicable, hormone replacement therapies for any other hormone deficiencies were adequate and stable for at least 90 days prior to randomisation.
- Insulin-like growth factor standard deviation score < -0.5.

*Doses*

**Table 4: Study 4054 Starting dose for somapacitan/placebo and somatropin patients**

| Group | Starting dose of somapacitan or placebo (mg/ week) | Starting dose of somatropin (expressed in mg/week) |
|---|---|---|
| Patients between 23 and 60 years of age | 1.5 | 1.4 |
| Women on oral oestrogen irrespective of age | 2.0 | 2.1 |
| Patients older than 60 years | 1.0 | 0.7 |

Note: the recommended dose of Norditropin for adults with growth hormone (GH) deficiency in the Product Information (PI) is a starting dose of 0.15 to 0.3mg, with dose titration based on insulin-like growth factor-1 (IGF-1). It is stated that dosing requirements decline with age, and doses seldom exceed 1 mg.

Dose adjustments were allowed for the first eight weeks of the titration period (Weeks 2, 4, 6 and 8). Dose adjustments were based on IGF-1 standard deviation score. The dose was fixed after Week 8. Blood samples were taken 10 to 11 days after each dose adjustment. The maximum recommended dose was 8 mg.

The target IGF-1 level was -0.5 to +1.75 standard deviation score. The dose adjustment algorithm is as follows

**Table 5: Study 4054 Dose titration algorithm for study treatment**

| IGF-1 SDS interval | Somapacitan or placebo Increment/reduction of weekly dose | | Somatropin Increment/reduction of weekly dose (i.e. seven times changes per day) | |
|---|---|---|---|---|
| | Δ IGF-1 SDS > 1 | Δ IGF-1 SDS ≤ 1 | Δ IGF-1 SDS > 1 | Δ IGF-1 SDS ≤ 1 |
| IGF-1 SDS > 3 | - 1 mg | | - 0.7 mg | |
| 1.75 < IGF-1 SDS ≤3 | - 0.5 mg | | - 0.35 mg | |
| -0.5 < IGF-1 SDS ≤ 1.75 | | + 0.5 mg | | + 0.35 mg |
| -2 < IGF-1 SDS ≤ -0.5 | +0.5 mg | + 0.5 mg | + 0.35 mg | + 0.35 mg |
| IGF-1 SDS ≤ -2 | +1 mg | + 1.5 mg | + 0.7 mg | + 1.4 mg |

Abbreviations: IGF-1 = insulin-like growth factor-1; IGF-1 SDS = insulin-like growth factor-1 standard deviation score.

Δ: change in IGF-1 SDS (insulin-like growth factor-1 standard deviation score) from screening.

*Objectives*

The primary objective was to demonstrate the efficacy of once weekly dosing of somapacitan compared to placebo after 34 weeks of treatment in AGHD patients

The secondary objective was to evaluate the efficacy and safety of somapacitan for up to 86 weeks of treatment in AGHD.

*Results*

A total of 301 subjects were randomised, with 277 completed the 34 weeks treatment period. 272 patients entered the extension period, 257 completed the study.

Of the 300 patients that participated, 91 were diagnosed as children. The mean age was 45 years (range 23 to 64 years).

The dose of somapacitan (2.33 to 2.61 mg/week) was greater than the dose of somatropin (1.89 mg/week). This is attributed to the lower binding capacity of somapacitan to the growth hormone receptor.

There was a small but statistically significant change in truncal body fat seen between the somapacitan and placebo group (-1.53%, -2.68 to -0.38, p = 0.009). A comparison between somapacitan and somatropin on the effects on body fat was a secondary endpoint. There was a greater reduction in body fat seen in the somatropin group (-2.39 % compared with -1.17%).

**Table 6: Study 4054 Estimated change in truncal fat percentage (%) from Baseline to Week 34 (full analysis set)**

| **Change from Baseline** | **Duration** | **Somapacitan (n = 120)*** | **Somatropin (n = 119)*** | **Placebo (n = 61)*** | **Primary comparison **: difference somapacitan** minus **placebo (95% CI)** **p-value** | **Secondary comparison **: difference somapacitan** minus **somatropin (95% CI)** **p-value** |
|---|---|---|---|---|---|---|
| Truncal fat (%) | Week -3 to Week 34 | 39.11<br>-1.17 | 38.1<br>-2.39 | 36.9<br>+0.49 | -1.53 (-2.68; -0.38)<br>p = 0.009 | 1.17 (0.23; 2.11)<br>p = not reported |
| | | | Secondary analysis *** | | -1.65 (-2.83; -0.47)<br>p = 0.006 | 1.4 (0.44; 2.35)<br>p = not reported |
| | | | Secondary analysis *** | | -1.68 (-2.87; -0.5)<br>p = 0.006 | 1.36 (0.4; 2.32)<br>p = not reported |

Abbreviations: CI = confidence interval(s); n = number of subjects.

* Observed changes in mean percentages.

** Primary analysis: change in truncal fat percentage from Baseline to the 34 week's measurements was analysed using an analysis of covariance model with treatment, growth hormones deficiency onset type, sex, region, diabetes mellitus and sex by region by diabetes mellitus interaction as factors and baseline as a covariate.

*** Changes in truncal fat percentage from Baseline to the 34 weeks measurements was analysed using an analysis of covariance model with treatment, growth hormone deficiency onset type, set, region, diabetes mellitus and sex by region, diabetes mellitus interaction as factors and baseline as a covariate. Subjects without Week 34 data for the endpoint are excluded from the analysis.

When body fat and lean body mass in other areas of the body were compared, there was a decrease in body fat in the somapacitan and somatropin groups, but an increase in body fat in the placebo group. The changes in body fat tended to be greater for somatropin. There was a greater increase in lean body mass in the somapacitan and somatropin groups than the placebo group. The changes in lean body mass were similar between the somapacitan and somatropin groups.

There was an increase in IGF-1 and IGF binding protein 3 from a Baseline low of less than -2 standard deviation score to the normal range. There was little change in the placebo group.

There was a small numerical increase in short form (36) health survey [7] scores at Week 34 compared to Baseline in the somapacitan compared to the placebo groups. There was no significant difference in the treatment related impact measure adult growth hormone deficiency scores between somapacitan and placebo.

Treatment satisfaction questionnaire for medication (TSQM-9) scores (effectiveness, convenience, global satisfaction) after 34 weeks of treatment were used to support the primary objective. At 34 weeks, the overall satisfaction score was greater for somapacitan than placebo, with no significant difference observed in effectiveness or convenience scores.

There were no significant changes in cholesterol and triglycerides or cardiovascular parameters at Baseline and at 34 weeks.

The Delegate notes that at the end of the 8 week titration phase, 47% of the AGHD study patients did not obtain an IGF-1 level above zero. The sponsor performed a modelling analysis. This showed that if patients received dose titration to receive the highest dose, 90% would achieve IGF-1 in the target range.

At the end of the open label extension period, over all there were similar changes in truncal fat, visceral adipose tissue, and lean muscle mass between all groups.

***Supportive studies***

Study 4504 was supported by Study 4043 in patients with AGHD previously treated with growth hormone, and Study 4244 in Japanese subjects with AGHD.

### Safety

The three Phase III studies included 333 AGHD patients to once weekly somapacitan at a mean dose of 2.38 mg/week. Of these, 253 were exposed for more than 12 months, and 109 for more than 18 months.

The adverse events profile was similar between somapacitan and somatropin. Most adverse events were mild.

## Risk management plan

The sponsor has submitted approved European Union (EU)-risk management plan (RMP) version 1.0 (12 April 2021; data lock point (DLP) 31 Mar 2019) and Australia specific annex (ASA) version 0.1 (19 April 2021) in support of this application. In response to TGA questions, sponsor has supplied ASA version 0.2 (15 October 2021).

The current evaluation is supported by a complete set of European Medicines Agency assessment reports, including RMP and Pharmacovigilance Risk Assessment Committee (PRAC) reports. The focus of the current assessment is ensuring the RMP-ASA is appropriate for the health settings, and setting of use, in Australia.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 7. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach.

[7] The short form (36) health survey is a 36-item, patient-reported survey of patient health. The SF-36 is a measure of health status, commonly used in health economics as a variable in the quality-adjusted life year calculation to determine the cost-effectiveness of a health treatment.

**Table 7: Summary of safety concerns**

| Summary of safety concerns | | Pharmacovigilance | | Risk Minimisation | |
|---|---|---|---|---|---|
| | | Routine | Additional | Routine | Additional |
| **Important identified risks** | None | – | – | – | – |
| **Important potential risks** | Neoplasms | ✓[1] | ✓[3] | ✓ | – |
| | Diabetes mellitus type 2 | ✓ | ✓[3] | ✓ | – |
| | Medication errors (Incorrect dose administration rate) | ✓[1,2] | ✓[3] | ✓ | ✓[4] |
| | Off-label paediatric use | ✓ | ✓ | ✓ | ✓[4] |
| **Missing information** | Patients with heart failure, NYHA class >2 | ✓ | ✓[3] | ✓ | – |
| | Patients with severe hepatic impairment | ✓ | ✓[3] | ✓ | – |
| | Long-term safety | ✓ | ✓[3] | ✓ | – |

Abbreviation: NYHA=New York Heart Association

1 Pre-defined relevant follow-up questions

2 Detailed evaluation of risk of medication error in PSURs to inform ongoing adequacy of risk minimisation

3 Planned multinational post-authorisation safety study (PASS) Study NN8640-4515

4 Dear Health Care Professional letter

Subject to agreement by TGA nonclinical and clinical evaluators on European Medicines Agency (EMA) assessment of the RMP summary of safety concerns, the summary is acceptable from an RMP perspective.

Routine pharmacovigilance (PV) activities are proposed for all safety concerns. PV data collection based upon pre-defined follow up questions for neoplasms and medication errors, and the requirement to provide detailed analysis of medication errors in Periodic Safety Update Reports (PSUR) submissions has been specified in the EU-RMP and will also apply to Australia. There is a planned additional post-marketing safety study to investigate long-term safety of somapacitan under normal clinical practice conditions. The RMP/ASA plan aligns with EU-RMP and is acceptable based on what is currently known on Sogroya's safety profile and that of growth hormone class of medicines.

Only routine risk minimisation activities (prescription only medicine status, labelling, PI, Consumer Medicines Information (CMI)) are proposed for all safety concerns. The RMP and ASA plan aligns with EU-RMP and is generally considered appropriate for the health settings, and setting of use, in Australia. It is agreed at second round of evaluation, that sponsor will disseminate a Dear Health Care Professional letter to prescribers of Sogroya prior to launch as an additional risk minimisation measure to address '*risk of medication error*' and '*off-label paediatric use*'.

### Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> *The Sogroya EU-Risk Management Plan (RMP) (version 1.0, dated 7 April 2021, data lock point 31 March 2019), with Australian Specific Annex (version 0.3, dated 20 December 2021), included with submission PM-2021-01699-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*

The following wording is recommended for the PSUR requirement:

> *An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).*
>
> *Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.*
>
> *The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.*

As Sogroya is a new biological entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> *Sogroya (somapacitan) is to be included in the Black Triangle Scheme. The PI and CMI for Sogroya must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.*

## Risk-benefit analysis

### Delegate's considerations

This was a COR-B application for the approval of somapacitan, a long acting growth hormone, for the treatment of adults with growth hormone insufficiency. A similar application has previously been approved by the EMA and US Food and Drug Administration (FDA).

The quality and nonclinical evaluators had no major concerns.

The clinical evidence in support of this application was from five pharmacology and three efficacy and safety studies. The pivotal studies main efficacy endpoint was change in truncal fat compared to placebo. There was small but statistically significant decrease in fat. It is possible that a bigger effect may have been achieved if more participants in the clinical study were able to achieve an IGF-1 around two standard deviation score. In the pivotal clinical study, after the 8 week dose titration period, only 53% of the somapacitan treated patients achieved a IGF-1 standard deviation score score over zero.

The starting dose recommendations in the PI are similar to that used in the clinical studies. However, in the clinical studies dose titration was not allowed until after the titration period, whereas in real life it may continue until IGF-1 levels are optimised. The sponsor has adequately described the dosing in the PI.

In Australia, most laboratories report a raw IGF-I value rather than a standard deviation score. It is recommended that the sponsor change the wording of the dose titration section in the PI to reflect this.

**Proposed action**

The Delegate was of the opinion that Sogroya should be approved for registration, pending updates to the PI, and addressing outstanding quality and RMP issues.

# Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Sogroya (somapacitan) 6.7 mg/mL, solution for injection, pre-filled pen (cartridge), indicated for:

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

## Specific conditions of registration applying to these goods

- Sogroya (somapacitan) is to be included in the Black Triangle Scheme. The PI and CMI for Sogroya must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Sogroya EU-Risk Management Plan (RMP) (version 1.0, dated 7 April 2021, data lock point 31 March 2019), with Australian Specific Annex (version 0.3, dated 20 December 2021), included with submission PM-2021-01699-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes.

Note that submission of a PSUR does not constitute an application to vary the registration.

- Laboratory testing & compliance with Certified Product Details (CPD)
  - i. All batches of: Sogroya somapacitan 6.7 mg/mL solution for injection prefilled pen supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
  - ii. When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/wslabs index and periodically in testing reports on the TGA website.
- Certified Product Details

  The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm, in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

# Attachment 1. Product Information

The PI for Sogroya approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

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