Product Information Form for Hospitals

Indications and Usage

Sogroya® (somapacitan-beco) injection 5 mg, 10 mg, or 15 mg is indicated for the:

- treatment of pediatric patients aged 2.5 years and older who have growth failure due to inadequate secretion of endogenous growth hormone (GH)
- replacement of endogenous GH in adults with growth hormone deficiency (GHD)

Important Safety Information

Contraindications

Sogroya® is contraindicated in patients with:

- acute critical illness after open-heart surgery, abdominal surgery, multiple accidental trauma, or acute respiratory failure because of the risk of increased mortality with use of Sogroya®
- hypersensitivity to Sogroya® or any of its excipients. Systemic hypersensitivity reactions have been reported postmarketing with Sogroya®
- pediatric patients with closed epiphyses
- active malignancy
- active proliferative or severe non-proliferative diabetic retinopathy
- pediatric patients with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment due to risk of sudden death

Product Information Form for Hospitals

1 AHFS CLASSIFICATION NUMBER

68:28 Hormones and Synthetic Substitutes: Pituitary

2 GENERIC NAME

Somapacitan-beco injection

3 SOURCE OF SUPPLY

Sogroya® is manufactured and distributed by Novo Nordisk Inc.

4 BIOLOGIC LICENSE APPLICATION (BLA) NUMBER AND DATE OF FDA APPROVAL

- N019721, Sogroya® August 28, 2020 FDA approval for adults with growth hormone deficiency (GHD)
- BLA 761156 Sogroya® April 28, 2023 FDA approval for children aged 2.5 years and older who have growth hormone deficiency

5 PHYSICAL PROPERTIES

a. Macroscopic appearance

Sogroya® (somapacitan-beco) injection is a clear to slightly opalescent and colorless to slightly yellow solution available as one 1.5 mL single-patient-use prefilled pen per carton:

- Sogroya® 5 mg/1.5 mL (3.3 mg/mL) pen (teal) NDC 0169-2035-11
- Sogroya® 10 mg/1.5 mL (6.7 mg/mL) pen (yellow) NDC 0169-2030-11
- Sogroya® 15 mg/1.5 mL (10 mg/mL) pen (red) NDC 0169-2037-11

b. Solubility

Sogroya® (somapacitan-beco) injection is supplied as a sterile, clear to slightly opalescent and colorless to slightly yellow solution for subcutaneous use in a single-patient-use prefilled pen with a deliverable volume of 1.5 mL. Inspect visually for particulate matter and discoloration. Sogroya® should be a clear to slightly opalescent and colorless to slightly yellow solution. If the solution is cloudy or contains particulate matter do not use.

6 CHEMICAL PROPERTIES

a. Structural similarities to other available compounds or groups of compounds

Somapacitan-beco is a human growth hormone (hGH) analog with a single substitution in the amino acid backbone (L101C) to which an albumin-binding moiety has been attached.

6 CHEMICAL PROPERTIES (cont'd)

a. Structural similarities to other available compounds or groups of compounds (cont'd)

The albumin-binding moiety (side-chain) consists of an albumin binder and a hydrophilic spacer attached to position 101 of the protein. The protein part consists of 191 amino acids. Somapacitan-beco is produced in *Escherichia coli* by recombinant DNA technology. The molecular formula (including the albumin-binding moiety) is $C_{1038}H_{1609}N_{273}O_{319}S_9$ and the molecular weight is 23305.10 g/mol, of which the albumin-binding moiety is 1191.39 g/mol.

b. Recommended storage conditions for Sogroya®

New, unused Sogroya® pens must be stored in a refrigerator at 36°F to 46°F (2°C to 8°C). New, unused pens should be stored with the cap on and in the original carton. Do not freeze. Avoid direct heat and light. If Sogroya® has been frozen or stored in temperatures warmer than 86°F (30°C), do not use. Do not use Sogroya® after the expiration date printed on the carton and the pen.

While in use, Sogroya® pens may be stored in the refrigerator at 36°F to 46°F (2°C to 8°C) and used within 6 weeks. In-use Sogroya® pens should be stored with the cap on and in the original carton.

If needed, unused and in-use Sogroya® pens can be stored out of the refrigerator. Sogroya® pens can be stored at room temperature no warmer than 77°F (25°C) for up to 3 days (72 hours) and then returned to the refrigerator.

c. Excipients contained in the commercially available product

Each mL of Sogroya® 5 mg/1.5 mL prefilled pen contains 3.3 mg of somapacitan-beco, histidine (0.68 mg), mannitol (44 mg), phenol (4 mg), poloxamer 188 (1 mg), and Water for Injection, USP. The pH is approximately 6.8. Hydrochloric acid and sodium hydroxide may be added to adjust the pH.

Each mL of Sogroya® 10 mg/1.5 mL prefilled pen contains 6.7 mg of somapacitan-beco, histidine (0.68 mg), mannitol (44 mg), phenol (4 mg), poloxamer 188 (1 mg), and Water for Injection, USP. The pH is approximately 6.8. Hydrochloric acid and sodium hydroxide may be added to adjust the pH.

Each mL of Sogroya® 15 mg/1.5 mL prefilled pen contains 10 mg of somapacitan-beco, histidine (0.68 mg), mannitol (44 mg), phenol (4 mg), poloxamer 188 (1 mg), and Water for Injection, USP. The pH is approximately 6.8. Hydrochloric acid and sodium hydroxide may be added to adjust the pH.

7 PHARMACOLOGIC CLASSIFICATION

a. Pharmacologic class

Hormone and synthetic substances

7 PHARMACOLOGIC CLASSIFICATION (cont'd)

b. Mechanism of action

Somapacitan-beco binds to a dimeric GH receptor in the cell membrane of target cells resulting in intracellular signal transduction and a host of pharmacodynamic effects. Some of these pharmacodynamic effects are primarily mediated by insulin-like growth factor 1 (IGF-1) produced in the liver, while others are primarily a consequence of the direct effects of somapacitan-beco.

c. Pharmacokinetic data

Somapacitan-beco has pharmacokinetic (PK) 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 PK of somapacitan-beco following subcutaneous administration have been investigated at clinically relevant doses (eg, 0.01 to 0.32 mg/kg in healthy adults, 0.02 to 0.12 mg/kg in adults with GHD, and 0.02 to 0.16 mg/kg in pediatric patients with GHD).

Overall, somapacitan-beco displays non-linear PK, however, in the clinically relevant dose range of somapacitan-beco in adults with GHD, somapacitan-beco PK are approximately linear. After subcutaneous administration of 0.02 to 0.16 mg/kg/wk somapacitan-beco in pediatric patients with GHD, a non-linear dose-exposure relationship with a greater than dose proportional increase in exposure was observed.

Absorption

In adults with GHD, a maximum concentration of somapacitan-beco is reached 4 to 24 hours post dose.

Steady state exposure is achieved following 1 to 2 weeks of once-weekly administration of subcutaneous somapacitan-beco.

In pediatric patients with GHD, maximum somapacitan-beco concentrations occurred 8 to 25 hours after dosing at doses from 0.02 to 0.16 mg/kg/wk and increased with increasing dose level. Steady state was achieved following 1 to 2 weekly administrations.

Distribution

Somapacitan-beco is extensively bound (>99%) to plasma proteins.

Based on population PK analyses, the estimated volume of distribution (V/F) of somapacitan-beco in adult GHD patients is approximately 14.6 L and 1.7 L in pediatric patients with GHD.

7 PHARMACOLOGIC CLASSIFICATION (cont'd)

c. Pharmacokinetic data (cont'd)

Elimination

The plasma elimination half-life of somapacitan-beco is approximately 2 to 3 days in adult patients with GHD. Following a dose of 0.16 mg/kg/wk, the terminal half-life of somapacitan-beco was about 34 hours in pediatric patients with GHD. Somapacitan-beco was cleared within one week after treatment discontinuation.

Metabolism: Somapacitan-beco is metabolized via proteolytic cleavage of the linker sequence between the peptide backbone and albumin binder sidechain.

Excretion: The primary excretion routes of somapacitan-beco-related material are via the urine and feces. Approximately 81% of the dose is excreted in the urine and approximately 13% is excreted in the feces. No intact somapacitan-beco is excreted indicating full breakdown of somapacitan-beco prior to excretion.

Specific Populations

Body weight:

Adults with GHD: The exposure of somapacitan-beco decreases with increasing body weight. However, the somapacitan-beco dose range of 0.1 to 8 mg/wk provides adequate systemic exposure to reach target IGF-1 levels over the weight range of 34.5 to 150.5 kg evaluated in the clinical trials.

Pediatric GHD patients: Based on PK analysis, gender and race do not have a clinically meaningful effect on the PK. The exposure of somapacitan-beco decreases with increasing body weight. However, the somapacitan-beco dose of 0.16 mg/kg/wk provides adequate systemic exposure for pediatrics to reach target IGF-1 levels over the weight range of 9.9 to 61.8 kg evaluated in the clinical trials.

Geriatric patients: Adult patients greater than 65 years of age and geriatric patients have a higher exposure than younger subjects at the same somapacitan-beco dose.

Female patients receiving estrogen: Female patients, and in particular female patients on oral estrogen, have lower exposure than males at the same somapacitan-beco dose.

Hepatic impairment: A somapacitan-beco dose of 0.08 mg/kg at steady state resulted in comparable somapacitan-beco exposure between patients with normal hepatic function and mild hepatic impairment (Child-Pugh A). However, higher exposure was observed in patients with moderate hepatic impairment (Child-Pugh B) (ratios to normal hepatic function were 4.69 and 3.52-fold increased for $AUC_{0\text{-}168h}$ and C_{max}, respectively). Lower somapacitan-beco stimulated IGF-1 levels were observed in patients with mild and moderate hepatic impairment (ratios to normal hepatic function were 0.85 and 0.75, respectively).

7 PHARMACOLOGIC CLASSIFICATION (cont'd)

c. Pharmacokinetic data (cont'd)

Renal impairment: In general, somapacitan-beco exposure tended to increase with decreasing estimated glomerular filtration rate. A somapacitan-beco dose of 0.08 mg/kg at steady state resulted in higher exposures in patients with renal impairment, that was most pronounced for patients with severe renal impairment and patients requiring hemodialysis ($AUC_{0\text{-}168h}$ ratios to normal renal function were 1.75 and 1.63, respectively). Higher IGF-1 $AUC_{0\text{-}168h}$ levels were also observed in patients with moderate and severe renal impairment and in patients requiring hemodialysis (ratios to normal renal function were 1.35, 1.40, and 1.24, respectively).

8 DOSAGE RANGE

a. Dosage range and route of administration

Pediatric Dosage

- Recommended dosage of Sogroya® is 0.16 mg/kg based on actual body weight once weekly for treatment-naïve patients and patients switching from daily growth hormone (somatropin).
- Individualize dosage for each patient based on the growth response.
- When switching from daily human growth hormone to once-weekly Sogroya®, choose the preferred day for the weekly dose. Take the final dose of daily treatment on the day before (or at least 8 hours before) the first dose of Sogroya®.
- When switching from a weekly human growth hormone to once-weekly Sogroya®, continue once weekly dosing schedule.
- Assess compliance and evaluate other causes of poor growth such as hypothyroidism, undernutrition, advanced bone age, and antibodies to recombinant human growth hormone if patients experience failure to increase height velocity, particularly during the first year of treatment.
- Patients who were treated with Sogroya® for GH deficiency in childhood and whose epiphyses are closed should be reevaluated before continuing Sogroya®.

Adult Dosage

- Initiate Sogroya® with a dosage of 1.5 mg once weekly for treatment naïve patients and patients switching from daily growth hormone (somatropin).
- Increase the weekly dosage every 2 to 4 weeks by approximately 0.5 mg to 1.5 mg until the desired response is achieved.
- Titrate the dosage based on clinical response and serum insulin-like growth factor-1 (IGF-1) concentrations. Draw IGF-1 samples 3 to 4 days after the prior dose.
- Decrease the dosage as necessary on the basis of adverse reactions and/or serum IGF-1 concentrations above the age- and sex-specific normal range.
- The maximum recommended dosage is 8 mg once weekly.

8 DOSAGE RANGE (cont'd)

a. Dosage range and route of administration (cont'd)

Patients Aged 65 Years and Older

- Initiate Sogroya® with a dosage of 1 mg once weekly and use smaller dose increment increases when titrating the dosage. See above for monitoring recommendations and the maximum recommended dosage of Sogroya®.

Patients with Hepatic Impairment

- Sogroya® is not recommended in adult and pediatric patients with severe hepatic impairment.
- For adult patients with moderate hepatic impairment, initiate Sogroya® with a dosage of 1 mg once weekly and use smaller dose increment increases when titrating the dosage. See above for monitoring recommendations. The maximum recommended dosage is 4 mg once weekly.
- For pediatric patients with moderate hepatic impairment, Sogroya® is not recommended.
- No dosage adjustment is recommended for adult and pediatric patients with mild hepatic impairment.

Women Receiving Oral Estrogen

- Initiate Sogroya® with a dosage of 2 mg once weekly. See above for titration and monitoring recommendations and the maximum recommended dosage of Sogroya®.

Administration and Use Instructions

- Sogroya® treatment should be supervised by a healthcare provider who is experienced in the diagnosis and management of pediatric patients with growth failure due to GHD and/or adults with GHD.
- Sogroya® should be administered by subcutaneous injection, once weekly, any time of the day, in the upper arms, thigh, abdomen or buttocks with weekly rotation of injection site.
- Inspect visually for particulate matter and discoloration. Sogroya® should be a clear to slightly opalescent and colorless to slightly yellow solution. If the solution is cloudy or contains particulate matter, do not use.
- Advise patients to read the Patient Information and Instructions for Use leaflets enclosed with the Sogroya® prefilled pen.
- Sogroya® is available in 3 single-patient-use prefilled pens with 3 different dosing ranges.
  - The Sogroya® 5 mg/1.5 mL (3.3 mg/mL) prefilled pen dials in 0.025 mg increments and delivers doses from 0.025 mg to 2 mg.
  - The Sogroya® 10 mg/1.5 mL (6.7 mg/mL) prefilled pen dials in 0.05 mg increments and delivers doses from 0.05 mg to 4 mg.
  - The Sogroya® 15 mg/1.5 mL (10 mg/mL) prefilled pen dials in 0.1 mg increments and delivers doses from 0.1 mg to 8 mg.
- Perform fundoscopic examination before initiating treatment with Sogroya® to exclude preexisting papilledema. If papilledema is identified, evaluate the etiology and treat the underlying cause before initiating treatment with Sogroya®

8 DOSAGE RANGE (cont'd)

b. Use in specific populations

Pregnancy

Risk Summary

There are no available data on the use of Sogroya® during pregnancy; however, published studies describing the use of short-acting recombinant growth hormone (rhGH) during pregnancy over several decades have not identified any drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, subcutaneously administered somapacitan-beco was not teratogenic in rats or rabbits during organogenesis at doses approximately 12 times the clinical exposure at the maximum recommended human dose (MRHD) of 8 mg/week. No adverse developmental outcomes were observed in a pre- and post-natal development study with administration of somapacitan-beco to pregnant rats from organogenesis through lactation at approximately 275 times the clinical exposure at the MRHD *(see Data)*.

The background risk of birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study in rats, somapacitan-beco was administered by subcutaneous injection at doses of 2, 6, and 18 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Fetal viability and development were not affected at doses up to 6 mg/kg/day (31 times the MRHD, based on AUC). Transient, fetal skeletal variations (short/bent/thickened long bones) were observed at 18 mg/kg/day (261 times the MRHD, based on AUC).

In an embryo-fetal development study in rabbits, somapacitan-beco was administered by subcutaneous injection at doses of 1, 3, and 9 mg/kg every two days during the period of organogenesis from gestation day 6 to 18. Fetal viability and development were not adversely affected at somapacitan-beco dose of 1 mg/kg/every two days (12 times the MRHD, based on AUC). Reduced fetal growth was observed at doses ≥3 mg/kg/every two days (≥130 times the MRHD, based on C_{12h}).

In a pre- and post-natal development study in pregnant rats, somapacitan-beco was administered by subcutaneous injection at doses of 4, 9, and 18 mg/kg twice a week from gestation day 6 through lactation day 18. No adverse developmental effects were observed in the offspring at doses up to 9 mg/kg (275 times the MRHD, based on AUC). Increased incidence of renal pelvic dilatation was observed on post-natal day 21 at 18 mg/kg (630 times the MRHD, based on AUC), but was not observed in the adult F1 generation.

8 DOSAGE RANGE (cont'd)

b. Use in specific populations

Lactation

Risk Summary

There is no information on the presence of somapacitan-beco in human milk, the effects on the breastfed infant, or the effects on milk production. Somapacitan-beco-related material was secreted into milk of lactating rats. When a substance is present in animal milk, it is likely that the substance will be present in human milk. Available published data describing administration of short-acting recombinant growth hormone (rhGH) to lactating women for 7 days reported that short-acting rhGH did not increase the normal breastmilk concentration of growth hormone and no adverse effects were reported in breastfed infants. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Sogroya® and any potential adverse effects on the breastfed infant from Sogroya® or from the underlying maternal condition.

Pediatric Use

The safety and effectiveness of Sogroya® have been established for the treatment of growth failure due to inadequate secretion of endogenous growth hormone (GH) in pediatric patients 2.5 years of age and older. The use of Sogroya® for this indication is supported by evidence from a 52 week randomized, multi-center, open-label, active-controlled, parallel-group phase 3 trial in 200 treatment-naïve, pediatric patients with GHD. The safety profile from the pediatric trial was similar to that reported in adults.

Risks in pediatric patients associated with growth hormone use include:

- Sudden death in pediatric patients with Prader-Willi Syndrome. Sogroya® is not indicated for the treatment of pediatric patients with growth failure secondary to genetically confirmed Prader-Willi syndrome.
- Increased risk of second neoplasm in pediatric cancer survivors treated with radiation to the brain and/or head.
- Slipped capital femoral epiphysis in pediatric patients.
- Progression of preexisting scoliosis in pediatric patients.
- Pancreatitis.

The safety and effectiveness of Sogroya® for the treatment of growth failure due to inadequate secretion of endogenous growth hormone have not been established in pediatric patients less than 2.5 years of age.

8 DOSAGE RANGE (cont'd)

b. Use in specific populations

Geriatric Use

In clinical studies a total of 52 (15.6%) of the 333 Sogroya®-treated patients were 65 years or older and 3 (0.9%) were 75 years or older. Subjects older than 65 years appeared to have higher exposure than younger subjects at the same dose level. Elderly patients may be more sensitive to the action of somapacitan-beco, and therefore may be at increased risk for adverse reactions. Initiate Sogroya® with a dose of 1 mg once weekly and use smaller increments when increasing the dose.

Hepatic Impairment

Adult patients: No dose adjustment of Sogroya® is required for patients with mild hepatic impairment. Higher somapacitan-beco exposure was observed in patients with moderate hepatic impairment. In patients with moderate hepatic impairment, initiate Sogroya® with a dose of 1 mg once weekly and use smaller increments when increasing the dose. The maximum dose should not exceed 4 mg once weekly. Somapacitan-beco was not studied in patients with severe hepatic impairment. Therefore, use of Sogroya® is not recommended in patients with severe hepatic impairment.

Pediatric patients: Based on the hepatic impairment study in adults, no dose adjustment of Sogroya® is recommended for patients with mild hepatic impairment. Higher systemic exposure of Sogroya® is expected in pediatric patients with moderate and severe hepatic impairment; therefore, Sogroya® is not recommended in these pediatric patients.

9 SAFETY

a. Adverse reactions, toxicities, and special precautions

Adverse Reactions

The following clinically significant adverse drug reactions are described elsewhere in the labeling:

- Increased mortality in patients with acute critical illness
- Severe hypersensitivity
- Increased risk of neoplasms
- Glucose intolerance and diabetes mellitus
- Intracranial hypertension
- Fluid retention
- Hypoadrenalism
- Hypothyroidism
- Slipped capital femoral epiphysis in pediatric patients
- Progression of preexisting scoliosis in pediatric patients
- Pancreatitis
- Lipohypertrophy/Lipoatrophy
- Sudden death in pediatric patients with Prader-Willi syndrome

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Pediatric Patients with GHD

Sogroya® was studied in a 52-week randomized, open-label, active-controlled, parallel-group clinical study in 200 treatment naïve, prepubertal pediatric patients with growth hormone deficiency. Table 1 shows common adverse reactions that occurred in ≥5% of patients treated with either Sogroya® or somatropin in this trial.

9 SAFETY (cont'd)

a. Adverse reactions, toxicities, and special precautions (cont'd)

Table 1. Adverse Reactions occurring ≥5% in Sogroya® or Somatropin-Treated Pediatric Patients (52 Weeks of Treatment)

	Somatropin (N=68)	Sogroya® (N=132)
Adverse reactions	**%**	**%**
Nasopharyngitis[a]	16.2	16.7
Headache	8.8	12.1
Pyrexia[b]	11.8	9.1
Pain in extremity[c]	2.9	9.8
Injection site reaction[d]	5.9	6.1
Diarrhea[e]	5.9	4.5
Nausea/vomiting[f]	5.9	4.5
Bronchitis	7.4	3

[a]Nasopharyngitis in the Sogroya® treatment group included nasopharyngitis (11.4%), rhinitis (3.8%), pharyngitis streptococcal (0.8%), acute sinusitis (0.8%), nasal congestion (0.8%), pharyngitis (0.8%), and sinusitis (0.8%).
[b]Pyrexia in the Sogroya® treatment group included pyrexia (8.3%) and hyperthermia (0.8%).
[c]Pain in extremity in the Sogroya® treatment group included pain in extremity (9.1%) and growing pains (0.8%).
[d]Injection site reaction in the Sogroya® treatment group included injection site bruising (1.5%), injection site pain (1.5%), injection site hematoma (1.5%), injection site reaction (0.8%), and injection site swelling (0.8%)
[e]Diarrhea in the Sogroya® treatment group included diarrhea (2.3%), gastroenteritis viral (1.5%), and gastrointestinal viral infection (0.8%)
[f]Nausea/vomiting in the Sogroya® treatment group included vomiting (4.5%) and nausea (1.5%)

Please see Important Safety Information on pages 1, 19-20.
Please **click here** for Prescribing Information.

9 SAFETY (cont'd)

a. Adverse reactions, toxicities, and special precautions (cont'd)

Adult Patients with GHD

Sogroya® was studied in adult patients with GHD in a 35-week, placebo-controlled, double-blind trial with an active-control arm. Adverse reactions occurring >2% with Sogroya® are presented in Table 2.

Table 2. Adverse Reactions Occurring >2% in Adults With GHD Treated With Sogroya® and More Frequently[b] Than in Placebo-Treated Patients for 34 Weeks

	Placebo (N=61)	Sogroya® (N=120)
Adverse reactions	**%**	**%**
Back pain	3.3	10
Arthralgia	1.6	6.7
Dyspepsia	3.3	5
Sleep disorder	1.6	4.2
Dizziness	1.6	4.2
Tonsillitis	1.6	3.3
Peripheral edema	1.6	3.3
Vomiting	1.6	3.3
Adrenal insufficiency	1.6	3.3
Hypertension	1.6	3.3
Blood creatine phosphokinase increase	0	3.3
Weight increased	0	3.3
Anemia	0	2.5

[b]Included adverse reactions reported with at least 1% greater incidence in Sogroya® group compared to the placebo group.

More Sogroya®-treated patients shifted from normal baseline levels to elevated phosphate and creatine phosphokinase levels at the end of the trial compared to the placebo group (17.5% vs 4.9% and 9.2% vs 6.6%, respectively); these laboratory changes occurred intermittently, and were non-progressive.

Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, include those of Sogroya® or other growth hormone analogs.

No anti-somapacitan-beco antibodies were detected in the clinical trials in adult patients with GHD.

Please see Important Safety Information on pages 1, 19-20.
Please **click here** for Prescribing Information.

9 SAFETY (cont'd)

a. Adverse reactions, toxicities, and special precautions (cont'd)

Immunogenicity (cont'd)

Anti-somapacitan-beco binding antibodies were evaluated in samples collected at baseline, week 13, and week 52 of treatment in the 52-week main period of the phase 3 trial in pediatric patients with GHD receiving somapacitan-beco. Of the 132 subjects exposed to somapacitan-beco, 16 (12.1%) showed detectable binding antibodies to somapacitan-beco at any time during the main period of the trial following exposure to Sogroya®. 14 out of 16 subjects showed detectable binding antibodies to somapacitan-beco only at one timepoint. Of the 68 patients exposed to daily somatropin, detectable binding antibodies were detected in 7 (10.3%) children. Of these, 6 children had positive antibody samples only at one timepoint. There was no identified clinically significant effect of anti-drug antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of Sogroya® over the treatment duration. No neutralizing antibodies to somapacitan-beco were detected.

b. Contraindications and Warnings and Precautions

Contraindications

Sogroya® is contraindicated in patients with:

- Acute critical illness after open-heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure because of the risk of increased mortality with use of pharmacologic doses of Sogroya®.
- Hypersensitivity to Sogroya® or any of its excipients. Systemic hypersensitivity reactions have been reported postmarketing with somatropin.
- Pediatric patients with closed epiphyses.
- Active malignancy.
- Active proliferative or severe non-proliferative diabetic retinopathy.
- Pediatric patients with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea or have severe respiratory impairment due to risk of sudden death.

Warnings and Precautions

Increased Mortality in Patients With Acute Critical Illness

Increased mortality has been reported after treatment with somatropin in patients with acute critical illness due to complications following open-heart surgery, abdominal surgery and multiple accidental trauma, as well as patients with acute respiratory failure. The safety of continuing Sogroya® treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Sogroya® is not indicated for the treatment of non-GH deficient adults.

9 SAFETY (cont'd)

Warnings and Precautions (cont'd)

Severe Hypersensitivity

Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with postmarketing use of somatropin. Inform patients and/or caregivers that such reactions are possible, and that prompt medical attention should be sought if an allergic reaction occurs. Sogroya® is contraindicated in patients with known hypersensitivity to somatropin or any excipients in Sogroya®.

Increased Risk of Neoplasms

Active Malignancy

There is an increased risk of malignancy progression with somatropin treatment in patients with active malignancy. Any preexisting malignancy should be inactive, and its treatment complete prior to instituting therapy with Sogroya®. Discontinue Sogroya® if there is evidence of recurrent activity

Risk of Second Neoplasm in Pediatric Patients

In childhood cancer survivors who were treated with radiation to the brain/head for their first neoplasm and who developed subsequent growth hormone deficiency (GHD) and were treated with somatropin, an increased risk of second neoplasm has been reported. Intracranial tumors, in particular meningiomas, were the most common of these second neoplasms. Monitor all patients with a history of GHD secondary to an intracranial neoplasm while on somatropin therapy for progression or recurrence of the tumor.

New Malignancy During Treatment

Because children with certain rare genetic causes of short stature have an increased risk of developing malignancies, thoroughly consider the risks and benefits of starting Sogroya® in these patients. If treatment with Sogroya® is initiated, carefully monitor these patients for development of neoplasms.

There is risk of malignant changes of preexisting nevi with somatropin treatment in patients. Monitor patients on Sogroya® therapy carefully for increased growth or potential malignant changes of preexisting nevi. Advise patients/caregivers to report marked changes in behavior, onset of headaches, vision disturbances, and/or changes in the appearance of preexisting nevi.

9 SAFETY (cont'd)

Warnings and Precautions (cont'd)

Glucose Intolerance and Diabetes Mellitus

Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses. New onset type 2 diabetes mellitus has been reported in patients taking somatropin. Patients with undiagnosed pre-diabetes and diabetes mellitus may experience worsened glycemic control and become symptomatic. Monitor glucose levels periodically in all patients receiving Sogroya®, especially in those with risk factors for diabetes mellitus, such as obesity, Turner syndrome, or a family history of diabetes mellitus. Patients with preexisting type 1 or type 2 diabetes mellitus or pre-diabetes should be monitored closely. The doses of antidiabetic agents may require adjustment when Sogroya® is initiated.

Intracranial Hypertension

Intracranial hypertension with papilledema, visual changes, headache, nausea, and/or vomiting has been reported in patients treated with somatropin. Symptoms usually occurred within the first 8 weeks after the initiation of somatropin therapy. In all reported cases, intracranial hypertension-associated signs and symptoms rapidly resolved after cessation of therapy or a reduction of the somatropin dose.

Perform fundoscopic examination before initiating treatment with Sogroya® to exclude preexisting papilledema and periodically thereafter. If papilledema is identified prior to initiation, evaluate the etiology and treat the underlying cause before initiating Sogroya®. If papilledema is observed by fundoscopy during Sogroya® treatment, treatment should be stopped. If intracranial hypertension is confirmed, treatment with Sogroya® can be restarted at a lower dose after intracranial hypertension-associated signs and symptoms have resolved.

Fluid Retention

Fluid retention during Sogroya® replacement therapy may occur. Clinical manifestations of fluid retention (e.g. edema and nerve compression syndromes including carpal tunnel syndrome/paresthesia) are usually transient and dose dependent.

Hypoadrenalism

Patients receiving somatropin therapy who have or are at risk for corticotropin deficiency may be at risk for 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 Sogroya® treatment. Monitor patients with known hypoadrenalism for reduced serum cortisol levels and/or need for glucocorticoid dose increases.

9 SAFETY (cont'd)

Warnings and Precautions (cont'd)

Hypothyroidism

Undiagnosed/untreated hypothyroidism may prevent an optimal response to Sogroya®. In patients with GH deficiency, central (secondary) hypothyroidism may first become evident or worsen during treatment with somatropin therapy. Therefore, patients should have periodic thyroid function tests and thyroid hormone replacement therapy should be initiated or appropriately adjusted when indicated.

Slipped Capital Femoral Epiphysis in Pediatric Patients

Slipped capital femoral epiphysis may occur more frequently in patients undergoing rapid growth. Evaluate pediatric patients with the onset of a limp or complaints of persistent hip or knee pain.

Progression of Preexisting Scoliosis in Pediatric Patients

Somatropin increases growth rate, and progression of preexisting scoliosis can occur in patients who experience rapid growth. Somatropin has not been shown to increase the occurrence of scoliosis. Monitor patients with a history of scoliosis for disease progression.

Pancreatitis

Cases of pancreatitis have been reported in patients receiving somatropin. The risk may be greater in pediatric patients compared with adults. Consider pancreatitis in patients who develop persistent severe abdominal pain.

Lipohypertrophy/Lipoatrophy

When Sogroya® is administered subcutaneously at the same site over a long period of time, tissue lipohypertrophy or lipoatrophy may result. Rotate injection sites when administering Sogroya® to reduce this risk.

Sudden Death in Pediatric Patients with Prader-Willi Syndrome

There have been reports of fatalities after initiating therapy with somatropin in pediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnea, or unidentified respiratory infection. Male patients with one or more of these factors may be at greater risk than females. Sogroya® is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

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.

9 SAFETY (cont'd)

c. List potential drug-drug interactions if deemed clinically significant

Table 3 includes a list of drugs with clinically important drug interactions when administered concomitantly with Sogroya® and instructions for preventing or managing them.

Table 3. Clinically Important Drug Interactions With Sogroya®

Replacement Glucocorticoid Treatment	
Clinical impact	Microsomal enzyme 11ß-hydroxysteroid dehydrogenase type 1 (11ßHSD-1) is required for conversion of cortisone to its active metabolite, cortisol, in hepatic and adipose tissue. GH inhibits 11ßHSD-1. Consequently, individuals with untreated GHD have relative increases in 11ßHSD-1 and serum cortisol. Initiation of Sogroya® may result in inhibition of 11ßHSD-1 and reduced serum cortisol concentrations.
Intervention	Patients treated with glucocorticoid replacement for hypoadrenalism may require an increase in their maintenance or stress doses following initiation of Sogroya®.
Examples	Cortisone acetate and prednisone may be affected more than others because conversion of these drugs to their biologically active metabolites is dependent on the activity of 11ßHSD-1.
Cytochrome P450-Metabolized Drugs	
Clinical impact	Limited published data indicate that GH treatment increases cytochrome P450 (CP450)-mediated antipyrine clearance. Sogroya® may alter the clearance of compounds known to be metabolized by CP450 liver enzymes.
Intervention	Careful monitoring is advisable when Sogroya® is administered in combination with drugs metabolized by CP450 liver enzymes.
Oral Estrogen	
Clinical impact	Oral estrogens may reduce the serum IGF-1 response to Sogroya®.
Intervention	Patients receiving oral estrogen replacement may require higher Sogroya® dosages.
Insulin and/or Other Hypoglycemic Agents	
Clinical impact	Treatment with Sogroya® may decrease insulin sensitivity, particularly at higher doses.
Intervention	Patients with diabetes mellitus may require adjustment of their doses of insulin and/or other hypoglycemic agents.

10 COMPARISONS

N/A

Important Safety Information (cont'd)

Warnings and Precautions

- **Increased Mortality in Patients with Acute Critical Illness:** Increased mortality has been reported after treatment with somatropin in patients with acute critical illness due to complications following open-heart surgery, abdominal surgery, multiple accidental trauma, and in patients with acute respiratory failure
- **Severe Hypersensitivity:** Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported postmarketing with use of somatropin. Inform patients and/or caregivers that such reactions are possible, and that prompt medical attention should be sought if an allergic reaction occurs
- **Increased Risk of Neoplasms:** There is an increased risk of malignancy progression with somatropin in patients with active malignancy. Any preexisting malignancy should be inactive, and its treatment complete prior to instituting Sogroya®. In childhood cancer survivors treated with radiation to the brain/head for their first neoplasm who developed subsequent GHD and were treated with somatropin, an increased risk of a second neoplasm has been reported. Monitor patients with a history of GHD secondary to an intracranial neoplasm for progression or recurrence of the tumor. Children with certain rare genetic causes of short stature have an increased risk of developing malignancies and should be carefully monitored for development of neoplasms. Monitor patients for increased growth or potential malignant changes of preexisting nevi. Advise patients/caregivers to report changes in the appearance of preexisting nevi
- **Glucose Intolerance and Diabetes Mellitus:** Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses. New onset type 2 diabetes has been reported. Monitor glucose levels in all patients, especially in those with existing diabetes mellitus or with risk factors for diabetes mellitus, such as obesity, Turner syndrome or a family history of diabetes mellitus. The doses of antidiabetic agents may require adjustment when Sogroya® is initiated
- **Intracranial Hypertension:** Has been reported usually within 8 weeks of treatment initiation. Perform fundoscopic examination prior to initiation of treatment and periodically thereafter. If papilledema is identified, evaluate the etiology, and treat the underlying cause before initiating Sogroya®. If papilledema is observed, stop treatment. If intracranial hypertension is confirmed, Sogroya® can be restarted at a lower dose after intracranial hypertension signs and symptoms have resolved
- **Fluid retention:** May occur during Sogroya® therapy. Clinical manifestations of fluid retention (e.g. edema and nerve compression syndromes including carpal tunnel syndrome/paresthesia) are usually transient and dose dependent
- **Hypoadrenalism:** Patients receiving somatropin therapy who have or are at risk for corticotropin deficiency may be at risk for reduced serum cortisol levels and/or unmasking of central (secondary) hypoadrenalism. Patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of Sogroya®. Monitor patients with known hypoadrenalism for reduced serum cortisol levels and/or need for glucocorticoid dose increases

Please see additional Important Safety Information on pages 1 and 20.
Please **click here** for Prescribing Information.

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

- **Hypothyroidism:** Undiagnosed/untreated hypothyroidism may prevent an optimal response to Sogroya®. Monitor thyroid function periodically as hypothyroidism may occur or worsen after initiation of Sogroya®
- **Slipped Capital Femoral Epiphysis in Pediatric Patients:** Slipped capital femoral epiphysis may occur more frequently in patients undergoing rapid growth. Evaluate pediatric patients with the onset of a limp or complaints of persistent hip or knee pain
- **Progression of Preexisting Scoliosis in Pediatric Patients:** Monitor patients with a history of scoliosis for disease progression
- **Pancreatitis:** Cases of pancreatitis have been reported in patients receiving somatropin. The risk may be greater in pediatric patients compared to adults. Consider pancreatitis in patients with persistent severe abdominal pain
- **Lipohypertrophy/Lipoatrophy:** May occur if Sogroya® is administered at the same site over a long period of time. Rotate injection sites to reduce this risk
- **Sudden death in Pediatric Patients with Prader-Willi Syndrome:** There have been reports of fatalities after initiating therapy with somatropin in pediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnea, or unidentified respiratory infection. Male patients with one or more of these factors may be at greater risk than females. Sogroya® is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome
- **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

Adverse Reactions

- Pediatric patients with GHD: Adverse reactions reported in ≥5% of patients are nasopharyngitis, headache, pyrexia, pain in extremity, and injection site reaction
- Adult patients with GHD: Adverse reactions reported in >2% of patients are back pain, arthralgia, dyspepsia, sleep disorder, dizziness, tonsillitis, peripheral edema, vomiting, adrenal insufficiency, hypertension, blood creatine phosphokinase increase, weight increase, and anemia

Drug Interactions

- **Glucocorticoids:** Patients treated with glucocorticoid for hypoadrenalism may require an increase in their maintenance or stress doses following initiation of Sogroya®
- **Cytochrome P450-Metabolized Drugs:** Sogroya® may alter the clearance. Monitor carefully if used with Sogroya®
- **Oral Estrogen:** Patients receiving oral estrogen replacement may require higher Sogroya® dosages
- **Insulin and/or Other Antihyperglycemic Agents:** Dose adjustment of insulin and/or antihyperglycemic agent may be required for patients with diabetes mellitus

Please see additional Important Safety Information on pages 1 and 19.
Please **click here** for Prescribing Information.

Novo Nordisk Inc., 800 Scudders Mill Road, Plainsboro, New Jersey 08536 U.S.A.

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SOGROYA® somapacitan-beco injection 5mg | 10mg | 15mg