CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761156Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
<table>
<thead>
<tr>
<th><strong>Application Type</strong></th>
<th>BLA</th>
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<tr>
<td><strong>Application Number</strong></td>
<td>761156</td>
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<tr>
<td><strong>PDUFA Goal Date</strong></td>
<td>August 28, 2020</td>
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<tr>
<td><strong>OSE RCM #</strong></td>
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<tr>
<td><strong>Reviewer Name(s)</strong></td>
<td>Till Olickal, Ph.D., Pharm.D.</td>
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<tr>
<td><strong>Acting Team Leader</strong></td>
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<td><strong>Review Completion Date</strong></td>
<td>July 14, 2020.</td>
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<tr>
<td><strong>Subject</strong></td>
<td>Review to determine if a REMS is necessary</td>
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<tr>
<td><strong>Established Name</strong></td>
<td>somapacitan-beco</td>
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<tr>
<td><strong>Trade Name</strong></td>
<td>Sogroya</td>
</tr>
<tr>
<td><strong>Name of Applicant</strong></td>
<td>Novo Nordisk Inc.</td>
</tr>
<tr>
<td><strong>Therapeutic Class</strong></td>
<td>long-acting recombinant human growth hormone derivative</td>
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<tr>
<td><strong>Formulation(s)</strong></td>
<td>10mg/1.5ml prefilled pen</td>
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<tr>
<td><strong>Dosing Regimen</strong></td>
<td>The recommended starting dose is approximately 1.5 mg/week for treatment naïve patients or for patients switching from daily growth hormone (somatropin).</td>
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</table>

Reference ID: 4640785
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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity somapacitan-beco is necessary to ensure the benefits outweigh its risks. Novo Nordisk Inc. submitted a Biologic Licensing Application (BLA) 761156 for Sogroya (somapacitan-beco) with the proposed indication for the replacement of endogenous growth hormone (GH) in adults with growth hormone deficiency. The serious risks associated with the use of somapacitan-beco are increased mortality in patients with acute critical illness, increased risk of neoplasms, glucose intolerance and diabetes mellitus, intracranial hypertension, severe hypersensitivity, fluid retention, hypoadrenalism, hypothyroidism, pancreatitis, lipohypertrophy, and laboratory tests. The applicant did not submit a REMS with this application but proposed Prescribing Information that includes Warnings and Precautions, as well as information to be included in Patient Counseling Information.

Division of Risk Management (DRM) and Division of Metabolism and Endocrinology Products (DMEP) have determined that if approved, a REMS is not necessary to ensure the benefits of somapacitan-beco outweigh its risks. GH deficiency is a rare disorder which affects both children and adults. The syndrome of adult growth hormone deficiency (AGHD) may contribute to the increase in morbidity and mortality among patients with hypopituitarism. GH therapy in AGHD is probably the best-documented therapeutic indication in pituitary endocrinology due to its effects on body composition and metabolic actions. Current GH therapy for AGHD is administered as daily subcutaneous injections in the vast majority of patients and often necessitates many years or life-long treatment. This treatment complexity further reinforces that a GH replacement therapy with less frequent injections would be an attractive and additional choice for AGHD patients. Inflexible treatment regimens restrict the patients’ lifestyle and can contribute to lack of adherence and failure. Therefore, there is a medical need for the development of safe and effective GH replacement therapy with less frequent injections formulated in ways that may increase compliance with therapy. Somapacitan-beco appeared efficacious in both its primary outcome of reduction in truncal fat percentage and secondary outcomes of reductions in truncal fat mass, total fat mass, android fat mass, and visceral adipose tissue. Based on the efficacy and safety information currently available, the clinical reviewer recommends approval of somapacitan-beco for the replacement of endogenous GH in adults with GH deficiency. The most concerning adverse reactions observed with the use of somapacitan-beco are increased mortality in patients with acute critical illness, increased risk of neoplasms, glucose intolerance and diabetes mellitus, intracranial hypertension, severe hypersensitivity, fluid retention, hypoadrenalism, hypothyroidism, pancreatitis, lipohypertrophy, and laboratory tests. Similar to other recombinant human growth hormone derivatives, Norditropin (somatropin) if approved, labeling would include Warnings and Precautions to communicate these safety issues and management of toxicities associated with somapacitan-beco. Information will also be included in Patient Counseling Information, and will include important information that a health care provider should convey to patients.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) somapacitan-beco is necessary to ensure the benefits outweigh its risks. Novo Nordisk Inc. submitted a Biologic Licensing Application (BLA) 761156 for Sogroya (somapacitan-beco) with the proposed indication for the replacement of endogenous growth hormone (GH) in adults with growth hormone deficiency. The applicant did not submit a REMS with this application but proposed
Prescribing Information that includes Warnings and Precautions, as well as information to be included in section 17, Patient Counseling Information.

2 Background

2.1 Product Information

Somapacitan-beco is a NME BLA type 351(a) pathway application. It is a long-acting recombinant human growth hormone (hGH) analog with a single substitution in the amino acid backbone (L101C) to which an albumin binding moiety has been attached. The albumin binding moiety (side-chain) consists of an albumin binder and a hydrophilic spacer attached to position 101 of the protein. Reversible binding to endogenous albumin delays elimination of somapacitan-beco and thereby prolongs the in vivo half-life (t½) and duration of action. The mechanism of action of somapacitan-beco is either directly via the GH-receptor and/or indirectly via insulin-like growth factor I (IGF-I) produced in tissues throughout the body, but predominantly by the liver. Somapacitan-beco will be supplied as 10 mg in 1.5ml prefilled pen. The recommended starting dose is approximately 1.5 mg/week for treatment naïve patients or for patients switching from daily growth hormone (somatropin). Recommendations are to increase the dose every 2-4 weeks by increments of approximately +0.5 mg to +1.5 mg, according to individual patient requirements based on the clinical response and serum insulin-like growth factor 1 (IGF-1) concentrations. IGF-1 samples should be drawn 3 to 4 days after the prior dose. Decrease the dose as necessary on the basis of adverse reactions and/or serum IGF-1 concentrations above the age- and gender-specific normal range. Maintenance dosages will vary from person to person, and between male and female patients, and should not exceed a dose of 8 mg/week. Somapacitan-beco is not currently approved in any jurisdiction.

2.2 Regulatory History

The following is a summary of the regulatory history for somapacitan-beco (BLA 761156) relevant to this review:

- 07/23/2014: Investigation New Drug IND 116327 submission for somapacitan was received.
- 08/28/2019: BLA 761156 submission for somapacitan-beco with the proposed indication for the replacement of endogenous GH in adults with GH deficiency, received.
- 02/13/2020: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for somapacitan-beco.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

GH deficiency is a rare disorder which affects both children and adults. It is characterized by

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\( a \) Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.

\( b \) Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.

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inadequate systemic availability of GH due to inadequate secretion from the anterior pituitary gland or destruction of the gland. Adult growth hormone deficiency (AGHD) is a clinical syndrome associated with alterations in body composition with reduced bone and muscle mass, diminished exercise performance and cardiac capacity, and altered lipid metabolism with increase in adiposity. AGHD has been estimated to affect 1 per 100,000 people annually, while its incidence rate is approximately 2 per 100,000 when child-onset GHD (growth hormone deficiency) individuals transition to adulthood.\(^c\) Approximately 6,000 new cases of adults with GHD are diagnosed each year in the US. Some, 15–20% of those cases represent the continuation of child-onset GHD into maturity; the remainder have adult-onset GHD resulting from damage to the hypothalamic-pituitary axis, which commonly arises from pituitary or peri-pituitary tumors, or by their treatment. Pituitary adenomas and their treatment account for nearly two-thirds of AGHD cases. AGHD has also been associated with impaired cognition as well as having psychological impact. All these features result in decreased quality of life. The syndrome of AGHD may contribute to the increase in morbidity and mortality among patients with hypopituitarism.\(^d\)

### 3.2 Description of Current Treatment Options

GH therapy in AGHD is probably the best-documented therapeutic indication in pituitary endocrinology due to its effects on body composition and metabolic actions. The change in body composition with reduced fat mass and increased lean body mass is the most robust effect. Most studies also record improvements in aerobic exercise capacity and cardiac function.\(^3\) GH replacement therapy improves exercise performance in patients with GH deficiency. Most adverse effects related to GH replacement therapy are endocrine effects as a result of fluid retention, and include edema, arthralgias, myalgias, paresthesias and carpal tunnel syndrome. These adverse effects occur in 5–18% of patients and respond to dose reduction. Elderly, overweight and female patients seem to be at increased risk of developing these adverse effects.\(^4\) International consensus guidelines have suggested that the insulin tolerance test (ITT) is the gold standard test for diagnosing AGHD.\(^5\) Endocrine society clinical practice guideline recommend that the ITT and the growth hormone-releasing hormone (GHRH)-arginine test have sufficient sensitivity and specificity to establish the diagnosis of GHD. The clinical guideline also recommends that GH dosing regimens be individualized rather than weight-based and start with low doses and be titrated according to clinical response, side effects, and IGF-I levels.\(^6\) Clinical understanding of GH deficiency in adults is still much more limited than that in children. Even when linear growth is no longer possible, GH has many important effects on lipids, body composition, strength, aerobic capacity and quality of life in patients with adult GH deficiency. Despite some concerns over long term risks, GH replacement for adult GH deficiency has a positive benefit/risk balance when dosing is individualized, and patients carefully monitored.\(^4\)

Current GH therapy for AGHD is administered as daily subcutaneous injections in the vast majority of patients and often necessitates many years or life-long treatment. Frequent pain from injection, bruising and stinging can contribute to the burden associated with daily GH treatment.\(^7\) This treatment complexity further reinforces that a GH replacement therapy with less frequent injections would be an attractive and additional choice for AGHD patients. Inflexible treatment regimens restrict the patients’

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\(^c\) Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.

\(^d\) Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.
lifestyle and can contribute to lack of adherence and failure. Therefore, there is a medical need for the development of safe and effective GH replacement therapy with less frequent injections formulated in ways that may increase compliance with therapy.

4 Benefit Assessment

The efficacy and safety of somapacitan-beco was evaluated in treatment-naïve adult patients with GHD based on a 35-week data from a multi-national, randomized, parallel-group, placebo-controlled (double-blind) and active controlled(open-label) trial (Tiral 4054; NCT02229851). The study was conducted in 300 treatment-naïve adult patients with GHD, who were randomized (2:1:2) and exposed to once-weekly somapacitan-beco 10 mg/1.5ml (n=120) or placebo (n=60) or to daily Norditropin 10 mg/1.5ml (n=119) for a 34-week treatment period (8 weeks titration and 26 weeks fixed dose) plus one week washout). The mean BMI was 27.4 kg/m². In the trial 4054, the primary efficacy endpoint was a change from baseline to end of main treatment period (week 34) in truncal fat percent. Body composition was measured by DXA scan and truncal fat percent was defined as 100 times truncal fat mass (kg) divided by the sum of truncal fat mass kilograms (kg) and truncal lean body mass kg.¹,⁸

At the time of this review, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant efficacy information to date for somapacitan-beco. Treatment with somapacitan-beco demonstrated superiority compared to placebo with a statistically significant reduction in truncal fat % after 34 weeks as shown in Table 1.¹,⁸,e

Table 1: Truncal Fat % Results for somapacitan-beco Compared to Placebo at Week 34 (C2301)¹,⁸,e

<table>
<thead>
<tr>
<th>Change from baseline at 34 weeks</th>
<th>Placebo</th>
<th>Somapacitan-beco</th>
<th>Difference from placebo [95% CI] p-value</th>
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<tr>
<td>Number of subjects in FAS (N)</td>
<td>61</td>
<td>120</td>
<td>-1.53 [-2.68; -0.38] 0.0090</td>
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<tr>
<td>Truncal fat %</td>
<td>0.47</td>
<td>-1.06</td>
<td></td>
</tr>
<tr>
<td>Primary analysis of primary endpoint</td>
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</table>

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

The results of the secondary comparison for the primary end point between somapacitan-beco and Norditropin showed a treatment difference in truncal fat percent at week 34 of 1.17 (95% CI 0.23; 2.11), in favor of Norditropin.

e Section 505-1 (a) of the FD&C Act: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.
The key secondary endpoints, reductions in truncal fat mass, total fat mass, android fat mass, and visceral adipose tissue that are associated with reductions in abdominal adipose tissue were observed at 34 weeks for somapacitan-beco compared with placebo. Across the lean body composition parameters of truncal lean body mass, lean body mass and appendicular skeletal muscle mass, increases from baseline were observed at 34 weeks with somapacitan-beco compared to placebo as well. No statistically significant differences were observed between somapacitan-beco and Norditropin in the reductions from baseline for visceral adipose tissue and android fat mass and in the increases from baseline for truncal lean body mass, lean body mass and appendicular skeletal muscle mass. Additionally, there were no clinically relevant changes in total body weight or waist circumference from baseline to week 34 for somapacitan-beco or Norditropin.1,8,e

5 Risk Assessment & Safe-Use Conditions

At the time of this review, labeling negotiations were ongoing with the applicant. The following section is a summary of relevant safety information to date for somapacitan-beco. The safety analysis of somapacitan-beco primarily focuses in Trial 4054 (see Section 4: Benefit Assessment), Trial 4244 and Trial 4043. The confirmatory clinical phase 3 trial 4054 assessed the efficacy and safety of once-weekly dosing of somapacitan-beco compared with once-weekly dosing of placebo and daily dosing of Norditropin in GH treatment-naive AGHD patients. The trial consisted of a 35-week main phase (double-blind for somapacitan-beco and placebo; open-label for Norditropin) followed by a 53-week open-label extension phase.

In the extension period, patients treated with somapacitan-beco continued their once-weekly treatment, patients treated with placebo were switched to somapacitan-beco treatment and patients treated with Norditropin were re-randomized to continue Norditropin treatment or switch to somapacitan-beco treatment. Trial 4244 was a national, multicenter, randomized, open-label, parallel-group, active-controlled trial in Japan. The trial was designed to compare the safety of once-weekly somapacitan-beco with daily Norditropin (3:1) in previously treated Japanese AGHD patients for 52 weeks. The trial consisted of a 20-week dose titration period, a 32-week fixed-dose period, and a 1-week washout. Trial 4043 was a multicenter, multinational, randomized, open-label, parallel-group, active controlled trial. The trial was designed to compare the safety and efficacy of once-weekly somapacitan-beco with daily Norditropin (2:1) in previously treated AGHD patients for 26 weeks. The trial consisted of an 8-week dose titration period, an 18-week fixed-dose period, and a 1-week washout period. A total of 333 AGHD patients were exposed to somapacitan-beco in the completed clinical trials in AGHD. Up to 86 weeks of exposure to somapacitan-beco has been evaluated in AGHD. After insulin-like growth factor 1 (IGF-I) standard deviation score (SDS) dose titration the mean somapacitan-beco dose was 2.38 mg/week (0.036 mg/kg/week). A total of 166 AGHD patients were exposed to daily Norditropin treatment as active comparator in the completed clinical trials in AGHD (up to 86 weeks of exposure). The mean Norditropin dose was 0.29 mg/day (0.005 mg/kg/day). A total of 61 AGHD patients were exposed to placebo. The total exposure was 363.7 patient years of exposure (PYE) for somapacitan-beco, 152.6 PYE for Norditropin and 38.2 PYE for placebo.9

The most common adverse reactions reported in ≥5% of patients treated with somapacitan-beco are back pain 9.2%, arthralgia (6.7%) and abdominal pain (5.8%).1
Deaths

A total of 5 deaths (1.3%) have been reported during trial 4054. The clinical reviewer stated that all the cases of death were not related to the trial drug considering relationship between time of exposure and event occurrence, underlying medical conditions and acute illnesses (i.e. pneumonia, influenza), which were the likely contributors in all cases. In addition, deaths are expected in the age group of the population being studied. No deaths were reported in trials 4043 and 4244.8

Serious Adverse Events (SAE)

A total of 32 SAEs occurred in 23 (7.7%) patients during the trial 4054, with 12 events in 7 patients (5.8%) in somapacitan-beco group, 13 events in 11 (9.2%) patients in Norditropin group, and 7 events in 5 (8.2%) patients in placebo group. With the exception of 1 SAE (hemoconcentration) in the Norditropin group, none of the SAEs were likely related to the study drug, as assessed by the investigator. Many cases of SAEs were classified as such because patients were hospitalized, with the need for hospitalization being questionable. SAEs in the somapacitan-beco group occurring in more than 2% of subjects were noted in SOCs Infections and infestations (3.3%, compared to 1.7% in Norditropin group) and Gastrointestinal disorders (2.5%, compared to 0.8% in Norditropin group). Upon detailed review of SAEs case narratives, the clinical reviewer stated that none of the events in somapacitan-beco group were likely related to the study drug. A total of 12 AEs led to permanent study drug discontinuation in 11 patients. Three SAEs were plasma cell myeloma (in Norditropin/ somapacitan-beco arm), hemoconcentration and dermatitis atopic in Norditropin arm. There were no discontinuations in the somapacitan-beco arm, but six patients were discontinued in the somapacitan-beco (extension arm) due to hepatic steatosis and elevated Hba1c (1 patient, fatigue, benign pituitary tumors (2 patients), thyroid follicular lesion and plasma cell myeloma while on Norditropin. Four patients discontinued Norditropin due to diabetes, hemoconcentration, gastroenteritis, dermatitis atopic. There were no discontinuations in the Norditropin arm extension.8

If approved, labeling will include the following risks in the Warnings and Precautions section.

5.1 INCREASED MORTALITY IN PATIENTS WITH ACUTE CRITICAL ILLNESS

Increase mortality in patients with acute critical illness were reported after treatment with pharmacologic amounts of growth hormone products due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n=522) with these conditions in intensive care units revealed a significant increase in mortality (42% vs. 19%) among somatropin-treated patients (doses 5.3-8 mg/day) compared to those receiving placebo. Similar to other recombinant human growth hormone derivatives such as somatropin (Norditropin)10, the risk of increased mortality in patients with acute critical illness is included in the draft label in the Warnings and Precautions as well as the Contraindications section of the somapacitan-beco.1

Other adverse events that somapacitan-beco has in common with currently approved recombinant human growth hormone derivatives will likely be communicated in the Warnings and Precautions section of the somapacitan-beco label as well. These adverse events include: the risk of risk of neoplasms, glucose intolerance and diabetes mellitus, intracranial hypertension, severe hypersensitivity, fluid retention, hypoadrenalism, hypothyroidism, pancreatitis, lipo hypertrophy and abnormal laboratory tests for serum levels of inorganic phosphorus, alkaline phosphatase, parathyroid
hormone and insulin-like growth factor-1 (IGF-I). As also present in the label of other growth hormone derivates, the risk of neoplasms and severe hypersensitivity will also be communicated with in the Contraindications section of the label, and the risks of intracranial hypertension and lipohypertrophy will also be communicated in the Dosage and Administration sections of the label.

6 Expected Postmarket Use

According to the current proposed indication, if approved, somapacitan-beco is a subcutaneous injection medication that will be used in both inpatient and outpatient settings and will likely be prescribed by endocrinologists.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for somapacitan-beco beyond routine pharmacovigilance and labeling. Similar to other recombinant human growth hormone derivates, somatropin (Norditropin), the applicant proposed a PI that includes Warnings and Precautions to address the risks of increased mortality in patients with acute critical illness, increased risk of neoplasms, glucose intolerance and diabetes mellitus, intracranial hypertension, severe hypersensitivity, fluid retention, hypoadrenalism, hypothyroidism, pancreatitis, lipohypertrophy and laboratory tests.

8 Discussion of Need for a REMS

Somapacitan-beco is a long-acting recombinant hGH analog, with the proposed indication for the replacement of endogenous GH in adults with GH deficiency. When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for somapacitan-beco, this reviewer considered that the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the likely prescribing population.

GH deficiency is a rare disorder which affects both children and adults. The syndrome of AGHD may contribute to the increase in morbidity and mortality among patients with hypopituitarism. GH therapy in AGHD is probably the best-documented therapeutic indication in pituitary endocrinology due to its effects on body composition and metabolic actions. Current GH therapy for AGHD is administered as daily subcutaneous injections in the vast majority of patients and often necessitates many years or lifelong treatment. This treatment complexity further reinforces that a GH replacement therapy with less frequent injections would be an additional option for AGHD patients. Inflexible treatment regimens restrict the patients’ lifestyle and can contribute to lack of adherence and failure. Therefore, there is a medical need for the development of safe and effective GH replacement therapy with less frequent injections formulated in ways that may increase compliance with therapy.

Somapacitan-beco appeared efficacious in both its primary and secondary outcomes in the clinical trials used in adult patients, and its risks can be communicated and managed through labeling. If somapacitan-beco is approved, the Applicant will be required to complete the ongoing Phase 2, randomized, open-label, active-control, dose-finding trial, and the Phase 3, randomized, parallel group, open-label trial as the post-marketing requirement (PMR) to study the efficacy and safety of once-weekly somapacitan-beco versus daily Norditropin (somatropin) in pre-pubertal children with GHD.
The likely prescribers for somapacitan-beco will be endocrinologists. The risks identified in the draft label are risks that these providers have likely encountered in their practice experience and can manage without additional risk mitigation measures.

DRM and DMEP have determined that if approved, a REMS is not necessary to ensure the benefits of somapacitan-beco outweigh its risks. The most concerning adverse reactions observed with the use of somapacitan-beco are increased mortality in patients with acute critical illness, increased risk of neoplasms, glucose intolerance and diabetes mellitus, intracranial hypertension, severe hypersensitivity, fluid retention, hypoadrenalism, hypothyroidism, pancreatitis, lipohypertrophy/ and laboratory tests.

At the time of this review, labeling negotiations were still ongoing with the Applicant; however, similar to other recombinant human growth hormone derivative, somatropin (Norditropin), if approved, the risks will be communicated in the label, including; Dosage and Administration, Contraindications, and Warnings and Precautions, and Patient Counseling Information. Similar to somatropin, at this time, none of the risks will receive a boxed warning.

9 Conclusion & Recommendations

If approved, DRM has determined that a REMS is not necessary to ensure the benefits outweigh the risks of somapacitan-beco. The management of the risks associated with somapacitan-beco treatment will be communicated through labeling. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 References

1 Draft Prescribing Information for somapacitan-beco as currently edited by the FDA, last updated June 23, 2020.

2 Reed ML, Merriam GR, Kargi AY. Adult growth hormone deficiency - benefits, side effects, and risks of growth hormone replacement. *Front Endocrinol (Lausanne).* 2013;4:64.

3 Jørgensen JOL, Juul A. THERAPY OF ENDOCRINE DISEASE: Growth hormone replacement therapy in adults: 30 years of personal clinical experience. 2018;179(1):R47.


10 Norditropin. Prescribing Information (last updated 02/2018).
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/s/

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