swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Sogroya

International non-proprietary name:	somapacitan
Pharmaceutical form:	solution for injection in pre-filled pen
Dosage strength(s):	5 mg/ 1.5 mL; 10 mg/ 1.5 mL; 15 mg/ 1.5 mL
Route(s) of administration:	Subcutaneous use
Marketing authorisation holder:	Novo Nordisk Pharma AG
Marketing authorisation no.:	69063
Decision and decision date:	approved on 26 April 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EFD	Embryofetal development
EMA	European Medicines Agency
E_{max}	Maximum increase in IGF-I production rate
ERA	Environmental risk assessment
F_{rel}	Relative bioavailability
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GH	Growth hormone
GHD	Growth hormone deficiency
GLP	Good Laboratory Practice
hGH	Human growth hormone
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IGF-I	Insulin-like growth factor 1
IGFBP-3	Insulin-like growth factor-binding protein 3
INN	International non-proprietary name
ITT	Intention-to-treat
K_{in}	Production rate of IGF-I
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
pGHD	Paediatric growth hormone deficiency
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PRLR	Prolactin receptor
PSP	Pediatric study plan (US FDA)
QoL	Quality of life
rhGH	Recombinant human growth hormone
RMP	Risk management plan

SAE	Serious adverse event
SC	Subcutaneous
SDS	Standard deviation score
SwissPAR	Swiss Public Assessment Report
T ½	Half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time to reach Cmax
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

New active substance status
The applicant requested new active substance status for somapacitan in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 9 October 2019.

2.2 Indication and dosage

2.2.1 Requested indication

Sogroya is indicated for the replacement of endogenous growth hormone (GH) in paediatric patients with a growth disorder caused by growth hormone deficiency (GHD).

2.2.2 Approved indication

Replacement of endogenous growth hormone (GH) in paediatric patients from 3 years of age with growth failure due to proven growth hormone deficiency (GHD).

2.2.3 Requested dosage

Starting dose:
The recommended dose for treatment-naive patients and patients being switched from other growth hormone products, is 0.16 mg/kg/week for all paediatric age groups.

Maintenance dose:
Dosage is individualised and adjusted based on clinical response. If the growth hormone deficiency still exists after growth has ended, growth hormone therapy should be continued until full somatic development to adulthood is achieved, including an increase in lean body mass and bone mineral density.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	1 August 2022
Formal objection	24 August 2022
Response to formal objection	29 August 2022
Formal control completed	23 September 2022

List of Questions (LoQ)	18 January 2023
Response to LoQ	18 April 2023
Preliminary decision	21 July 2023
Response to preliminary decision	29 September 2023
2nd Preliminary decision	18 December 2023
Response to 2nd preliminary decision	26 January 2024
Final decision	26 April 2024
Decision	approval

3 Medical context

Human growth hormone (hGH) is a 191-amino-acid pituitary protein that stimulates production and release of insulin-like growth factor 1 (IGF-I) into the systemic circulation and local milieu. hGH and IGF-I are instrumental in the promotion of linear growth in children and in the control of metabolism and body composition in children and adults. These factors are regulated through complex feedback mechanisms involving hGH, insulin-like growth factor-binding protein 3 (IGFBP-3) and their complexes.

In children, growth hormone deficiency (GHD) manifests primarily in abnormal linear growth. GHD also impacts bone, lipid, protein, and glucose metabolism in children, with findings that include decreased bone mineral density, decreased lean body mass, and increased fat mass. In adults, GHD results in decreased lean body mass, increased fat mass, weakness, reduction in exercise capacity, muscle mass/strength, cardiac performance, and bone density, and in neuropsychological disturbances.

Childhood GHD can be congenital, acquired, or idiopathic. Underlying causes of congenital malformation include pituitary dysfunction due to abnormal neurodevelopment in utero of certain brain regions and genetic abnormalities. The aetiology for acquired GHD includes brain tumours in the hypothalamic region, traumatic brain injury, infiltrative disease, cranial irradiation, and surgical intervention. The idiopathic origin of GHD is poorly understood, but appears to be multifactorial.

Only a small amount of data is available on the incidence and prevalence of GHD. Establishing its frequency is complicated by the fact that the diagnostic criteria are not uniform and differing methods exist for determining GH. Moreover, the figures stated in the literature depend on whether they refer to childhood GH deficiency exclusively or the prevalence of all patients with GH deficiency across all age groups. The prevalence of childhood GH deficiency is thought to be around 1:5,000.

In children, the growth attenuation and short stature resulting from GHD begins in early childhood and continues through attainment of final adult height, which can lead to a reduced quality of life (QoL). This is exacerbated by delayed puberty and deficits in facial, dental, and (in males) genital development. Approximately 5% of children with GHD have episodes of hypoglycaemia, particularly in infancy. Paediatric growth hormone deficiency (pGHD) is also associated with a metabolic profile similar to that of metabolic syndrome, including dyslipidaemia, insulin resistance, haemostatic alterations, oxidative stress, and chronic inflammation, all of which represent cardiovascular risk factors that, if left untreated, persist into adulthood.

From the patient/caregiver perspective, the burden of GHD on children goes well beyond short stature and its physiological effects. The inability to achieve normal growth and age- and gender-appropriate height can lead to early onset of psychosocial problems related to short stature, including behavioural and cognitive disorders. Parents have rated physical health, as well as psychosocial factors, as having a large impact on decisions to seek medical care for their child’s short stature.

Treatments for growth hormone deficiency have been available for more than 50 years. GH obtained from cadavers was originally used for this purpose, but following the discovery of Creutzfeldt-Jacob disease, the corresponding preparations were withdrawn from the market. Recombinant GH preparations have since been used for over 30 years to treat tens of thousands of patients (primarily children), and these have proved to be effective and safe.

The treatment of childhood GH deficiency is based on international guidelines (see, in particular, A. Grimberg et al.: Guidelines for growth hormone and insulin-like growth factor-1 treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-1 deficiency; Horm. Res. Paediatr 2016; 86: 361-397).

Recombinant human growth hormone (rhGH) treatment improves growth outcomes, as evidenced in increased height velocity and normalisation of adult height. rhGH treatment also has positive effects on the metabolic consequences of GHD, including improved body composition (fat/lean mass) and reduction in lipids (total cholesterol, LDL-cholesterol, and triglycerides), and improvements in QoL/psychosocial aspects of pGHD.

The current standard of care for paediatric GHD is daily subcutaneous (SC) injection of rhGH. Treatment response is assessed by measurements of height and height velocity, and is generally continued until final height, epiphyseal closure, or both, have been recorded. Early intervention produces the optimal outcome as growth potential decreases overtime.

The formulations currently available require a daily subcutaneous injection, and injection pens are used nowadays to simplify administration. Nevertheless, non-compliance remains a major problem. According to the literature, frequency differs considerably between various studies and depends to some extent on the definition of non-compliance. Furthermore, direct measurement is difficult, and the way of determining compliance differs between various studies. Overall, compliance across several studies is only between 34% and 64%, and usually declines with increasing treatment duration. Some studies have shown a correlation between compliance and height velocity.

One approach to improving adherence to treatment has been the development of long-acting GH formulations that require less frequent injections than the current daily-injection standard of care. The aim of such long-acting GH formulations is to increase long-term therapeutic success by improving compliance compared to formulations with comparable safety and efficacy that are administered once a day, and to reduce the stress on patients and their families arising from the need for daily injections. Several different technological approaches have been evaluated, including sustained-release preparations that utilise microsphere encapsulation (Nutropin Depot, LB03002), pegylated formulations (Jintrolong), glycosylation (somatrogon), prodrugs (TransCon), and Fc GH fusion formulations (GX-H9, albutropin). One potential drawback is the IGF-I profile, which differs from that associated with daily administration, although the extent to which this differing profile influences the safety and efficacy of such formulations in the long term is not known. Last but not least, a relevant factor here is the timing of IGF-I measurement for the purposes of treatment monitoring.

4 Quality aspects

4.1 Drug substance

Somapacitan is a long-acting recombinant human growth hormone (hGH) derivative 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. When somapacitan is injected, the albumin-binding moiety binds non-covalently to endogenous albumin, thereby prolonging the in vivo half-life and duration of action of somapacitan. The manufacturing process for somapacitan drug substance comprises fermentation of the somapacitan precursor in *Escherichia coli*, followed by harvesting, homogenisation, solubilisation, clarification, and capture. The somapacitan drug substance is obtained by several purification steps and a final concentration and diafiltration step. The manufacturing process has been validated, and validation demonstrated a consistent manufacturing process that effectively reduces process-related impurities. Characterisation of the physicochemical and biological properties of the drug substance and its impurities was performed using state-of-the-art methods.
The release and stability specifications for the drug substance include relevant tests and acceptance criteria, e.g. for appearance, identity, several purity and impurity tests, quantity, and a potency test (cell-based bioassay). All the analytical methods are described and non- compendial methods were validated in accordance with ICH guidelines. Batch analysis data for several batches were provided. All batch release data comply with the drug substance specifications valid at the time of batch release.
The drug substance is stored under appropriate storage conditions. No significant changes have been observed within the proposed shelf life. A shelf-life of 24 months under long-term (<-70°C) storage has been accepted.

4.2 Drug product

Somapacitan is available in three strengths (5 mg drug product solution for injection, 10 mg drug product solution for injection and 15 mg drug product solution for injection). Each strength is provided in a 1.5 mL cartridge and assembled in a PDS290 pen-injector.
Somapacitan is supplied as a clear to slightly opalescent, colourless to slightly yellow sterile solution, intended for subcutaneous administration with an extractable volume of 1.5 mL.
Somapacitan is formulated as an aqueous buffered solution with a pH of 6.8, containing histidine, mannitol, poloxamer 188, and phenol (for microbial preservation). All excipients comply with European Pharmacopoeia requirements.
The manufacturing process for the finished drug product consists of formulation, sterile filtration, filling, and visual inspection steps and further assembling of the pen injector. Process validation studies were executed at commercial scale using several validation batches for each somapacitan strength.
The specifications for the drug product were based on compendial requirements, experience from clinical trials, and commercial process capability. They include relevant tests and limits, e.g. for appearance, pH, content, identity, purity and impurity tests, phenol content, osmolality, sterility, bacterial endotoxins, dose accuracy, and extractable volume. All non-compendial methods have been validated in accordance with ICH guidelines.
Batch analysis data for development, clinical, and process validation batches were provided. All batch release data comply with the commercial drug product specifications. Comparability between batches used in the development phase and batches from the commercial manufacturing process was demonstrated.
The primary packaging is a 1.5 mL cartridge made of colourless hydrolytic glass (type 1 glass). The closure at one end of the cartridge is a cap that consists of a rubber disc and an aluminium seal. The rubber disc, which is in contact with the drug product, is made of laminated bromobutyl rubber (type 1 rubber). The closure at the other end of the cartridge is a plunger made of chlorobutyl rubber (type 1 rubber). The laminated rubber and rubber plunger are not made with natural rubber latex. The 1.5 mL cartridge is assembled in a pen-injector.
The storage and shelf life for somapacitan pen-injectors is 24 months at 2-8°C and protected from light, and includes the possibility of storage at or below 30°C for a maximum of 72 hours.
The manufacturing processes for the drug substance and drug product incorporate adequate control measures to prevent contamination and maintain control with regard to viral and non-viral contaminants.

4.3 Quality conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf lives of the drug substance and drug product are supported by data from recommended storage conditions, as well as accelerated and stress studies.

5 Nonclinical aspects

5.1 Pharmacology

Pharmacological activity of somapacitan (activation of growth hormone receptor, GHR) was demonstrated *in vitro* and *in vivo*. In primary rat hepatocytes and human hepatoma cells, somapacitan induced phosphorylation of signal transducer and activator of transcription 5 (STAT5) at low nanomolar concentrations. Compared to human growth hormone (hGH), somapacitan showed *in vitro* a slightly lower potency to activate the human GHR and an approx. 8-fold lower potency to stimulate human prolactin receptor (PRLR).
In male hypophysectomised rats, once-weekly subcutaneous (SC) administration of somapacitan at 14 nmol led to significant increases in body weight gain, body length, as well as bone weight and thickness. The main effect on body weight occurred within 2-3 days after the weekly dose, correlating with significant elevations in plasma concentrations of insulin-like growth factor-1 (IGF-I). Once peak concentration had been reached at ca. 3 days postdose, IGF-I levels decreased to vehicle control levels until the next dose. In contrast, daily administration of 2 nmol hGH to rats led to continuous body weight gain and steadily increased IGF-I plasma concentrations. Over the 4-week treatment period, IGF-I plasma exposure and body weight gain were higher in the group treated with somapacitan as compared with the group treated with hGH. Thus, for a comparable weekly dose, somapacitan had a higher *in vivo* potency than hGH.
Administration of somapacitan also induced transient increases in plasma IGF-I levels in other nonclinical species (mouse, monkey, rabbit, and minipig). IGF-I served as the PD marker in the repeated-dose toxicity studies in rats and monkeys.
Secondary pharmacology screens did not indicate a risk for clinically relevant off-target interactions. Based on *in vitro* safety pharmacology studies and the *in vivo* toxicity studies in monkeys, there is no risk of clinically relevant effects of somapacitan on cardiovascular, central nervous system, and respiratory function.

5.2 Pharmacokinetics

The pharmacokinetics (PK) of somapacitan was characterised in the nonclinical species used for safety assessment (rat, monkey, and rabbit). Somapacitan displayed nonlinear PK with more than dose-proportional increases in exposure at lower doses, and approximately dose-proportional increases in exposure at higher dose levels, indicating saturation of one or more disposition mechanisms. SC bioavailability was estimated to be 39% in rats and 69% in monkeys.
In rats, repeated administration of somapacitan generally led to decreased exposure, which was not observed in monkeys and humans. There was a trend towards higher exposure in male rats as compared with females in several studies. The time of maximum plasma concentration (t_{max}) in the repeated-dose studies was about 12 h in rats and 8-48 h in monkeys, similar to that in humans (4-24 h). Plasma elimination was shorter in rats (t_{last} 24-48 h) than in monkeys ($t_{1/2}$ 58-70 h). In children with GHD, $t_{1/2}$ was estimated to be 34 h at the 0.16 mg/kg/week dose.
ADAs were observed in both rats and monkeys after treatment with somapacitan. Whereas the incidences of ADA-positive animals were moderate to high in rats, somapacitan was only a weak immunogen in monkeys, with one mid-dose animal testing positive in the pivotal 26-week study. Based on the pharmacological responses and high exposures achieved, the presence of ADAs did not affect the validity of the toxicity studies.
The plasma protein binding of somapacitan was >99% across species (mouse, rat, monkey, rabbit, pig, and human). Following SC administration of 9 mg/kg to pigmented and albino rats,

[^{3}H]-somapacitan-related radioactivity showed a wide tissue distribution. The highest tissue concentrations generally correlated with excretion pathways (kidney cortex, urinary bladder, liver, and bile duct). Blood-plasma ratios were <1, indicating no specific binding to red blood cells. Only very low concentrations were seen in the brain and spinal cord. There was reversible binding of drug-related material to melanin and relatively slow excretion from tissues. Studies with rats showed transfer of drug-related radioactivity via the placenta and into milk.
Based on the analysis of plasma and excreta samples from rats and monkeys treated with [^{3}H]-somapacitan, somapacitan metabolism in these species is considered comparable to that in humans. Metabolism involves proteolytic cleavage of the peptide backbone followed by hydrolytic degradation of the linker sequence in the side chain. The major human plasma metabolites were qualified by the repeated-dose toxicity studies.
Metabolism was the main route of somapacitan elimination in rats, monkeys, and humans; intact somapacitan was not detected in excreta. Most of the drug-related material was excreted via urine in both rats and monkeys, as it was in humans.

5.3 Toxicology

Rats and cynomolgus monkeys were selected for the general toxicity studies. Both species are pharmacologically relevant and showed sufficient similarity to humans with regard to PK profile and metabolism. However, as described in the literature, hGH activates both GHR and the PRLR in rodents, whereas rodent GH only activates the GHR. This physiological difference has implications for the risk assessment, as discussed below. Reproductive toxicity studies were conducted in rats and rabbits, in accordance with ICH S5. The rabbit is also a pharmacologically relevant species.
Animals were treated by SC administration, the intended clinical route of administration. Dosing frequency in the toxicity studies was higher than the one-week dosing regimen envisaged for clinical use (daily or twice weekly in rats, twice weekly in monkeys, and every 2nd day in rabbits).
Somapacitan treatment of rats and monkeys up to 26 weeks produced effects that are directly or indirectly related to the pharmacological mode of action of hGH and similar to those described in the literature. Rats were more sensitive than monkeys. In line with published literature on the effects of hGH in rats and monkeys, the mammary gland was a target organ in both species, and effects such as hyperplasia occurred even at the lowest dose levels. Likewise, increases in plasma glucose concentrations were occasionally seen in both species, and male rats treated daily with 9 mg/kg somapacitan developed diabetes and cataracts. Hyperglycaemia is a known class effect of GH and was also seen in clinical trials with somapacitan.
In monkeys, twice-weekly treatment with up to 9 mg/kg for 26 weeks (associated with an exposure (AUC) >1000-fold the clinical exposure at 0.16 mg/kg/week) was well tolerated overall. The thymus and injection sites were identified as target organs in addition to mammary gland. The changes in the thymus (involution/atrophy) were considered to be stress-related and the local reactions were only mild. Notably, somapacitan-related changes in the mammary gland (ductal dilation, acinar dilation, and papillary hyperplasia) were also observed in one animal after the 6-week recovery period.
In rats, changes such as hyperplasia in the bone, hypertrophy in the kidneys and heart, and increased collagen content were considered to be directly related to the growth-promoting activity of GH. Islet cell hypertrophy/hyperplasia in the pancreas was probably secondary to the effects on insulin and glucose homoeostasis, and reversible. In the liver, somapacitan treatment induced hepatocellular vacuolation and increases in mitotic figures. The latter finding was considered to be related to the non-physiological activation of the PRLR, and this is supported by the lack of a proliferative response in liver tissue from monkeys treated with somapacitan. Administration of somapacitan at ≥2 mg/kg/day led to an exacerbation of chronic nephropathy in the 13-week study, probably as a result of GH-induced proteinaemia. Chronic nephropathy was not observed in the subsequent 26-week study with twice-weekly administration of up to 4 mg/kg, resulting in an exposure margin of 5.7-fold the clinical exposure at 0.16 mg/kg/week. The minimal dilatation of brain ventricles observed in rats might correlate with the common occurrence of headache in the clinical trials. It is known that GH therapy can lead to increased intracranial pressure.

Overall, most of the somapacitan-associated effects in the repeated-dose studies were considered to be due to exaggerated pharmacology and were in general reversible or exhibited a trend towards reversal. Since somapacitan is intended for replacement therapy, the risk of relevant side effects other than those already known from clinical experience with the marketed GH drug products is considered to be low.
Somapacitan tested negative for genotoxicity in standard tests *in vitro* and *in vivo*. Carcinogenicity studies were not conducted. This was justified by the non-physiological activation of PRLR by hGH in rats and mice. In line with ICH S6, the applicant submitted a carcinogenicity risk assessment, and this was considered to be adequate. Based on current knowledge of the carcinogenic risk of GH therapy to patients and the nonclinical data for somapacitan, the risk associated with the tumorigenic or tumour-promoting potential of somapacitan by the proposed replacement therapy is considered to be low. As with other GH drug products, however, a carcinogenic risk cannot be excluded given the nature of the pharmacological action (growth stimulation). The Information for healthcare professionals contains appropriate warnings and precautions; active malignancy is a contraindication.
The results of the reproductive toxicity studies do not indicate a risk of effects on fertility, pregnancy performance, and offspring development at clinically relevant exposures. Somapacitan did not adversely affect male or female rat fertility when administered twice weekly up to 4 mg/kg (about 5-fold the clinical exposure at 0.16 mg/kg/week). In male rats, decreased seminal vesicle weight was noted at ≥2 mg/kg, and in female rats there was an increased incidence of irregular oestrus cycles and a trend towards cycle length of 5 days at all doses (≥1 mg/kg); however, these effects were not associated with significant effects on mating performance/fertility. In the studies on embryofetal development (EFD) in rats, somapacitan-related findings included increased fetal weights at all doses, incompletely ossified/unossified sternebrae at ≥6 mg/kg/day, and skeletal abnormalities (*i.a.* short, bent and/or thickened long bones) at the high dose of 18 mg/kg/day. Maternal exposure at the developmental NOAEL (6 mg/kg/day) was about 6-fold the clinical exposure. In the EFD study in rabbits, dosing up to 9 mg/kg every 2nd day did not result in maternal toxicity, embryofetal mortality or teratogenic effects. Decreased fetal weights were observed at all doses (≥1 mg/kg) and skeletal variations (incompletely ossified/unossified sternebrae and/or metacarpals/phalanges) were observed at 9 mg/kg. Maternal exposure at the fetal NOAEL of 1 mg/kg was estimated to be about 4fold the clinical exposure at 0.16 mg/kg/week. In the pre- and postnatal development study in rats, which involved twice-weekly dosing of maternal (F0) animals with up to 18 mg/kg to day 8 of lactation (exposure >100-fold clinical exposure), no adverse effects on F1 offspring survival and development were observed. Due to its pharmacological action and the transfer of drug-related material across the placental barrier and into milk in nonclinical species, use of somapacitan during pregnancy and lactation should be avoided. This is addressed in the Information for healthcare professionals.
Juvenile toxicity studies have not been conducted with somapacitan. This can be accepted since the toxicity studies did not identify any target tissue of specific concern for paediatric patients.
SC administration of somapacitan to rats and monkeys in the repeated-dose studies was generally well tolerated; no or only slight local reactions were observed.
Dedicated immunotoxicity studies have not been conducted. This is acceptable since no signs of immunotoxicity were observed in the general toxicity studies.
The excipients and impurities raise no concerns. All excipients are already approved for SC use and were present in the formulations used for the pivotal toxicity studies. The specified impurities were qualified by the toxicity studies.
The description and evaluation of the nonclinical data in the RMP is accepted.
The introduction of somapacitan to the market is not expected to create a significant risk to the environment.

5.4 Nonclinical conclusions

Overall, the nonclinical studies adequately characterised the pharmacological and toxicological profile of somapacitan. Most effects observed in the toxicity studies were related to exaggerated pharmacology, which is not expected to occur in the course of the proposed replacement therapy in

the clinical setting. Changes in glucose homoeostasis and possible tumour-promoting properties are known risks with GH drug products; appropriate warnings are included in the Information for healthcare professionals. From a preclinical perspective, the application can be approved.

6 Clinical aspects

6.1 Clinical pharmacology

ADME

The pharmacokinetic profiles following a single subcutaneous dose of somapacitan (0.02 mg/kg to 0.16 mg/kg) in paediatric patients with GHD were investigated in one phase 1 study. The sparse PK data from one ongoing phase 2 study and one ongoing phase 3 study contributed solely to the population PK/PD and exposure-response analyses. Overall, the paediatric age range is only covered from 2.5 to 11 years.

Absorption

Following single doses of 0.02 mg/kg, 0.04 mg/kg, 0.08 mg/kg, and 0.16 mg/kg, maximal somapacitan serum concentrations were reached within 8.0 h to 25.5 h.

The steady-state PK of somapacitan was evaluated based on population PK/PD analysis using data from all three paediatric studies. Steady state was reached after 1 to 2 doses, and little to no accumulation was observed, suggesting an appropriate dosing interval as regards somapacitan half-life. Following the proposed somapacitan dose of 0.16 mg/kg, maximal serum concentrations at steady state were reached after 21.1 h. Overall, the PK of somapacitan was subject to moderate to high variability. Somapacitan concentrations were stable over the treatment period of four years.

The absolute bioavailability following SC administration was not determined.

Following single and multiple doses, somapacitan exposures increased with the dose. Overall, greater than dose-proportional increases in exposure were observed across the investigated dose range.

The impact of injection site on the bioavailability of somapacitan was not investigated in a dedicated study or in the context of the population PK analysis. As recommended in the submitted Information for healthcare professionals, administration sites were changed between thigh, abdomen, upper arms or buttocks for every injection in the paediatric phase 3 study.

Simulations of somapacitan concentrations and IGF-I SDS (standard deviation score) levels demonstrated that the flexibility of administering a dose up to 2 days prior to or 3 days after the regular dosing day, as well as of changing the regular administration day by administering the dose up to 3 days earlier or postponing it by up to 3 days, is possible. Consequently, a missed dose of somapacitan can be administered with up to 3 days' delay. If more than 3 days have passed, the dose should be skipped.

Distribution

Based on an *in vitro* study, plasma protein binding was found to be >99%.

Based on the population PK analysis, the volume of distribution was estimated at 1.73 L.

Metabolism and elimination

No metabolic turnover of somapacitan was observed *in vitro* using human hepatocytes, which suggests the absence of hepatic metabolism. Somapacitan is metabolised via proteolytic cleavage of the peptide backbone.

The disposition of somapacitan and its metabolites was investigated in healthy adult subjects. Somapacitan is excreted via urine (80.9% of the administered dose) and via faeces (12.9% of the administered dose). In serum, the predominant entity is unchanged somapacitan, accounting for 59% of the total exposure. Three primary serum metabolites (P1, M1, and M1B) were identified, which accounted for 21% and 12% (sum M1/M1B), respectively. Whereas M1 and M1B were structurally characterised, this was not feasible for P1, most likely because its high polarity. No parent drug was detected in urine and faeces, suggesting complete degradation of somapacitan. Two primary urine metabolites (M4 and M6) were identified and structurally characterised, and these accounted for 37.4% and 7.77%, respectively, of the administered dose. The most abundant metabolite in faeces accounted for 3.2% of the administered dose.

After single doses, the half-lives of somapacitan decreased with increasing dose levels. Based on the population PK/PD analysis, the half-life for 0.16 mg/kg somapacitan at steady state was estimated to be 33.6 h in paediatric patients.

Special populations/intrinsic factors

The exposures following multiple doses of 0.08 mg/kg somapacitan increased up to 75% ($AUC_{0\text{-}168h}$) and 47% (C_{max}), respectively, in adult subjects with mild, moderate, or severe renal impairment and adults requiring haemodialysis. In line with these findings, IGF-I SDS levels were increased in the subjects with renal impairment or requiring haemodialysis.

Although mild hepatic impairment had no impact on somapacitan exposure, exposure was substantially increased by 369% ($AUC_{0\text{-}168h}$) and 252% (C_{max}) in adult subjects with moderate hepatic impairment following multiple doses of 0.08 mg/kg. No subjects with severe hepatic impairment were included in the study. Intriguingly, IGF-I SDS levels were lower in subjects with mild or moderate hepatic impairment, most likely because of GH-resistance.

Using data from the paediatric studies, a population PK/PD analysis was conducted to identify factors that account for the variability in somapacitan PK and PD in paediatric patients with GHD. The PK of somapacitan was well described by a one-compartment model with dual first and zero-order absorption through a transit compartment and with saturable elimination. The effect of somapacitan on IGF-I was described by an indirect response model. The covariates body weight on F_{rel}; body weight, sex, and race (Asian non-Japanese) on E_{max}; body weight, and race (Asian Japanese and Asian non-Japanese) on K_{in} were retained in the final population PK/PD model. Body weight was the only significant covariate on the somapacitan PK; however, the impact on somapacitan exposure was minor due to the weight-based dosing.

Based on graphical analysis and additional analyses using the population PK model, ADA formation had no observable impact on the PK and PD of somapacitan.

Interactions

Somapacitan is a large therapeutic protein, and is therefore not considered to be a substrate for cytochrome P450 (CYP) enzymes and drug transporters. Considering the excess of albumin in human serum, protein displacement DDIs are unlikely.

Since the backbone of somapacitan, except for one amino acid in a non-binding region, and the mechanism of action are identical to those of hGH, it is unlikely that the risk of DDIs would be different fromthat of other marketed GH products.

Pharmacodynamics

Somapacitan is a long-acting recombinant human growth hormone (GH) derivative. The long-acting effect is mediated via non-covalent, reversible binding to endogenous albumin, which delays the elimination of somapacitan by decreased renal clearance and protection from metabolic degradation.

The pharmacological effects are identical to those of the human GH. It exerts its action either directly via the GH receptor or the via the IGF-I pathway. The primary PD markers were serum levels of IGF-I and IGFBP-3.

IGF-I profiles at steady state were evaluated by population PK/PD analysis. A clear dose-response relationship was observed between somapacitan and IGF-I response, i.e. change from baseline IGF-I_{avg} SDS. Following the proposed 0.16 mg/kg dose, steady state was reached following 1 to 2 doses. IGF-I levels t_{max} was estimated at 57.6 h. IGF-I_{avg} SDS were stable over the treatment period of four years.

Overall, the IGF-I average SDS were below +2 following the administration of 0.16 mg/kg somapacitan; however, individual measurements were above this threshold.

Only small effects on the IGF-I response were observed based on the covariates body weight, sex, and race.

Following the administration of 0.16 mg/kg somapacitan, the IGF response was higher, in particular for C_{max}, as compared to Norditropin®.

The model-derived change from baseline IGF-I_{avg} SDS for 0.16 mg/kg somapacitan was comparable to the observed change for Norditropin® at week 52. However, lower trough levels at the end of the dosing interval and larger peak-to-trough ratios were observed following the administration of weekly somapacitan.

IGFBP3 exposures also increased dose-dependently.

Secondary pharmacology (safety)

No dedicated tQT study was conducted. No effect of somapacitan on QT prolongation was observed in adults at therapeutic doses.

Pharmacodynamic interactions with other medicinal products or substances

Overall, the class effects for other marketed GH products apply.

Relationship between plasma concentration and effect

Positive relationships between somapacitan serum levels (C_{avg}) and IGF-I_{avg} SDS change from baseline and the primary efficacy endpoint of height velocity were observed. The same applies to the supportive endpoints of change from baseline height SDS and change from baseline height velocity SDS. The linear relationship by covariate group was comparable. However, lower height velocity was observed in male, older (≥6 years), Japanese, and taller (≥100.9 cm) subjects.

6.2 Dose finding and dose recommendation

The conventional GH preparation Norditropin® for daily injection was used as the active comparator in all phase II/III studies.

A correlation between exposure and administered dose had been demonstrated in phase I. Moreover, an exposure response analysis showed that height velocity increased with rising somapacitan exposure on the one hand, and with increasing change in IGF-I compared with baseline on the other.

In phase II, an open-label, randomised study involving n=59 treatment-naive, prepubertal patients (aged 2.5 years or over) with confirmed GH deficiency was conducted for dose-finding purposes. This compared three different doses of somapacitan (0.04mg/kg, 0.08mg/kg and 0.16mg/kg) administered once weekly with the daily administration of the active comparator Norditropin® (0.034mg/kg/day). The doses investigated in the study were chosen on the basis of the findings from phase I. The aim of the dose-finding study was to determine the dose with the most similar efficacy to the comparator.

Phase I modelling had shown that with a dose of 0.08mg/kg, a mean IGF-I value (the recognised surrogate marker in this indication) equivalent to that of the comparator could be expected. However, at a dose of 0.16mg/kg mean IGF-I was slightly higher than with the comparator, although the mean was still below the upper limit of normal of +2 SDS.

The choice of comparator dose is considered critical because at 0.034mg/kg, this was only minimally below the authorised maximum dose of 0.035mg/kg.

This study comprised several phases. First, efficacy of the doses under investigation was investigated relative to the comparator over a period of 26 weeks. In this first phase, the three dose groups were double blinded, whereas comparison with the comparator was open.

This phase of the study, which was named the "main phase", was followed by a second 26-week phase, during which patients continued treatment with the treatment to which they had originally been randomly assigned and which was primarily intended to investigate safety. After week 52, all patients in the somapacitan groups were switched to a dose of 0.16mg/kg. However, comparison with the Norditropin® group continued until week 156 (i.e. to a total treatment period of up to 3 years). Only then were the patients in the comparator group switched to somapacitan, resulting in all patients being treated with 0.16mg/kg somapacitan from then on. The study protocol envisages a treatment duration of up to 7 years. For the authorisation application, an interim report covering the data up to and including the fourth year of treatment was submitted.

The primary endpoint was height velocity (HV) during the first 26 weeks of the study.

There was a clear increase in HV compared with baseline in all four treatment groups, with somapacitan showing dose-dependency. The comparator showed significant superiority over the 0.04mg/kg dose, while its numerical findings were between those of the 0.08mg/kg and 0.16mg/kg dose. This reflects the finding from the underlying modelling that an IGF-I level between those for the two somapacitan dosages could be expected with Norditropin®. For the secondary endpoints, too, efficacy of the comparator was between that of 0.08mg/kg and 0.16mg/kg somapacitan.

HV after 26 weeks for the individual treatment groups was calculated as follows: 0.04mg/kg: 7.75cm/year; 0.08mg/kg: 10.87cm/year; 0.16mg/kg: 13.08cm/year; Norditropin: 11.41cm/year.

The fact that no additional dosage (e.g. 0.12mg/kg) was investigated in the substantial interval between 0.08 and 0.16mg/kg must be regarded as a relevant shortcoming. On the other hand, confirmation that the dose of 0.04mg/kg does not produce adequate efficacy was obtained.

Increase in IGF-I also demonstrated clear dose-dependency, and here again the 0.16mg/kg dose resulted in a significantly stronger increase than the comparator. By week 26, the corresponding values were:

- 0.04mg/kg: increase by 1.08 SDS
- 0.08mg/kg: increase by 2.15 SDS
- 0.16mg/kg: increase by 3.21 SDS
- Norditropin®: increase by 2.03 SDS

In this context, not only is the increase relevant, but also the attained absolute value for HV SDS, which has an upper limit of normal of +2 SDS. For treatment with growth hormone, the aim is generally to achieve a value >0, as was achieved with the comparator in the dose-finding study. However, the maximum value for the dose of 0.16mg/kg was >4 SDS. This seems critical as repeatedly exceeding the upper IGF-I may be associated with safety risks.

Therefore, Swissmedic regarded the dose of 0.16mg/kg, the only dose investigated in the pivotal studies, as too high for a general starting dose.

The study extension revealed a comparable picture up to week 52 – in other words, the findings for the comparator remained between those for 0.08mg/kg and 0.16mg/kg somapacitan. Whereas the comparator performed significantly better than the 0.04mg/kg dose, 0.16mg/kg produced a significantly better result than the comparator. (However, given the established good efficacy of the comparator, especially at the relatively high dose used in the study, greater efficacy does not seem necessary.)

6.3 Efficacy

A pivotal phase III study with n=200 treatment-naive prepubertal patients with GHD was conducted. This was an open-label, randomised, active-controlled, non-inferiority study in which efficacy and safety of somapacitan at a dosage of 0.16mg/kg once weekly were compared with those for conventional GH (0.034mg/kg/day) over a treatment period of 12 months. This was followed by an open-label extension in which all patients are treated with somapacitan. The intended overall duration of treatment was 4 years. With the authorisation application, only the study report for the 12-month controlled phase was submitted, while no interim reports from the extension were available.

In the event of persistent AEs that were classified as treatment-related, the dose was to be reduced in steps of 25%. Dose was also to be reduced by the same amount if IGF-I exceeded a value of +2.5 SDS at two consecutive visits. It remains unclear why a threshold of 2.5 SDS was chosen rather than the usual value of 2 SDS.

The study enrolled prepubertal children aged between 2.5 and <10 years for girls or between 2.5 and <11 years for boys.

The primary endpoint was the annualised height velocity (HV) in cm/year after 52 weeks. Important secondary endpoints were the standard deviation scores (SDS) for HV and body size. In addition, IGF-I and IGFBP-3 levels were determined and bone maturation was monitored. In addition, three disease-specific questionnaires that had been developed for the studies with somapacitan were employed.

Blood sampling for IGF-I determination was conducted during the first 4 days following somapacitan administration at some visits and predose at others. The aim of this was to determine the average concentrations across the dosing interval as a basis for possible dose adjustment.

The non-inferiority margin was pre-specified as a treatment difference of -1.8 cm/year between the test preparation and the active comparator, as already used in the past in other studies in children with GH deficiency.

Two different methods were used to analyse the primary endpoint because of differing requirements of EMA and the FDA. The approach demanded by the FDA is described as follows:

“The treatment difference between somapacitan and Norditropin® in mean annualised HV at week 52 for all randomised subjects regardless of treatment adherence or initiation of ancillary therapy in children with GHD.”

The analysis was conducted using ANCOVA.

The approach required by EMA applied an "ancillary therapy not available" assumption and is described as a "hypothetical strategy". This approach is described as follows:

“The treatment difference between somapacitan and Norditropin® in mean annualised HV at week 52 if ancillary therapy had not been available prior to week 52 (i.e., assuming no initiation of ancillary therapy) in children with GHD.”

The analysis was conducted using MMRM with an assumption of missing at random.

A good quarter of patients were recruited in the USA, while the combined contribution of the European countries to the study population was 18%. The remaining patients in this global study came primarily from Japan, Russia and India.

Demographic characteristics were balanced across treatment groups. Mean age was 6.4 years (range: 2.5–11 years). Around half of patients were <6 years, old and three quarters were boys. 57% of patients were white, a further 37% were Asian.

By contrast, there were some differences in baseline characteristics, which could suggest a somewhat lower severity of GH deficiency in the somapacitan group. At 4.93µg/l, the mean GH peak at the screening visit was somewhat higher in the somapacitan group than in the comparator group (4.1µg/l). Similarly, the SDS for body size (HSDS) was slightly higher in the somapacitan group (102.3) than in the comparator group (100.2). However, these differences are not expected to create any relevant bias.

Non-inferiority was clearly achieved for the primary endpoint. The treatment difference between somapacitan and the active comparator was -0.5cm/year after 52 weeks, with a 95% confidence interval of -1.1 to +0.2cm. However, superiority over the comparator could not be demonstrated. By the time of the first visit after 13 weeks, HV had approximately tripled in both treatment groups, after which it largely remained at this level until week 52.

Findings for the secondary endpoints were consistent with this and also showed a slight, clinically non-relevant numerical advantage in favour of the comparator.

Bone age increased by around 1.2 years by week 52 (i.e. somewhat more than chronological age). There were no relevant differences between the two groups.

IGF-I increased mainly during the first 4 weeks of treatment, but continued to rise after that, without a plateau being clearly reached by week 52. Mean values remained within the target range of -2 SDS to +2 SDS up to week 52; in week 52; the mean was just above 0 in both treatment groups. However, as it is already known for long-acting GH preparations, fluctuations in IGF-I level were significantly greater with somapacitan than with the comparator.

As expected, the health questionnaires showed a somewhat lower treatment burden with the once-weekly injections compared with daily administration. The pen was generally felt to be straightforward to use.

Data from the open-label extension of this study were not available at the time of authorisation. However, long-term data up to a treatment duration of 208 weeks (i.e. 4 years) were available from the extension to the dose-finding study. Overall, the limited data suggest that efficacy of somapacitan is maintained even during longer-term treatment.

No placebo-controlled studies are available (for ethical reasons).

6.4 Safety

While for efficacy, data from the pivotal study are limited to the double-blind study period, for safety, data from the open-label extension are also available.

For the evaluation of safety, in addition to the safety data from the individual studies, a data pool was created consisting of the data from all patients who had been exposed at least once to the requested somapacitan dose of 0.16 mg/kg in the pivotal study (up to week 52) or in the dose-finding study (up to week 208). This data pool comprised n=194 patients treated with somapacitan (132 of whom in the pivotal study) who were compared with 82 patients who had received the comparator. It should be noted that part of patients were exposed to both somapacitan and the active comparator in the course of the study.

Thus, the available sample size is limited and, in a relevant proportion of cases, safety data are available for a limited period (i.e. 12 months) only. Given the well-known safety profile of recombinant GH, however, data may still be regarded as sufficient.

The observed safety profile essentially corresponded to the one already known for GH treatment. There were no relevant differences between somapacitan and the active comparator in terms of the incidence of AEs and local tolerability, and no new, unexpected safety signals were observed. Conversely, several of the known rare risks associated with GH therapy have not been observed with somapacitan to date. However, this can be attributed to the small number of patients who have been exposed to somapacitan so far and is to be expected on statistical grounds.

In the pivotal study, the overall incidence of AEs was 73% for somapacitan, versus 67% for the comparator. The corresponding figures for serious adverse events (SAEs) were 5.2% vs. 4.9%. Temporary discontinuation of treatment owing to AEs was more common with the comparator (8.5%) than with somapacitan (3.1%). A similar situation applies to dosage reduction in response to AEs, with 2.4% versus 0.5% (the latter corresponding to n=1). There were no permanent treatment discontinuations of somapacitan because of AEs in either the dose-finding or the pivotal study.

The most common AEs were fever (12.1%), headache (9.8%), pain in the extremities (6.4%) and vomiting (6.0%). The only relevant difference between somapacitan and the comparator was for pain in the extremities (7.2% versus 3.7%). Overall, however, AEs in the musculoskeletal system (a known side effect of GH preparations) were slightly less common with somapacitan than with the comparator (3.6% versus 4.9%).

The most common SAEs were infections (primarily Covid-19). With the exception of vomiting (2 cases in the somapacitan group), all SAEs were each only observed in a maximum of one case per treatment group. Only 2 of the total of 14 SAEs were classified as treatment-related, namely one case each of vomiting and generalised oedema.

The incidence of reactions at the injection site documented as AEs was <6%, without any difference between treatment groups. All these reactions were classified as mild, and none of them resulted in premature withdrawal from the study. Overall, local tolerability of the requested preparation was acceptable and no relevant disadvantages compared with the comparator were evident.

Similarly, somapacitan and the comparator did not differ in any relevant way in terms of incidence of anti-drug antibodies. Although the incidence appeared to increase slightly as duration of treatment increased, it was still low overall, at 15.2% for somapacitan in week 52. Furthermore, the presence of antibodies was transient in most cases. No neutralising antibodies were observed during the development programme. No influence of antibodies on pharmacokinetics, pharmacodynamics, efficacy or safety was evident.

No deaths were observed during the paediatric development programme.

However, a difference between the two treatment groups was noted for IGF-I. This applied, for example, to the percentage of patients who exceeded a value of 2 SDS in at least two consecutive visits. This was 3.8% for somapacitan but only 2.9% for the comparator. However, IGF-I was not always measured at the same time. At some visits, it was measured predose, at others 1 to 4 days after administration of study drug (i.e. the expected time of tmax). Given this difference in procedure, it can be assumed that more patients actually exceed the threshold of +2 SDS with somapacitan than is apparent from these results. The greater variability in IGF-I compared with a conventional GH treatment (which, however, applies to all long-acting GH preparations) must therefore be regarded as a potential risk.

There was no case in which elevated IGF-I levels were associated with the occurrence of particular AEs. However, it is not yet possible to provide a definitive statement on the potential long-term risks of repeated or persistent IGF-I values.

Subgroup analyses of safety data were conducted by age and sex. In children < 6 years, AEs classified as treatment-related were clearly more frequent with somapacitan than with the comparator (31% versus 9%), whereas the situation was vice versa in children aged ≥ 6 years (18% versus 29%). Given the small sample size, the significance of these findings cannot be interpreted. The incidence of AEs was significantly higher in girls than in boys; however, the smaller number of female patients has to be taken into account.

Overall, safety data have to be considered limited and only permit a restricted assessment of long-term safety. For short-term safety, on the other hand, owing to the similarity between somapacitan and conventional GH, the data can be deemed sufficient, despite the small sample size.

6.5 Final clinical benefit risk assessment

Somapacitan is a recombinant GH preparation, the half-life – and thus duration of action – of which have been extended by modifying the molecule. For this reason, and unlike conventional preparations, Sogroya only has to be administered once weekly.

Overall, the clinical pharmacology package covered all the relevant aspects. Based on PK/PD modelling, average IGF-I levels across the week were similar following the administration of somapacitan and daily Norditropin®.

Benefits

Efficacy of somapacitan in increasing height velocity in children with a growth disorder associated to GH deficiency was demonstrated in a pivotal study. In this study, somapacitan fulfilled non-inferiority criteria compared with the active comparator, a conventional GH preparation for daily administration.

Uncertainties regarding benefit

A standard starting dose of 0.16mg/kg, as requested in the application and investigated in the pivotal study, seemed too high, not least because it caused IGF-I concentrations higher than with the active comparator. For this reason, a starting dose of 0.12mg/kg was defined for treatment-naive patients, after which the dose may be modified within the range of 0.08 to 0.16mg/kg depending on individual patient response (i.e. height velocity and IGF-I). However, the dose of 0.12mg/kg is based on models only and has not been investigated in clinical studies.

In patients who have previously received GH treatment, the starting dose of somapacitan should be based on the dose required in the past. For adjusting dose in response to IGF-I or adverse reactions, a specific algorithm is recommended (see Information for healthcare professionals).

No data are available for doses > 0.16mg/kg. Accordingly, increasing dosage beyond this dose in the event of poor response cannot be recommended.

The data available on final height, the parameter most relevant for patients, are still limited. HV investigated as the primary endpoint has to be viewed as a surrogate parameter. However, the comparison with historical data undertaken by the applicant appears plausible and acceptable in this case, not least because the study would have to last up to 20 years (an impractical duration) to investigate final height.

Since only an active-controlled study was submitted, assay sensitivity cannot be formally considered proven. However, efficacy results for the active comparator were comparable to those described for conventional GH in the literature.

As yet, sufficient data are available for prepubertal children only. However, from the many years of experience with conventional GH preparations, there is no evidence to suggest that a modified response should be expected after puberty, and this experience appears to be transferable to the long-acting preparation.

As Sogroya is only authorised in Switzerland until final height is reached, it is unclear how further treatment should be conducted if a GH deficiency requiring therapy persists in adulthood.

Risks

The safety profile of the proposed product essentially corresponds to what can be expected from GH treatment. Overall, safety and tolerability can be considered good. There were no relevant differences between somapacitan and the active comparator in terms of either antibody incidence or local tolerability. Overall, immunogenicity of the product seems uncritical.

The main risk associated with somapacitan (and with long-acting GH preparations in general) compared with conventional GH therapy is that IGF-I levels tend to be higher and, in particular, exceed the upper limit of normal of 2 SDS more frequently (see "Uncertainties regarding risks").

Uncertainties regarding risks

IGF-I variability is higher with long-acting GH preparations such as somapacitan than with conventional GH therapy, and it is not yet sufficiently known whether repeated exceeding of the upper limit of normal is associated with any risks and, if so, what these risks might be. In adults, an association between high IGF-I levels and an elevated risk of malignant tumours has been observed (see, for example, Mukama et al. 2023 and Qian & Huo 2020). The extent to which this may also apply to a paediatric population is unknown.

Due to the timing of the IGF-I measurements in the clinical studies, it is not possible to state with any accuracy how often values greater than 2 SDS are likely to occur in everyday clinical practice.

For long-acting GH-preparations, it is unclear at which time point within the dosing interval blood samples for determination of IGF-I should be taken in order to best reflect the concentration-time profile. Determination on day 4 seems to best reflect the mean concentration in the dosing interval and is thus recommended (see Information for healthcare professionals).

In patients with hepatic impairment, somapacitan exposure is increased, while the liver's ability to secrete more IGF-I following GH stimulation is reduced. Since the net effects cannot be predicted, Sogroya is not recommended for patients with moderate or severe hepatic impairment.

Finally, on the basis of the currently available data, long-term safety of the preparation cannot be deemed sufficiently demonstrated. However, ongoing studies are still generating additional data.

Overall, findings described in the literature suggest that a large proportion of the critical points listed here are a problem shared by all long-acting GH preparations (i.e. a consequence of modifying the molecule) and not specific to somapacitan.

Final risk-benefit profile

Overall, the benefit-risk balance for growth disorders associated with confirmed GH deficiency is considered positive for children from 3 years of age until epiphyseal closure.

Precautions described in the Information for healthcare professionals for conventional GH preparations also apply to Sogroya.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Sogroya was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Sogroya®

Composition

Active substances

Somapacitanum*

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

Excipients

Histidinum
Mannitolum (E 421)
Poloxamerum 188
Phenolum
Aqua ad iniectabile
Acidum hydrochloridum (for pH adjustment)
Natrii hydroxidum (for pH adjustment)

The maximum amount of sodium is 0.05 mg per mL of solution for injection.

Pharmaceutical form and active substance quantity per unit

Solution for injection in ready to use pen for subcutaneous injection.

Sogroya® 5 mg/1.5 ml
1 ready to use pen contains 5 mg somapacitan in 1.5 ml solution for injection, 3.3 mg/ml, respectively. For dose delivery in increments of 0.025 mg (0.0075 ml). Highest adjustable single dose: 2 mg.
Sogroya® 10 mg/1.5 ml
1 ready to use pen contains 10 mg somapacitan in 1.5 ml solution for injection, 6.7 mg/ml, respectively. For dose delivery in increments of 0.05 mg (0.0075 ml). Highest adjustable single dose: 4 mg.

Sogroya® 15 mg/1.5 ml

1 ready to use pen contains 15 mg somapacitan in 1.5 ml solution for injection, 10 mg/ml, respectively. For dose delivery in increments of 0.1 mg (0.01 ml). Highest adjustable single dose: 8 mg.

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

Indications/Uses

Replacement of endogenous growth hormone (GH) in paediatric patients from 3 years of age with growth failure due to proven growth hormone deficiency (GHD).

Dosage/Administration

Somapacitan treatment should be initiated and monitored by physicians who are appropriately qualified and experienced in the diagnosis and management of patients with GHD (e.g. endocrinologists).

Documentation of the batch number

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Method of Administration

Sogroya® is to be administered once weekly at any time of the day. Sogroya® is to be injected subcutaneously in the abdomen, thighs, buttocks or upper arms. The injection site should be rotated every week. For further information, see “Instructions for Handling”.
The injection should be administered on a scheduled dosing day each week. On occasions when administration at the scheduled dosing day is not possible, the dose can be taken up to 2 days before or 3 days after the scheduled weekly dosing day as long as the time between two doses is at least 4 days or 96 hours (see also "Missed Dose" below). Thereafter, the usual dosing scheme for the next dose should be resumed at the regularly scheduled dosing day.

For available pens and their dose increments, see "Pharmaceutical form and active substance quantity per unit".

Usual dosage

The recommended dose is 0.08-0.16 mg/kg/week.

In treatment-naive patients, the treatment should be initiated with a dose of 0.12 mg/kg/week and adjusted as described in the "Dose Adjustment" section, if necessary.
In patients previously treated with growth hormone (GH), the patient's previously required dose should be considered when deciding the somapacitan starting dose.
Doses of >0.16 mg/kg/week were not studied.

Dose adjustment

Therapy monitoring can be done based on growth velocity and concentrations of insulin-like growth factor 1 (IGF-1). For this purpose samples should be collected 4 days after application of the last dose. The target value for IGF-1 SDS (Standard Deviation Score) should be in the upper normal range and not exceed 2 SDS.

In case of insufficient efficacy (insufficient increase in IGF-1 concentrations, insufficient increase in growth velocity), the dose may be increased in 0.02 mg/kg/week increments at intervals of 4-6 weeks. However, a maximum dose of 0.16 mg/kg/week must not be exceeded.
In the event of elevated IGF-1 concentrations, as well as occurrence of severe adverse effects, the dosage of Sogroya can be adjusted as follows:
If the IGF-1 SDS is >2, it should initially be reassessed 4-6 weeks later. If the value remains >2, the dose should be reduced by 0.02 mg/kg/week. The next check of IGF-1 should be done 4-6 weeks after the dose reduction. If the value is still >2, the dose should be further reduced in increments by 0.02 mg/kg/week. If the IGF-1 SDS remains >2 at a dose of 0.08 mg/kg/week, the risk-benefit ratio of continuing therapy must be weighed individually.

During long-term treatment with Sogroya, efficacy and safety should be monitored at intervals of 6-12 months. To do so, in particular growth velocity, IGF-1 and glucose levels should be determined.

Therapy duration
Treatment with Sogroya should be discontinued when final height is (nearly) achieved, i.e., when growth velocity is <2 cm/year, and when bone age reaches >14 years in girls or >16 years in boys (which corresponds to epiphyseal plate closure).

Missed dose

Patients who miss a dose are advised to inject Sogroya upon discovery as soon as possible within 3 days after the missed dose, and then resume their usual once-weekly dosing schedule, i.e. the regularly scheduled injection day can be maintained. If more than 3 days have passed or more than one dose has been missed, the missed dose/doses should be skipped, and the next dose should be

administered on the regularly scheduled day. Thereafter, the original dosing scheme can be continued.

Change of the dosing day

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

Switching from other growth hormone drugs

Switching a patient from another type or brand of growth hormone should be done by physician who has experience in the management of growth hormone deficiency. When switching from daily human growth hormone to once-weekly Sogroya, first of all, the preferred day for the weekly dose should be determined. The final dose of daily treatment is then to be administered the day before (or at least 8 hours before) taking the first dose of Sogroya.
Patients switching from a weekly human growth hormone to Sogroya are recommended to maintain their once weekly dosing schedule (i.e. their scheduled injection day).

Special dosage instructions

Children below 3 years

Limited data are available on the safety and efficacy of somapacitan in children <3 years of age; somapacitan has not been studied in patients <2.5 years of age. Therefore, the use of Sogroya is not recommended in this age group.

Elderly patients

Sogroya is only approved for use in paediatric patients.

Patients with hepatic disorders

Somapacitan has not been studied in paediatric patients with hepatic impairment. For the findings in adults, see "Pharmacokinetics", section "Kinetics in specific patient groups".
No dose adjustment is required in mild hepatic insufficiency (Child Pugh A). However, the use should be monitored with special caution and regular measuring of IGF-1.
In patients with moderate or severe hepatic insufficiency (Child Pugh B and C), use of Sogroya is not recommended.

Patients with renal disorders

Somapacitan has not been studied in paediatric patients with renal impairment. For the findings in adults, see "Pharmacokinetics", section "Kinetics in specific patient groups".
No adjustment of the initial dose is required for patients with renal impairment, the use of Sogroya, however, should be monitored with special caution (and, if necessary, monitoring of IGF-1).

Contraindications

- Any evidence of activity of a tumour. (see “warnings and precautions”)
- Critically ill patients with acute respiratory failure or with complications after major abdominal or cardiac surgery or after polytrauma
- Bloom syndrome
- Fanconi anaemia
- Hypersensitivity to the active substance or to any of the excipients

Warnings and precautions

After closure of epiphyses, somapacitan is no longer effective for longitudinal growth promotion and should not be used further.

Intracranial tumours must be inactive and antitumour therapy must be completed prior to starting somapacitan therapy. Treatment should be discontinued if there is evidence of tumour growth.

By administering somapacitan, higher IGF-1 concentrations were observed at the beginning of each dosing interval as compared to conventional GH-therapy with daily applied GH-preparations. In particular, the exceeding of the upper normal limit of 2 SDS occurred more frequently than with conventional therapy. It is not known whether this is associated with increased long-term risks (such as tumours or type II diabetes mellitus).

The risks described below have been observed with the use of recombinant growth hormone. They are expected to apply similarly to somapacitan. For somapacitan itself, only limited experience is available to date.

Neoplasms
Patients on treatment with somapacitan should generally be carefully monitored for possible development of tumours.
Patients with a history of tumour disease (including intracranial tumours) were excluded from the clinical trials. Sogroya should therefore not be used in these patients as a precautionary measure. If

treatment is nevertheless to be given, the patient must be monitored closely for possible tumour recurrence while on therapy with somapacitan.
The occurrence of leukaemia has been reported in a small number of children treated with GH. However, there is no evidence that GH therapy increases the incidence of leukaemia in patients without predisposing factors.

An overall slight increase in second neoplasms has been observed in childhood cancer survivors treated with growth hormone, with the most frequent being intracranial tumours, especially meningiomas. These tumours were observed mainly in patients who had received radiotherapy of the head for the treatment of their first neoplasia.

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

Glucose metabolism impairment
Treatment with growth hormone may decrease insulin sensitivity, particularly at higher doses in susceptible patients, and consequently hyperglycaemia may occur in subjects with inadequate insulin secretory capacity. As a result, previously undiagnosed impaired glucose tolerance or overt diabetes mellitus may be unmasked during growth hormone treatment. Therefore, glucose levels should be monitored periodically in all patients treated with growth hormone, especially in those with risk factors for diabetes mellitus, such as obesity, or a family history of diabetes mellitus or co-medication with corticosteroids.
In patients with pre-existing diabetes mellitus or impaired glucose tolerance somapacitan should only be administered with caution and with close monitoring of the glucose metabolism. The doses of antihyperglycaemic drugs may require adjustment when growth hormone therapy is instituted in these patients (also see “Interactions”).

Thyroid function
Growth hormone increases the extrathyroidal conversion of T4 to T3 and may as such unmask incipient hypothyroidism. Especially in patients with progressive pituitary disease, hypothyroidism may develop. As hypothyroidism interferes with the response to growth hormone therapy, thyroid function

should be tested regularly, and a replacement therapy with thyroid hormone should be initiated when indicated.

Pancreatitis
There have been reports of the occurrence of pancreatitis during GH treatment, particularly in children. If acute upper abdominal discomfort occurs in a patient receiving treatment with Sogroya, the possibility of pancreatitis should be considered.

Adrenocortical insufficiency
Growth hormone therapy may reduce the activity of 11β-hydroxysteroid dehydrogenase type 1, an enzyme involved in cortisol synthesis. This can unmask latent secondary adrenocortical insufficiency, which may necessitate glucocorticoid substitution therapy. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of growth hormone treatment (see “Interactions”). Hence, patients with known hypoadrenalism should be monitored for reduced cortisol serum levels and in particular be checked for need for glucocorticoid dose increases.

Skeletal changes
Epiphyseolysis capitis femoris may be common in patients with endocrine disorders (such as GH deficiency). Legg-Calvé-Perthes disease may also be common in patients of short stature. This may manifest as limping or hip or knee pain. Parents should be informed to watch out for such symptoms and, if necessary, to report them immediately to the treating physician.

Scoliosis can manifest or worsen in any child during periods of rapid growth. Because somapacitan increases the rate of growth, attention should be paid to possible signs of scoliosis during treatment. However, there is no evidence to date that treatment with growth hormone increases the incidence or severity of scoliosis.

Injection site reactions
In the clinical studies injection site reactions were observed in around 5% of patients. All cases were of mild severity, and the majority of cases recovered after short durations. The injection site reactions were haematoma (3%), pain (1.5%), or swelling (0.8%).

Immunogenicity
Growth hormone therapy can lead to the development of antibodies against the administered drug. In the pivotal study, the incidence of antibodies did not differ in a relevant way between somapacitan and the conventional GH drug used as comparator. The binding capacity of the found antibodies was

low, and no effect on efficacy or safety was evident. Neutralizing antibodies were not detected. Nevertheless, antibodies to somapacitan should be determined in any patient who does not respond to therapy, in addition to investigating other possible causes.

Hypersensitivity reactions
Serious systemic hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported with the use of other GH therapies. If such a reaction occurs, the use of Sogroya must be discontinued immediately, appropriate treatment initiated, and the patient monitored until symptoms resolve.

Lipohypertrophy
When Sogroya is administered at the same site over a long period of time, lipohypertrophy may occur. The injection site should be rotated to reduce the risk (see “Dosage/Administration”).

Interaction with exogenous estrogens
Exogenous estrogens (e.g., in combined hormonal contraceptives), especially when administered orally, may reduce serum IGF-1 concentrations and thereby attenuate the efficacy of growth hormone treatment. Therefore, if necessary, non-hormonal methods should be used for contraception and patients should be advised accordingly.

Acute critical illness
The use of GH in pharmacological doses has been associated with increased mortality in patients with acute critical illness following open heart or abdominal surgery, or multiple trauma, or with acute respiratory failure (see «Contraindications»). No corresponding data are available for substitution therapy in patients with GHD. In patients treated with Sogroya developing an acute critical illness, the expected benefit of further treatment should be carefully weighed against the potential risk.

Other precautions
In the presence of impaired liver function, somapacitan exposure is increased (see "Pharmacokinetics", section "Kinetics in specific patient groups"). On the other hand, in hepatic impairment, the ability of the liver to increase secretion of IGF-1 after stimulation by GH is reduced, so that the response to therapy may be diminished. Therefore, the use of Sogroya is not recommended in patients with moderate or severe hepatic insufficiency (Child Pugh B and C).

In a placebo-controlled study in adults, a shift from normal to elevated serum phosphate concentrations was observed more frequently with somapacitan than with placebo. In a paediatric study (with a limited number of cases), such a shift was also more frequent with somapacitan than in the comparison group receiving a daily administered somatropin preparation.

In adult patients with GH deficiency, it is known that women have a higher GH requirement than men. There is currently insufficient data on possible gender-specific differences in female patients with paediatric GH deficiency after reaching puberty. However, it cannot be ruled out that girls may expect a lower therapeutic success than boys at the same dose after puberty. Therefore, it is recommended to monitor the response to GH therapy particularly carefully in girls after puberty.

In paediatric population somapacitan has been studied exclusively in GHD (so-called pituitary short stature). No data is available on other forms of growth disorders such as short stature in Turner syndrome, growth disorders in chronic renal failure, Prader-Willi syndrome or growth disorders in patients with Small-for-Gestational-Age (SGA). Sogroya should therefore not be used in these patient groups.

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

Interactions

No interaction studies have been conducted with somapacitan. The following information is based on the corresponding experience with daily applied recombinant GH. It is expected that these also apply to somapacitan.

Pharmacokinetic interactions

Effect of growth hormone on the pharmacokinetics of other agents

Cytochrome P450 metabolized drugs

Growth hormone administration may increase the clearance of compounds known to be metabolised by cytochrome P450 isoenzymes resulting in lower plasma levels of these compounds. This applies, for example, to corticosteroids, sex steroids, anticonvulsants and cyclosporine. The clinical significance of this is unknown.

Pharmacodynamic interactions

Effect of other medicinal products on the efficacy of growth hormone

The efficacy of growth hormone can be influenced by concomitant therapy with other hormones, e.g. testosterone or thyroid hormones.

Effect of growth hormone on the efficacy of other medicinal products

Glucocorticoids

Growth hormone decreases the conversion of cortisone to cortisol and may unmask previously latent secondary hypoadrenalism or render low glucocorticoid replacement doses ineffective (see “Warnings and precautions”).

Antihyperglycaemic products

Antihyperglycaemic treatment may require dose adjustment in diabetic patients in case of somapacitan co-administration since somapacitan may decrease insulin sensitivity.

Pregnancy, lactation

Pregnancy

There are no data from the use of somapacitan in pregnant women. Studies in animal have shown reproductive toxicity (see “Preclinical data”). Administration of Sogroya is therefore not recommended during pregnancy.
In patients of childbearing age, Sogroya should not be used without reliable contraception, and non-hormonal methods should be chosen, see “Warnings and precautions”. If treatment with Sogroya is continued in girls after the onset of menstruation, advice on non-hormonal contraceptive methods must be provided.

Lactation

It is unknown whether somapacitan and/or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of somapacitan in milk.
A risk to the breastfed infants can therefore not be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Sogroya therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There is no clinical experience with the potential effect of somapacitan on fertility. No adverse effects on fertility were observed in animal studies (see section “Preclinical data”).

Effects on ability to drive and use machines

Corresponding studies have not been conducted. An influence of somapacitan on the ability to drive and use machines, however, is not expected.

Undesirable effects

Regarding the serious risks of a therapy with growth hormone it is also referred to section "Warnings and precautions".

The adverse reactions listed below are based on the safety data from one 52-weeks phase 3 trial, in which n=132 paediatric patients with growth hormone deficiency (GHD) were treated with somapacitan.

The most frequently observed Adverse Drug Reactions (ADRs) in the clinical trials with somapacitan are Headache (12%), Hypothyroidism (5%), Injection site reactions (5%) and Peripheral oedema (3%).
In general, the ADRs were transient.

The adverse drug reactions are listed below by MedDRA system organ class and frequency category defined as: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Immune system disorders

Common: Hypersensitivity reactions (such as skin rash, itching, urticaria)

Endocrine disorders

Common: Hypothyroidism, adrenocortical insufficiency

Metabolism and nutrition disorders

Common: Hyperglycaemia

Nervous system disorders

Very common: Headache (12%)

Musculoskeletal and connective tissue disorders

Common: Arthralgia, myalgia

General disorders and administration site conditions

Common: Peripheral edema, injection site reactions (e.g., hematoma, pain, swelling; see also "Warnings and precautions"), fatigue

Uncommon: Lipodystrophy

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is only limited clinical experience with overdose of somapacitan. A short term overdose can lead to low blood glucose levels initially, followed by high blood glucose levels. These decreased glucose levels have only been detected biochemically and were clinically asymptomatic. Long-term overdosage could result in the typical symptoms consistent with human growth hormone excess.

Properties/Effects

ATC code

H01AC07

Mechanism of action

Somapacitan is a long-acting recombinant human growth hormone derivative. It consists of the amino acid sequence of the endogenous human growth hormone with a single substitution (L101C), to which an albumin binding moiety has been attached. The reversible binding to endogenous albumin delays elimination of somapacitan and thereby prolongs the in vivo half-life and duration of action.
The albumin binding moiety (side-chain) consists of a fatty acid moiety and a hydrophilic spacer attached to position 101 of the protein. The mechanism of action of somapacitan is either directly via the GH-receptor and/or indirectly via IGF-1 produced in tissues throughout the body, but predominantly by the liver.
Somapacitan distributes to the epiphyses. It stimulates skeletal growth as a result of its effects on the growth plates (epiphyses) of bones.

Pharmacodynamics

Somapacitan stimulates skeletal growth in paediatric patients with GHD and increases growth velocity.

A dose-dependent IGF-1 response is induced following somapacitan administration. IGF-1 is a generally accepted biomarker for efficacy in GHD. Steady state of IGF-1 concentrations was reached after 1-2 doses.

In paediatric GHD patients somapacitan produced a dose linear IGF-1 response, with a change of 0.02 mg/kg on average resulting in a change in IGF-1 standard deviation score (SDS) of 0.32.

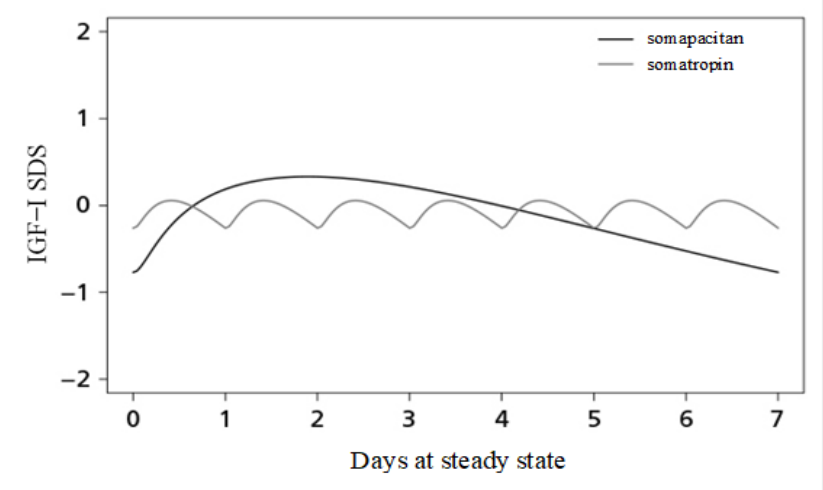

Figure 1: Model- derived IGF-1 profiles during steady-state of somapacitan and somatropin (based on data from AGHD = Adult Growth Hormone Deficiency)

QTc-duration

No tQT study was performed. The potential effect of somapacitan in adults on cardiac repolarisation was assessed based on ECGs collected at around the time of C_{max} for somapacitan at therapeutic doses in a phase 3 trial. There was no association between the change from baseline in QTcF and the somapacitan concentration.

Clinical efficacy

The efficacy and safety of once weekly somapacitan was evaluated in a 52 weeks multi-center, open-label, randomized, active-controlled, parallel-group phase 3 trial (REAL 4) in n=200 treatment-naïve, pre-pubertal paediatric patients with GHD. Patients received 0.16 mg/kg/week once weekly somapacitan (N=132) or 0.034 mg/kg/day daily somatropin (N=68).
Children with proven GHD (i.e., pituitary short stature) aged 2.5 years to <10 years (girls) or <11 years (boys) were included. Patients with other causes of growth failure were excluded from study participation. Inclusion criteria were a height velocity below the 25th percentile and an IGF-1 SDS <-1. Primary efficacy endpoint was height velocity after 12 months of treatment. Essential secondary endpoint was e.g. change from baseline in body height SDS.

At baseline, the mean age was 6.4 years (range: 2.5 to 11). 25.5% patients were female and 74.5% were male. 57% of patients were Caucasian, 37% were Asian. The mean body height was -2.99 SDS in the somapacitan group and -3.47 SDS in the comparator group. The proportion of patients with an IGF-1 SDS <-2 (i.e., a more severe degree of GH deficiency) was 42% in the somapacitan group and 57% in the comparator group.

Treatment with once weekly somapacitan for 52 weeks resulted in an annualized height velocity of 11.2 cm/year. Patients treated with daily somatropin achieved an annualized height velocity of 11.7 cm/year after 52 weeks of treatment. The treatment difference (-0.5; 95-CI: -1.1; 0.2) thereby met the predefined criterion of noninferiority of somapacitan to daily somatropin.

The findings for the main secondary endpoints were consistent with this and also showed comparable efficacy of somapacitan and the daily somatropin.

In addition, limited long-term data is available from the extension of a Phase II study in initially n=59 also prepubertal, treatment-naïve patients with GH deficiency over a treatment period of up to 4 years. This limited data suggests that the efficacy of somapacitan is maintained with longer-term use.

Even in patients who were switched from the daily somatropin to somapacitan after 3 years, pre-treatment efficacy was maintained. After 4 years of therapy, the mean body height SDS was -1.06.

Pharmacokinetics

Absorption

In paediatric patients with GHD median t_{max} ranged from 8 to 25.5 hours at doses from 0.02 mg/kg/week to 0.16 mg/kg/week. Steady state exposure was achieved following 1-2 weekly administration. Absolute bioavailability of somapacitan in human has not been investigated.

Distribution

Somapacitan is extensively bound (>99%) to plasma proteins and is expected to be distributed like albumin. Based on population PK analyses, the estimated volume of distribution (V/F) was 1.7 L in paediatric GHD patients.

Metabolism

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

Elimination

Following a single dose of 0.16 mg/kg/week the terminal half-life was 34 h in paediatric GHD patients. Little to no accumulation (mean accumulation ratio: 1-2) of somapacitan following multiple dosing has been observed.

Data on elimination of somapacitan is available only from adult patients with GHD. Here, somapacitan in the form of its metabolites was excreted predominantly in the urine (81%) and only to a smaller extent (13%) via the faeces. Unchanged somapacitan was not detected in urine or faeces.

Linearity/non-linearity

The pharmacokinetics of somapacitan following subcutaneous administration have been investigated at dose levels from 0.02 to 0.16 mg/kg/week in paediatric population. Somapacitan displayed non-linear pharmacokinetics.

Kinetics in specific patient groups

Based on population pharmacokinetic analysis gender, race and body weight do not have a clinically meaningful effect on the pharmacokinetics of somapacitan in paediatric GHD patients following weight-based dosing. Somapacitan has been dosed in paediatric patients with body weight up to 62 kg.

Patients with hepatic impairment

There is no data available on the pharmacokinetics of somapacitan in paediatric patients with impaired liver function.

In adults with GHD, a somapacitan dose of 0.08 mg/kg at steady state resulted in higher exposure in subjects with moderate hepatic impairment with ratios to normal hepatic function of 4.69 for $AUC_{0\text{-}168h}$ and 3.52 for C_{max}. Mild hepatic impairment had no effect on somapacitan exposure.

Patients with renal impairment

There is no data available on the pharmacokinetics of somapacitan in paediatric patients with impaired renal function.

In adults, a somapacitan dose of 0.08 mg/kg at steady state resulted in higher exposures in subjects with renal impairment, most pronounced in subjects with severe renal impairment and in subjects requiring haemodialysis, where $AUC_{0\text{-}168h}$ ratios to normal renal function were 1.75 and 1.63, respectively. In general, somapacitan exposure tended to increase with decreasing GFR.

Preclinical data

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

Carcinogenicity

No carcinogenicity studies have been performed with somapacitan.

Reproductive toxicity

No adverse effects were observed on male and female fertility in rats at a dose resulting in exposure at least 5 times greater than the expected maximum clinical exposure at 0.16 mg/kg/week in paediatric patients. However, irregular female oestrus cycle was seen at all doses treated.

No evidence of foetal harm was identified when pregnant rats and rabbits were administered subcutaneous somapacitan during organogenesis at doses leading to exposures 4- to 6-fold above expected exposure at the maximum clinical dose of 0.16 mg/kg/week in paediatric patients. At high doses leading to exposure at least 50-fold above the expected clinical exposure at 0.16 mg/kg/week, short/bent/thickened long bones were found in pups from female rats receiving somapacitan. Such findings in rats are known to resolve after birth and should be regarded as minor malformations, not permanent abnormalities.

In the study with pregnant rabbits subcutaneous administration of Somapacitan at all doses resulted in reduced fetal growth. At the low dose (exposure about 4-fold higher than the expected clinical exposure at 0.16 mg/kg/week), the effects were mild and not classified as adverse.

Toxicity tests with juvenile animals

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

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

After the first use

Shelf life for pen in use: 6 weeks

Store in refrigerator (2°C - 8°C). See also "Special precautions for storage".

Special precautions for storage

Keep out of the reach of children.

Before and during use

Store in a refrigerator at 2°C to 8°C with the cap on and in the original carton to protect the content from light. Do not freeze or store directly adjacent to the refrigerator cooling element. Do not use Sogroya if it has been frozen. Discard pre-filled pen if kept above 30°C. Avoid direct or excessive heat. Avoid sunlight.

If refrigeration is not possible (e.g. during travelling), Sogroya may be kept temporarily at temperatures up to 30°C for up to a total of 72 hours (3 days). Return Sogroya to the refrigerator again after storage at this temperature. If stored out of refrigeration multiple times and then returned to refrigeration, the total combined time out of refrigeration must not exceed 3 days. This must be monitored carefully. The Sogroya pen should be discarded, if it has been kept up to 30°C for more than 72 hours (3 days) or for any period of time kept above 30°C.

Instructions for handling

For detailed information, see the instructions for use in the patient information leaflet (package insert).

Write the date of first use in the space provided on the carton.

Please advise the patient, or his/her caregiver, to read the instructions in the package insert very carefully before using Sogroya.

The pen is for use by one person only.

Sogroya should only be used if the solution does appear clear to slightly opalescent, colourless or slightly yellow and free from visible particles

Sogroya can be administered with a needle up to a length of 8 mm. The pen is designed to be used with NovoFine® or NovoTwist® disposable needles. The needles are not included in the carton.

Always remove and safely discard the needle after each injection and store the Sogroya pre-filled pen without an injection needle attached. Always use a new needle for each injection to prevent contamination.

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

Needles and other waste material should be disposed of in accordance with local requirements.

Authorisation number

69063 (Swissmedic)

Packs

Sogroya® 5mg/1.5ml somapacitan pre-filled pen (coloured teal): packs of 1 piece. (A)
Sogroya® 10mg/1.5ml somapacitan pre-filled pen (coloured yellow): packs of 1 piece. (A)
Sogroya® 15mg/1.5ml somapacitan pre-filled pen (coloured red): packs of 1 piece. (A)
The needles are not included in the carton.

Marketing authorisation holder

Novo Nordisk Pharma AG, Kloten
Domizil: Zürich

Date of revision of the text

December 2023