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National Program of Severe Growth Hormone Deficiency Treatment in Adults and Adolescents after Completion of Growth Promoting Therapy

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Abstract
Growth hormone (GH) has been used in the treatment of short stature in children with GH deficiency (GHD) for 60 years, and for about 30 years also in the treatment of adults with GHD, in whom such treatment is carried out due to metabolic indications.
In Poland, GH treatment is reimbursed only in children with GHD, while so far it has not been refunded in adults with GHD.
There are two groups of adults (or adolescents after growth completion) with GHD, who require GH therapy: patients with GHD that occurred in childhood (childhood-onset GHD — CO-GHD) and patients with GHD acquired in adulthood (adulthood-onset GHD — AO-GHD).
This review presents a brief outline of the history of GH treatment in humans, the latest data on the causes and symptoms of GHD in adults, and the complications of untreated GHD. Current recommendations regarding diagnosis, treatment and monitoring of GH therapy in adults are also discussed. Moreover, the review paper presents the objectives, assumptions, and plans of implementation of the "National Treatment Program for Severe Growth Hormone Deficiency in Adults and Adolescents after Completion of the Growth Promoting Therapy", as well as the expected health and economic effects of introduction of GH treatment in adults with GHD in Poland.
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Key words: *treatment program, growth hormone treatment, growth hormone deficiency that occurred in childhood (childhood-onset GHD), growth hormone deficiency acquired in adulthood (adulthood-onset GHD)*

1. Introduction

For 60 years, growth hormone (GH) has been used in the treatment of children with growth disorders primarily those associated with GH deficiency (GHD). For about 30 years, adults with GHD have also been qualified for treatment for metabolic indications. In Poland, currently approved applications of recombinant human GH (rhGH) reimbursable therapies include GHD in children, growth deficiency in chronic renal failure, Turner syndrome, Prader-Willi syndrome, and short stature in children born with intrauterine growth retardation (IUGR) or small for gestational age (SGA); however, no GHD treatment is currently refundable in adults.

The last decades of the twentieth century brought rapid development of knowledge about the role of GH not only in the processes of growth, but also in the regulation of metabolic processes. In addition to the primary stimulatory effect on growth of bone, cartilage, and connective tissue, GH also affects the lipid, carbohydrate, protein, and water-electrolyte balance [1].

At the same time, severe GHD was defined in adults as a separate disease entity, requiring precise diagnosis and

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adequate substitution treatment [2]. The most serious consequences of long-term severe GHD in the adult population are associated with an increased frequency of deaths due to cardiovascular complications and osteoporotic bone fractures, as well as a deterioration of the quality of life. Therefore, severe GHD found in an adult is an indication for substitution treatment with rhGH. In recent years, special attention has been paid to the possibility of development of GHD-associated metabolic disorders in patients treated in childhood with rhGH preparations, who completed growth promoting therapy [3].

The first recommendations regarding the diagnosis and treatment of GHD in adults were developed in 1997 by the GH Research Society [2]. Twenty years later these recommendations were updated and a common position of endocrinology societies from Europe, the United States, Japan and Australia was established [4]. For the last 10 years, a number of papers regarding both complications of untreated GHD in adults and optimisation of therapeutic procedures in this group of patients have been published. In 1999, issues regarding rhGH therapy in adults were the subject of a publication in the Supplement of the Polish Journal of Endocrinology, and in 2000 a team of doctors under the leadership of Prof. Andrzej Lewiński developed the "National Program for Treatment with Growth Hormone in Adults" [5], which, however, was never implemented.

Reimbursement of rhGH preparations is currently available in Poland for growth promoting treatment, carried out as therapeutic programs in children with GHD, Turner syndrome, Prader-Willi syndrome, short stature in the course of chronic renal failure, and in children born small for gestational age (with SGA or IUGR). The use of rhGH preparations in adults after growth completion is currently not reimbursed, except for patients with Prader-Willi syndrome treated previously in childhood, whose therapy after growth completion is carried out for metabolic indications. According to the current state of art, in the case of severe GHD, continuation of therapy with rhGH preparations is important to prevent complications related to metabolic disorders and deterioration of the quality of life occurring in this group of patients. However, there are currently no convincing data to support continuation of treatment with rhGH after completion of growth in other indications than severe GHD and Prader-Willi syndrome.

2. Growth hormone deficiency in adults

2.1. Definition

GH deficiency is an impairment of GH secretion by the pituitary somatotroph cells.

In adults, only severe GHD was defined as a disease entity, and — in contrast to the classification used in children — so-called "partial" GHD is not recognised in adults [4, 6]. The classification of GHD in adults currently distinguishes:

— childhood-onset GHD (CO-GHD);
— adult-onset GHD (AO-GHD).

2.2. Causes of growth hormone deficiency in adults; epidemiological issues

There are no detailed epidemiological studies on the occurrence of GHD in adults in Poland. Population studies conducted in Spain in the 1990s determined the prevalence of various forms of hypopituitarism in adults at 45.5:100,000, and the number of new cases per year (incidence) at 4.2:100,000 [7], which in recent years has been verified by assessing the prevalence in the same population at 37.5:100,000 and the incidence rate at 2.07:100,000 [8]. A study conducted in Denmark in 1980–1999 determined the incidence of AO-GHD at 1.9:100,000 in men and 1.4:100,000 in women [9]. In France in the years 1994–95, the incidence of AO-GHD was assessed at 1.2:100,000 [10]. Assuming a similar frequency of AO-GHD in the Polish population and the number of adults as 31,500,000 (data from the Central Statistical Office for 2016), the incidence of AO-GHD in Poland can be estimated at about 400 cases per year; however, it is difficult to assess what percentage of these patients will meet the eligibility criteria for rhGH therapy.

Due to the different criteria for the diagnosis of GHD in children and severe GHD in adults, some of the patients with CO-GHD treated in childhood with rhGH preparations have no indications for continuing treatment in adulthood. Therefore, re-evaluation of GH secretion after the end of growth promoting therapy is required. Epidemiological data on the prevalence of persistent GHD are divergent in different studies, with high values amounting to over 70% [11] and much lower values, around 30% [12] and even below 20% [13] presented in the literature. These differences are probably the result of the different criteria for the diagnosis of GHD in childhood and adulthood, used by different authors, as well as the diversity of the population covered by the analyses. In the cohort of patients with isolated CO-GHD treated in childhood with rhGH preparations in the Department of Endocrinology and Metabolic Diseases, Polish Mother's Memorial Hospital — Research Institute, the frequency of persistent severe GHD after the end of the growth promoting therapy was assessed as 12.0% [14], while in the group of patients with morphologic lesions in the pituitary area (i.e. with pituitary stalk transection syndrome or after

neurosurgical procedures due to craniopharyngioma), persistent GHD affected all patients [15]. Considering the number of children currently being treated for GH deficiency, it can be estimated that in the whole country approximately 50 patients per year will meet the criteria for diagnosis of severe CO-GHD and thus will meet the eligibility criteria for rhGH therapy in adulthood.

According to KIMS data (Pfizer International Metabolic Database, formerly Pharmacia) published in 2009, the most common causes of GHD in adults included pituitary tumours (44%) and craniopharyngioma (11%), less frequent reasons were radiotherapy of brain tumours (7%), brain injuries and Sheehan's syndrome (about 3% each), and lymphocytic hypophysitis (1%), while about 16% of patients were diagnosed with idiopathic GHD [16]. In the HypoCCS Study (The Hypopituitary Control and Complications Study, Eli Lilly), GHD causes in adults were as follows: pituitary tumours 38.6%, craniopharyngiomas 8.4%, and pituitary haemorrhage 2.8%, while idiopathic GHD were diagnosed in 19.3% of cases [17]. Compared to previous reports [18, 19], the increasing percentages of patients after injuries and head irradiation for reasons other than pituitary and suprasellar tumours, as well as of patients with the diagnosis of idiopathic GHD were observed [17]. GHD is found at diagnosis in about 50% of patients with pituitary adenomas, while the frequency of GHD increases up to 80% after neurosurgery and up to 100% within five years of subsequent radiotherapy [20]. It should be taken into account that pituitary insufficiency, including impaired GH secretion, may also affect patients previously treated for acromegaly [21].

2.3. Clinical symptoms and metabolic disorders in the case of growth hormone deficiency in adults

2.3.1. Symptoms

— Weakness and malaise, feeling of constant fatigue;
— Low mood;
— Reduction of vital energy;
— Deterioration of social contacts with an increased tendency towards isolation;
— Disturbance of emotional reactions;
— A sense of deterioration in the quality of life;
— No sense of health.

2.3.2. Signs

— Reduction of muscle mass, muscle strength, and physical performance;
— Increase in body fat mass, so-called "central fat tissue", increase in the thickness of skin fold and epigastric fat, increase in waist: hip ratio (WHR);
— Skin is pale, especially on the face, dry, thin, not very elastic, with numerous visible small vertical and horizontal wrinkles on the forehead;
— Thinning head hair; hair is soft, silky, and thin;
— Lanugo on the forearms, thinning hair of armpits and pubic area
— Sweating markedly reduced due to atrophic changes in sweat glands;
— Often hypertension and features of cardiac failure [22].

2.3.3. Changes observed in additional tests

— Lipid metabolism disorders favouring the development of atherosclerosis (increase in total cholesterol, LDL-cholesterol, and triglycerides, reduction of HDL-cholesterol);
— Atrophy of the left ventricular myocardium;
— Decreased bone mineral density (osteoporosis, T score < –2.5 SD);
— Impaired renal function (reduced glomerular filtration and renal flow) [23, 24].

2.3.4. Metabolic disorders

2.3.4.1. Lipid metabolism

Growth hormone has a lipolytic effect, triggers hydrolysis of adipose tissue triglycerides with the release of free fatty acids (FFA) into the circulation. In addition, it intensifies lipid oxidation processes and the formation of ketones [25]. Adults with GHD usually present an android type of obesity and increased body fat by about 10%. In addition, in this group of patients an atherogenic lipid profile is observed: elevated total cholesterol, LDL-cholesterol, triglycerides, apolipoprotein B, and reduced HDL-cholesterol.

It has been known for over 20 years that substitution treatment with rhGH improves lipid metabolism [26], reduces the percentage of body fat, and thus reduces the risk of cardiovascular disease [27]. Long-term (at least a few years) use of rhGH preparations in adults with GHD lowers total cholesterol and LDL-cholesterol and — at the same time — increases HDL-cholesterol levels [28, 29]. In adults with GHD, increased lipid peroxidation decreases after rhGH substitution [25, 30].

In patients with severe GHD, withdrawal of rhGH therapy after the growth completion leads to an increase in total cholesterol and LDL-cholesterol as well as an increase in body fat mass and in blood pressure (especially systolic) [31]. These disorders are reversible after restarting rhGH therapy [31, 32].

2.3.4.2. Carbohydrate metabolism

The effect of GH on carbohydrate metabolism is complex. Growth hormone, acting directly on carbohydrate metabolism, works antagonistically to insulin, while acting

indirectly via insulin-like growth factor I (IGF-I) it has an insulin-like effect [33]. GH inhibits glucose transport to tissues and glucose oxidation, and increases gluconeogenesis in the liver, which leads to an increase in blood glucose level. It is suggested that GH is a potent hormone that counteracts hypoglycaemia. Growth hormone is also responsible for the dawn phenomenon — consisting in reduced insulin sensitivity in the morning hours.

Patients with GHD have insulin resistance probably associated with visceral fat accumulation [34]. Increased fasting insulin, increased incidence of type 2 diabetes, or elevated glycosylated haemoglobin in non-diabetic subjects, correlated with higher body mass index (BMI), are observed [35].

Substitution treatment with rhGH in adulthood enhances insulin resistance, but despite the observed hyperinsulinaemia there is no deterioration of carbohydrate metabolism. Reports from recent years indicate that the initial adverse effects of rhGH are completely reversible during long-term therapy. A two-phase influence of rhGH substitution on carbohydrate metabolism is described — in the initial period unfavourable action inhibiting tissue glucose consumption is of basic importance, and in long-term periods favourable effects related to changes in body composition (mainly a decrease in visceral fat) prevail [28, 36]. In the case of severe GHD, it is particularly advantageous to use low doses of rhGH, which increase insulin sensitivity and may have a beneficial effect on reducing the risk of type 2 diabetes in this group of patients [37].

2.3.4.3. Protein metabolism

Growth hormone has an anabolic effect on protein metabolism. It was found that GH stimulates protein synthesis in skeletal muscles and in myocardium, and facilitates transport of amino acids and their incorporation into protein molecules. It also causes a positive nitrogen balance by lowering the concentration of circulating amino acids and urea.

In patients with GH deficiency, reduced amino acid transport to cells and reduced protein biosynthesis were demonstrated [38].

Substitution treatment with GH increases protein biosynthesis [38].

2.3.4.4. Water and electrolyte balance

Growth hormone causes retention of sodium ions in the body. It is suggested that the antinatriuretic effect of GH is the result of stimulation of the sodium pump activity in renal tubules. GH also has a stimulating effect on the renin-angiotensin-aldosterone system. It causes an increase in water content in the body, in particular an increase in water volume in the extracellular space [23, 27, 39–41].

2.3.5. Consequences of long-term GHD in adults. The effects of substitution treatment

The most serious consequences of long-term GHD in adults include:

— increased frequency of deaths due to cardiovascular complications;
— frequent bone fractures due to osteoporosis;
— deterioration of quality of life [36].

2.3.5.1. Effects on the cardiovascular system

Severe GHD in adults is an important risk factor of cardiovascular disease, resulting in increased mortality [36]. The unfavourable influence of GHD on the cardiovascular system is mainly caused by disorders of carbohydrate and lipid metabolism [28, 36]. In recent years attention has also been paid to the importance of oxidative stress [25, 30], increased secretion of pro-inflammatory cytokines and procoagulant factors, as well as vascular endothelial dysfunction in the pathomechanism of GHD-related disorders [36]. These disorders are at least partially reversible under rhGH substitution [28, 42].

In patients with severe GHD, reduction of left ventricular muscle mass, impaired contractility, decreased ejection fraction, diastolic dysfunction, and decreased cardiac reserve are observed [36, 43]. The substitution with GH results in thickening of the left ventricular wall and increased left ventricular mass and ejection fraction, increased number of muscle fibres, increased end-diastolic left ventricular volume and stroke volume, as well as a reduction in peripheral vascular resistance [23, 27, 44].

2.3.5.2 Effects on muscles

Growth hormone works indirectly on muscles through IGF-I. This factor increases the number of anabolic processes in muscle cells by binding to the specific receptor on the surface of myoblasts [45].

In adults with GH deficiency, application of this hormone increases the mass and strength of skeletal muscles [46].

2.3.5.3. Effect on the bone system

Growth hormone increases bone turnover, bone mineral density (BMD), and bone mineral content (BMC) [47, 48]. It works on bones in a direct and indirect way. Directly it stimulates the activity and proliferation of osteoblasts through specific receptors located in osteoblasts. In addition, it increases the number and differentiation of osteoclasts [49]. Therefore, the effect of GH on the bone is based on the acceleration of bone turnover, with the simultaneous increase in bone formation and resorption, with the predominance of the formation processes [50].

The indirect effects of GH on the bone are mediated by IGF-I and insulin-like growth factor binding protein-3 (IGFBP-3), which are produced both in the liver and locally by osteoblasts. Local production of IGF-I in bone tissue is influenced by oestrogens, cortisol, and parathyroid hormone [51]. IGF-I derived from osteoblasts can act in an autocrine and paracrine manner, playing an important role in the regulation of bone density [52]. IGFBP-3 enhances the effect of IGF-I on osteoblast proliferation and increases the production of type I collagen in osteoblasts [53].

Growth hormone also affects the bone tissue indirectly, by increasing the weight and strength of skeletal muscles and myocardial performance. Thus, it increases physical activity, which stimulates osteoblasts and increases bone mass [46, 54]. By acting on gonads, it increases the secretion of oestrogen and testosterone, enhancing their beneficial effects on bone tissue [55, 56]. In kidney, GH activates 1-alpha-hydroxylase and increases the synthesis of 1.25 $(OH)_2D_3$ and — acting via IGF-I — it increases the reabsorption of phosphate in the renal tubules. Acting on the kidneys and intestines it causes a positive calcium balance [51].

GH deficiency in adults is associated with a decrease in BMD and BMC and an increased risk of fractures [47]. Therapy with rhGH in these patients initially results in a small reduction in BMD with its subsequent increase after two years of treatment progressing up to 5–7 years of therapy, with subsequent stabilisation of BMD and BMC values. The most beneficial effects are provided by rhGH doses maintaining IGF-I concentration in the age--specific reference range. Higher initial doses of rhGH reduce the effectiveness of long-term therapy [47].

It is known that peak bone mass is achieved within 1–7 years after growth completion [57, 58]. After withdrawal of rhGH therapy, in adolescents and young adults with CO-GHD a decrease in BMD and in cortical bone thickness is observed, which in turn leads to an increased risk of bone fractures [59, 60]. Similarly, in these patients re-treatment with rhGH causes the initial small decrease in BMD, followed by a significant BMD increase as compared to the untreated group [59].

2.3.5.4. Effect on the gonads

Growth hormone regulates the function of the hypothalamic-pituitary-gonad axis. In the paracrine manner, it stimulates pituitary gonadotropic cells to produce and secrete gonadotropins. Growth hormone increases the sensitivity of Leydig and Sertoli cells to gonadotropins by increasing the density of receptors for follitropin (FSH) and lutropin (LH), and increases the sensitivity of the ovaries to gonadotropins, enhancing production of oestradiol and progesterone. It also acts directly, binding to its receptors in ovarian granulosa cells and corpus luteum cells, thereby increasing the production of oestradiol and progesterone, respectively. It also stimulates local production of IGF-I in testes [55, 56].

In female patients with panhypopituitarism receiving replacement therapy including gonadotropins (FSH, hCG), L-thyroxine, and hydrocortisone, as well as in ones with isolated GHD, rhGH substitution may be mandatory to obtain pregnancy [61, 62].

2.4. Diagnosis of growth hormone deficiency in adults

The principles for the diagnosis of growth hormone deficiency were first developed comprehensively in 1997 at the Conference organised by the Growth Hormone Research Society (GRS) in Port Stephens, Australia [2]. After 10 years, i.e. in 2007, the same society together with the European Society for Paediatric Endocrinology (ESPE), the Lawson Wilkins Society, the European Society of Endocrinology (ESE), Japan Endocrine Society, and the Endocrine Society of Australia, presented an update based on the consensus prepared during a conference in Sydney, Australia [4].

The following main issues were addressed in the above-mentioned consensus:

1. the risk groups of patients requiring assessment of GH secretion were specified;
2. the principles for performing stimulation tests and their standardisation were established;
3. the principles for the assessment of GH action biochemical markers and interpretation of the results were established;
4. the principles for management with patients with GHD diagnosed in childhood who have completed growth-promoting therapy were presented;
5. the principles of GH dosage and treatment monitoring in adults were established, including additional hormonal therapies used in these patients in the case of panhypopituitarism and the assessment of the treatment safety.

In 2011, American authors proposed another amendment to these recommendations [63].

2.4.1. Risk groups for patients with growth hormone deficiency

According to the current recommendations [4, 63], three groups of patients requiring evaluation of GH secretion were distinguished:

1. Patients with documented abnormalities within the hypothalamic pituitary axis, including hormonal, morphological, and /or genetic causes.
2. Patients after irradiation of the skull or treatment of intracranial tumours.
3. Patients after cranial injury or subarachnoid haemorrhage (in this group, it is recommended that the

secretion of GH should be assessed not earlier than 12 months after injury or haemorrhage, due to the possibility of spontaneous recovery of the normal function of the somatotropin axis).

In the case of ambiguous test results, clinical observation should be continued and a re-testing should be considered. There are no indications for isolated testing of adult-onset GHD in patients who do not meet any of the criteria listed in points 1–3. However, GHD may be the first diagnosed pituitary dysfunction in approximately 25% of adults with morphologic lesions in the pituitary region or patients after irradiation [4].

It is also necessary to re-evaluate the secretion of GH in adolescents after achieving the goals of therapy conducted in childhood, i.e. after the completion of growth and puberty [64]. However, it is not recommended to continue the treatment with rhGH doses used to promote growth (much higher than those used after the end of growth) at the moment of growth deceleration below 2–2.5 cm per year and after reaching bone age of 16–17 years for boys and 14–15 years for girls [65]. According to the Summary of Product Characteristics of Omnitrope, "somatropin should not be used for growth promotion in children with fused epiphyses"; this document also indicates that "fusion of epiphyseal growth platelets" corresponds to the bone age > 14 years in girls and > 16 years in boys. Nevertheless, according to the current description of the Treatment Program for children with GH deficiency, patients with bone age in the range of 16–18 years for boys and 14–16 years for girls do not meet the Program exclusion criteria regardless of the rate of growth, in contrast to patients with less advanced bone age, in whom slow growth rate is the criterion for therapy withdrawal. Adjusting the criteria for termination of the growth-promoting therapy to current recommendations will result in an increase in the pool of patients under 18 years of age requiring treatment in the currently developed Program.

2.4.2. Growth hormone stimulation tests

The diagnosis of severe growth hormone deficiency is based on the clinical symptoms of GHD and reduced GH secretion (below 3 ng/ml) in stimulation tests after prior compensation of cortisol, thyroxine, and sex steroid deficiencies, if such deficiencies occur [2, 4, 63].

Performing stimulation tests is necessary due to:

— pulsatile rhythm of GH secretion, precluding correct interpretation of the basic concentration of serum GH based on a single lab result;
— the existence of many physiological factors stimulating the GH secretion (sleep, physical exercise, psychological stress, postprandial amino acid rise, relative hypoglycaemia), as well as factors reducing GH secretion (hyperglycaemia and elevated levels of free fatty acids);
— altered GH secretion in various pathological states:
  • increased GH concentration is found in acromegaly / gigantism, protein deficiency states, starvation, cachexia, *anorexia nervosa*, chronic renal failure, and ectopic GHRH secretion,
  • decreased GH levels are found in obesity, hypothyroidism, and hyperthyroidism.

The purpose of dynamic tests is to assess the secretion of GH after pharmacological stimulation.

The following stimulants are used for tests:

— direct stimulation of somatotopic cells (after using GHRH or other substances showing such activity, so-called GH secretagogues — [GHS]) [66]:
— induction of absolute hypoglycaemia (after insulin injection);
— induction of relative hypoglycaemia (after glucagon injection);
— stimulation of α-adrenergic receptors (after clonidine application);
— inhibition of β-adrenergic stimulation (after propranolol);
— stimulation of dopaminergic receptors (after the use of L-DOPA, apomorphine, bromocriptine);
— other mechanisms.

According to the 2007 recommendation, for the diagnosis of GHD in adults it is sufficient to perform only one stimulation test, and it is not necessary to perform tests in patients with deficiency of at least three other pituitary hormones and decreased serum IGF-I concentration [4]. However, both previous recommendations from 1997 [2] and the last update from 2011 [63] suggest that two different stimulation tests would be required to confirm the diagnosis of isolated GHD in an adult.

In GHD patients diagnosed in childhood, GH secretion should be assessed after completion of growth-promoting therapy, at least one month after the last dose of rhGH, following the same principles. The latest reports suggest the possibility of abandoning tests in patients with a deficiency of at least three other hormones of the anterior pituitary gland, in patients with confirmed mutations of genes encoding transcription factors, e.g. *POUF1 (Pit-1)*, *PROP 1*, *HESX-1*, *LHX-3,* and *LHX-4* and with mutations leading to isolated GHD (e.g. *GH-1* gene or GHRH receptor gene) and in the case of morphologic changes in the hypothalamic-pituitary region with the exception of isolated posterior pituitary ectopy or anterior pituitary hypoplasia [4, 63, 65]. In these cases, a decreased IGF-I level at least one month after the end of rhGH therapy is considered to be sufficient confirmation of severe GHD [63]. In patients with morphologic lesions in the hypothalamic-pituitary area, as well as patients after radiotherapy in childhood, who do not have

confirmed severe GHD after the end of the growth promoting therapy, re-evaluation of GH secretion after a few years should be considered due to the possibility of later manifestation of severe deficiency of this hormone [65].

In adults, the test of choice is the insulin tolerance test [4]. In patients with contraindications to the insulin test (ischaemic heart disease, epilepsy, old age) alternative tests should be used. In such cases, combined tests with arginine and GH releasing hormone (GHRH), arginine and GH releasing peptide (GHRP), and with glucagon are considered the most reliable [4, 67]. According to 2011 US recommendations [63], in the evaluation of GHD in adults, insulin test and the GHRH test are the most sensitive and specific ones, while in the case of contraindications to the insulin test and/or unavailability of GHRH, glucagon test can be performed.

The above tests allow for the differentiation between GHD and GH lowering resulting from either physiologically reduced GH secretion during the so-called somatopause or patient obesity. However, it should be borne in mind that tests with GHRH assess only the maximal secretory capacity of the pituitary gland, not the function of the entire somatotropin axis, and thus may not identify patients with disorders of the hypothalamus [4]. In patients after radiotherapy of the skull and in patients with inflammatory or infiltrative lesions in the pituitary area with a normal GHRH test, an additional insulin test is recommended. Due to the possibility of revealing GHD after many years from irradiation, one should consider repeating the tests depending on clinical indications [4].

The clonidine test, usually used in the diagnosis of GHD in children, as well as L-DOPA test are now considered unsuitable in adults, while the arginine test can only be reliable in adolescents after the end of growth-promoting therapy [4].

The following cut-off points have been established for the diagnosis of severe GHD in adults for different stimulation tests [4]:

— for insulin test and glucagon test — 3.0 ng/ml;
— for the test with GHRH and arginine: patients with BMI below 25 kg/m^2 — 11.0 ng/ml, patients with BMI 25–30 kg/m^2 — 8.0 ng/ml, and patients with BMI above 30 kg/m^2 — 4.0 ng/ml.

After the end of the growth-promoting therapy, in adolescents with GHD diagnosed in childhood it is recommended to use a threshold value for insulin and glucagon tests at the level of 6.0 ng/ml and to carry out re-evaluation at the age of about 25 years, using the adult thresholds for the interpretation of stimulation tests, performed in order to establish indications for continuing therapy throughout the person's life [4, 6].

The most commonly used GH stimulation tests in adults and adolescents after completion of growth-promoting therapy, the mechanism of action of GH stimulating factors, the methods of testing, side effects, contra-indications, and recommended precautions are presented in the Appendix 1.

Methods for measuring GH concentration

For the GH assay, it is recommended that kits calibrated for human recombinant growth hormone IRP 98/574 are used. The necessity of working out universal standards of testing and of validation of used reagent sets with respect to the detection of different GH isoforms and interference with the GH binding protein (GHBP) is underlined [4].

2.4.3. Biochemical markers of growth hormone action

Insulin-like growth factor I (IGF-I) is a peripheral mediator of growth hormone action, synthesis of which is controlled by GH. There are two IGF-I pools in the body: endocrine pool and paracrine pool. The endocrine pool is mainly synthesized in the liver. In some tissues, such as uterus, IGF-I synthesis is independent of GH, but it is regulated by oestrogens. The local synthesis of IGF-I may also be influenced by other hormones, e.g. TSH, for the synthesis of this growth factor in the thyroid gland. IGF-I activity is multidirectional and consists of stimulating cell growth processes, cell migration and differentiation. IGF-I is an important factor stimulating nitric oxide synthase. The beneficial effects of IGF-I on cardiovascular parameters were also found: increased myocardial contractility, decreased vascular resistance and increased ejection fraction. It has also been shown that IGF-I may act as an anti-apoptotic agent that facilitates cell survival. IGF-I is a factor that enhances the gonadal effect of gonadotropins.

The IGF-I concentration is measured fasting in the morning and the obtained results are compared with the reference ranges adjusted for age and sex. The literature underlines the need to refine the reference ranges for the adult population, and to standardise the assay methods [4].

Low levels of IGF-I suggest GH deficiency after exclusion of other conditions that may cause IGF-I reduction (malnutrition, liver disease, decompensated diabetes, hypothyroidism).

In current classifications of somatotropic axis dysfunction in children, GHD is defined as a synonym for secondary IGF-I deficiency [68]. In adults, however, normal concentration of IGF-I does not exclude the diagnosis of GHD [4].

IGF-I activity is modulated by binding proteins, especially **insulin-like growth factor binding protein-3 (IGFBP-3)**, synthesis of which depends on GH action.

The concentration of IGFBP-3 is measured fasting in the morning, and finding of low serum levels is considered to be less reliable than IGF-I deficiency [27].

2.5. Treatment of growth hormone deficiency in adults

2.5.1. Indications for treatment

The indication for substitution treatment in adults is the diagnosis of severe GHD. The aim of the treatment is to resolve adverse clinical symptoms, eliminate metabolic disorders associated with GHD, and improve the quality of life [2, 4, 44, 63].

In contrast to GHD, decreased GH levels in the elderly — probaby caused by physiological changes in secretion of neurohormones which regulate GH secretion — do not require therapy. However, in patients with severe GHD, continuation of therapy is also recommended in the elderly, but with lower doses of rhGH [4].

2.5.2. Contraindications for treatment with growth hormone

The absolute contraindications are [4, 27, 63, 69]:

— active cancer processes;
— acute critical conditions.

In children after cured cancer disease, who receive rhGH therapy, there is an increased risk of a second cancer [4]. Despite the lack of direct evidence that rhGH substitution therapy increases the risk of tumour recurrence in adults, there is a correlation between elevated serum IGF-I levels and higher risk of malignancies [63].

In patients in critical conditions, especially in the cases of unfavourable prognosis, GH secretion increases several times [70]. In adults in critical conditions (in patients after cardiac surgery and abdominal surgery, multi-organ trauma, and in patients with acute respiratory failure) the use of rhGH increased mortality, and in survivors it prolonged the period of mechanical ventilation and of hospitalisation in the intensive care unit [71]. However, these patients received rhGH doses many times higher than it is currently recommended in adult substitution treatment.

According to the recommendations from 1998 [2], the absolute contraindications to rhGH therapy included: active neoplastic processes, benign intracranial hypertension, proliferative and pre-proliferative diabetic retinopathy, and second and third trimester of pregnancy.

According to the current recommendations, patients with type 2 diabetes may receive rhGH substitution, but they require appropriate adjustment of diabetes treatment [63]. Retinopathy may be associated with elevated IGF-I levels because it occurs in patients with acromegaly [72]. In patients with diabetic retinopathy treated with rhGH, discontinuation of this treatment was associated with a reduction of the retinopathy severity [73, 74], but there was no correlation between treatment with rhGH and retinopathy development (published studies were conducted in children, not in adults) [63, 75].

Mild intracranial hypertension during rhGH therapy is observed less frequently, than it was reported earlier [63, 76]. In adults, only sporadic cases of this complication have been described [59, 77]. Currently, it is assumed that in the case of intracranial hypertension rhGH therapy should be discontinued, and its resumption requires special attention and usually lower doses of the drug [65].

Severe GHD may be associated with decreased fertility and complications in early pregnancy. It has been reported that the use of rhGH during the preconception period and early pregnancy may be beneficial. In normal pregnancy, pulsatile GH secretion is gradually suppressed and is replaced by continuous release of placental GH, which is the main stimulus of IGF-I secretion in pregnant women. Therefore, it seems reasonable to continue rhGH therapy until sufficient GH synthesis is achieved in the placenta [78]. Nevertheless, the safety of rhGH in pregnancy has not been sufficiently documented, and therefore this therapy cannot currently be the subject of recommendation [62].

In the elderly, it is recommended to reduce the dose of rhGH, adequately to the physiological decrease in endogenous GH secretion in healthy people during this period of life [4].

2.5.3. Expected treatment effects

The substitutional use of rhGH results in the elimination of all disorders associated with GH deficiency. Some changes are observed after a short-term treatment, others occur later in time, depending on the degree of GH deficiency, rhGH dose and mechanism of action at the level of individual tissues [79].

In people immediately after growth completion, the primary purpose of rhGH treatment is to achieve full somatic development, including optimal peak bone mass and muscle mass, as well as to prevent deterioration of quality of life [4, 6].

In the case of starting rhGH therapy in adults, its most important goals are [4, 63, 80, 81]:

— improving the body composition — increasing lean body mass and reducing fat mass, especially visceral fat mass;
— increasing exercise capacity;
— reducing the risk of osteoporosis and bone fractures due to the beneficial effects of rhGH on the bone; long-term (at least 12-month) therapy leads to improvement of bone mass and BMD due to increased bone production processes;
— prevention of cardiovascular complications due to beneficial effects on the lipid metabolism

(reduction of total cholesterol, LDL-cholesterol, and ApoB and increase in HDL-cholesterol and ApoE), endothelial function, myocardial function, as well as lowering of proinflammatory and procoagulant factors;
— improving the quality of life and mental functions.

2.5.4. Dosing of rhGH

The dose of growth hormone should be established individually in order to obtain the best results with good tolerance of treatment. When establishing the initial dose, it should be noted that GH secretion is higher in women than in men, while in both sexes it is the highest in young people and decreases with age. Proposed starting doses of rhGH are 0.2 mg/day for young men and 0.3 mg/day for young women, and 0.1 mg/day for older people. In adolescents with severe GHD, after the end of the growth-promoting therapy, intermediate doses between "paediatric" and adult ones are recommended [4].

Determining the dose per square metre of body area or per kilogram of body weight in adult patients is currently not recommended [4] because it was proven to be imprecise due to the different individual sensitivity to the hormone and the different rate of drug absorption from the subcutaneous tissue [2, 82].

At this point, it should be emphasised once again that every time the current document refers to the supplementation of GH deficiency in adult people, the authors mean the supplementation of GH deficiency to the reference concentrations for a given age, and not to higher concentrations, e.g. values found in young people.

The following factors should be taken into consideration when determining the optimal dose of growth hormone:

— **The patient's age**

It is known that after growth completion GH secretion decreases physiologically with age by about 14% per a decade of life [83] and a simultaneous decrease in IGF-I concentration is observed [84]. Therefore, the principle is that the applied dosage of rhGH should ensure the maintenance of IGF-I levels in the age-adjusted reference range (optimally — in the upper range of the range of reference values for age and sex) [4, 63]. Particular care should be taken in elderly patients.

— **Patient gender**

Healthy premenopausal women secrete 0.2 mg GH daily, while men at a similar age — 0.1 mg/day. On the basis of this assumption, it is proposed that the treatment with rhGH should be started from the dose of 0.2 mg/day in men and 0.3 mg/day in women [4]; however, it is necessary to closely monitor the metabolic effects of rhGH because these doses may be insufficient, especially in women [85].

— **Simultaneous substitution treatment with hydrocortisone or L-thyroxine**

This situation requires extreme caution in determining GH dose. In the first case there is a risk of lowering cortisol concentration due to the decrease in 11β-hydroxysteroid dehydrogenase activity, which may lead to increased requirement of hydrocortisone dose in already treated patients. In the second case, in patients already receiving substitution treatment with L-thyroxine, the required dose may be increased due to the increased conversion of thyroxine to triiodothyronine [4, 86]. It should also be borne in mind that after starting rhGH therapy, secondary adrenal insufficiency or secondary hypothyroidism may also be revealed.

— **Simultaneous use of sex steroids**

In women receiving sex steroids, in particular oral oestrogens, the need for rhGH may be increased. It is recommended to choose a different route of oestrogen administration and to adjust rhGH dosage after each modification of oestrogen therapy [4, 63]. The use of androgens does not necessitate the modification of rhGH therapy [4].

Growth hormone is given once a day in the evening (in order to best imitate the physiological rhythm of GH secretion) in subcutaneous injections made with pre-filled pens.

2.5.5. Monitoring of rhGH treatment

Treatment control should include [2, 63]:
— a medical history with a focus on changes in the quality of life, assessed using a standardised Quality of Life (QoL) questionnaire [87];
— clinical examination (including WHR, BMI, and blood pressure);
— determination of serum IGF-I concentration (initially every 1–2 months, then every 6–12 months);
— assessment of serum glycaemia or glycated haemoglobin (HbA1c) level once a year;
— determination of serum lipid concentration once a year;
— assessment of the body composition by electrical bioimpedance method every six months or by X-ray absorptiometry every 12 months;
— assessment of BMD every 18–24 months [63];
— imaging of the central nervous system (magnetic resonance imaging — MRI, computed tomography — CT), depending on the needs;
— reassessment of the need for L-thyroxine and/or hydrocortisone in patients with hypopituitarism and the assessment of L-thyroxine and cortisol secretion in patients with previously diagnosed isolated GHD in the presence of symptoms suggestive of adrenal insufficiency and/or hypothyroidism after introduction of rhGH therapy;
— applying generally recommended cancer prevention rules.

2.5.6. Adverse effects and complications of substitution treatment with rhGH preparations

Adverse effects of treatment are usually mild and are more frequent in the elderly and in people with a higher body weight. The severity of adverse effects is proportional to the dose of rhGH. The side effects often decrease in intensity or disappear completely after reduction of the rhGH dose [2]. They occur less frequently in adults who continue treatment started in childhood.

The most common side effects are as follows:

— swelling due to fluid retention;
— pain in the joints and muscles;
— nausea;
— muscle stiffness;
— paraesthesia [44].

Occasionally reported side effects include:

— gynaecomastia in older men;
— carpal tunnel syndrome;
— headaches with tinnitus;
— benign intracranial hypertension;
— papilloedema;
— glucose intolerance, hyperinsulinaemia, and diabetes;
— arterial hypertension [2, 63, 88].

The most serious concerns regarding the safety of long-term substitution therapy with rhGH were related to the risk of possible left ventricular hypertrophy, increased insulin resistance, and increased incidence of malignant tumours or recurrences of pituitary tumours. However, 10-year prospective studies did not show any of these complications [69]. Particular attention is paid to newer reports, which also do not confirm such dependencies [89, 90]. In 2012, data indicating increased mortality of adults treated with rhGH in childhood, especially with higher doses, were published, with a statistically significant increase in the risk of death due to bone tumours and intracranial haemorrhages, and increased incidence of deaths in the course of cardiomyopathy and cardiomegaly [91]. The latest meta-analysis from 2017 [92] did not confirm the increased risk of death in children and adults treated with rhGH. There is also no evidence that rhGH therapy increases the risk of malignant tumours, leukaemia, other cancers located outside the skull, or recurrent intracranial tumours, in patients without additional risk factors [92, 93]. Additionally, the analysis of the material collected in the KIMS database showed that the risk of death within the first three years of rhGH use was higher in patients with lower IGF-I concentrations during treatment [94]. Only the risk of a second cancer is increased, especially in people with CO-GHD and after CNS irradiation [92, 95, 96]. There is also no evidence that rhGH replacement therapy increases the risk of colon cancer, as it was reported in acromegalic patients [2]. Nevertheless, the principles of prophylaxis and early detection of neoplastic diseases, widely recommended in the entire population, are even more relevant in this group of patients. Patients after radiotherapy for pituitary tumours have an increased risk of cardiovascular complications, but this risk decreases during long-term rhGH substitution [80]. Adult rhGH-treated patients also had an increased incidence of type 2 diabetes, but it appears to be primarily associated with the presence of other concomitant risk factors rather than the rhGH therapy itself [92].

Reports on the complications of substitution treatment with rhGH are found in databases developed with the participation of rhGH-producing pharmaceutical companies: KIMS (Pharmacia Corporation, formerly Pharmacia & Upjohn), Nordireg (NovoNordisk), NCSS database (Genentech), and HypoCCS (Eli Lilly). The largest number of patients (over 16,000 until its closure in 2012) was gathered in the KIMS program database. In the analysis of 14,752 patients treated with rhGH as part of the KIMS program up to March 2010, malignant tumours were diagnosed in 469 patients (most often skin tumours, including malignant melanoma in 87 people, prostate cancer in 77 men, and breast cancer in 34 women) [96]. In the HypoCCS database of 6840 adults treated with rhGH, 24 cases of prostate cancer, 16 cases of breast cancer, 15 cases of malignant melanoma, 11 cases of colorectal cancer, 9 cases of thyroid cancer, and 9 cases of glioblastoma were reported; the risk of these tumours was similar to that in the general population [96]. Data from both the KIMS and HypoCCS databases did not show increased incidence of recurrences of pituitary tumours and craniopharyngiomas compared to patients not receiving rhGH [97].

Although databases are a great source of information, undeniably useful in population analyses, it should be noted that they do not meet the criteria for statistical elaboration. The incidence of complications in these studies may be distorted due to the registration of all ailments and diseases, regardless of their causal relationship with rhGH therapy. In addition, patients treated with rhGH remain under constant, systematic medical care, which increases the possibility of early diagnosis of cancer and other diseases.

According to the current state of knowledge, it can be assumed that [97]:

— the benefits of adult rhGH substitution therapy outweigh the theoretical risk of malignancy;
— if the safety rules regarding rhGH dosing and therapy monitoring are maintained, this treatment does not increase the risk of *de novo* malignancy;

— patients after childhood cancer have an increased risk of secondary tumours;
— one should be aware of the presence of other modifiable risk factors for cancer, such as obesity, insulin resistance, sedentary lifestyle, disturbance of circadian rhythms, increased concentrations of proinflammatory factors, and the use of sex steroids;
— data on people with a high family burden of cancer and on elderly patients do not allow to lead to conclusions about the safety of the therapy in these groups of patients, and therefore they require particularly careful monitoring.

2.5.7. Criteria for cessation of treatment

It seems that substitution of GH, like other hormones, should last from the moment of diagnosis throughout the patient's life. There are reports on the beneficial effects of treatment initiated after the age of 65 years [98]. In the elderly, the dose of GH should be reduced over time [4, 63, 93].

The indications to treatment cessation should be as follows:
— occurrence of serious complications of treatment or contraindications to treatment (mentioned earlier);
— recurrence of pituitary tumours;
— lack of therapeutic effects, especially in older age;
— lack of patient's consent to continue treatment or failure to follow treatment recommendations, perform check-ups, and modify lifestyle.

Based on the analysis of the KIMS data, a point evaluation of the effectiveness of rhGH treatment based on the determination of total cholesterol and IGF-I, waist circumference measurement, and quality of life assessment based on the QoL questionnaire was proposed; prediction models, which can be used to make decisions about continuing treatment, have also been developed [99]. When assessing the effectiveness of rhGH therapy in Polish patients the Polish version of the QoL-AGHDA questionnaire, developed by Karbownik-Lewińska et al. [87], should be applied.

2.5.8. Preparations of rhGH registered in Poland

Currently, only growth hormone preparations obtained by DNA recombination are used. The active substance is either in the form of a ready-made solution or a lyophilised powder with an attached solvent ampoule. The solvent, containing the preservative, provides full activity of the drug throughout 2–3 weeks after dissolving, provided that the drug is stored at 2–8°C. Similar requirements apply to the storage of preparations in the form of ready-made solutions. Each of the companies also produces injection pens adapted to their own preparations, which facilitate dosing and administration of the drug.

Currently, the following preparations of rhGH are registered in Poland:
1. Omnitrope (Sandoz);
2. Genotropin (Pfizer);
3. Norditropin (Novo Nordisk).

3. The existing model of health care for adults with GHD in Poland

Until now, adults with GHD, irrespective of its aetiopathogenesis, have not been registered, diagnosed, and treated in Poland in a coordinated way; however, a small part of these patients have received rhGH outside of public funding (in clinical trials or with the full purchase of a drug); moreover, no prevention of diseases that are possible complications of growth hormone deficiency has been carried out, and no appropriate psychological help for this group of patients has been implemented.

In our community, GHD in adults was a problem not sufficiently understood and not very carefully analysed. It resulted from the common stereotypical thinking that growth hormone is needed during the period of body growth and has no significant importance after growth completion.

In the last few decades, the issue of GH deficiency in adults has become the focus of many leading endocrine centres. For over 30 years, in many countries in Europe and worldwide, adult patients with GHD have been treated with rhGH preparations in order to improve health and prevent the consequences of the disease. In Poland, few adult patients were treated with rhGH, due to the lack of appropriate standards of management as well as the high price of the drug in the case of individual purchase. There are no studies on epidemiology, aetiology, and natural history of GHD in adults in Poland.

4. National Program of Severe Growth Hormone Deficiency Treatment in Adults and Adolescents after Completion of Growth-Promoting Therapy

4.1. Objectives of the Program

4.1.1. General assumptions

The aim of the Program is to implement planned, systematic, controlled treatment with growth hormone in adults and adolescents with severe GHD after completion of growth-promoting therapy.

The treatment continuation in adolescents and adults treated in childhood for GHD, and the treatment initiation in the case of GHD diagnosis in adults who were not previously treated for this indication, are assumed.

4.1.2. Detailed objectives of the Program

— development of a clear qualification algorithm for diagnostic procedures enabling the correct early diagnosis of GHD in adults and adolescents after the end of growth-promoting therapy;
— development of standards for qualification procedures for rhGH treatment;
— development of a treatment algorithm compliant with global standards;
— development of principles of cooperation of healthcare centres at the primary and specialist level;
— extension of the Coordination Team for Growth Hormone Application with persons dealing primarily with the therapy of adult and adolescent patients after the end of the growth-promoting therapy, defining their tasks and responsibilities;
— creation of a central database of adult patients qualified and treated with rhGH;
— providing reimbursement of rhGH treatment to all adults and adolescents after growth completion, who require continuation of substitution therapy;
— execution of a central purchase and creating a rhGH distribution system ensuring the lowest possible price of the drug thanks to planned, controlled wholesale purchases;
— elaboration of data on epidemiology and aetiopathogenesis of GHD in adults;
— analysis of data on side effects, complications, and adverse events occurring during the course of therapy;
— elaboration and analysis of data regarding health and economic benefits resulting from the implementation of therapy.

4.2. Methods of the Program implementation

4.2.1. Principles of referring patients with suspected GHD to endocrinology outpatient clinics

All patients with suspected GH deficiency will be referred to endocrinology outpatient clinics for adults in order to perform observation and diagnosis towards disorders of secretion of pituitary hormones. Due to the diverse aetiology of the disease, adults with suspected GHD will be recruited from various medical centres. These should be the following groups of patients:

1. Patients treated during childhood due to GHD, who ended the growth promoting therapy, and who have reached the age of 18 years, will be transferred from the paediatric endocrinology centres to endocrinology outpatient clinics for adults with a "Referral card for patient treated with rhGH due to growth hormone deficiency from the paediatric endocrinology centre to the Reference Centre for GH Treatment in Adults" (Appendix 2), containing full documentation on the current diagnosis and course of treatment; at least 30 days after cessation of rhGH therapy, the diagnosis will be verified in accordance with the established criteria, and possible re-implementation of therapy will be performed at the Reference Centre for GH Treatment in Adults. In the case of patients terminating the growth-promoting therapy before the age of 18 years, reassessment of GH secretion and possible qualification for treatment continuation will be performed in the paediatric centre conducting the treatment, and patients will be referred to the Reference Centre for GH Treatment in Adults at the age of 18 years.
2. Patients from neurosurgery centres, after surgery due to pituitary adenomas or other tumours of the hypothalamic-pituitary area (e.g. craniopharyngioma).
3. Patients from radiotherapy centres, after head radiotherapy.
4. Patients from traumatology centres after head injuries, who have symptoms suggestive of GHD.
5. Adults presenting to a mental health outpatient clinic, psychologist, neurologist, or psychiatrist, who also have somatic symptoms suggestive of GHD.
6. Adults whose GP identifies symptoms suggestive of GHD, especially when there is a possible underlying cause of GH deficiency.

In endocrinology outpatient clinics for adults, patients will undergo the qualification for hospitalisation in selected Reference Centres for Growth Hormone Treatment in Adults in order to carry out diagnostic procedures confirming or excluding GHD.

4.2.2. Reference Centres for Growth Hormone Treatment in Adults

Hospitalisation of patients qualified for diagnostics will take place in designated reference clinics and endocrinology departments, in which there is a possibility of performing comprehensive diagnostic tests: hormonal, imaging (including MRI of the central nervous system), and conducting multi-specialised care.

During hospitalisation, tests recommended in the standards of diagnostic procedures to confirm or exclude growth hormone deficiency should be performed, after proper substitution treatment compensating for any other deficiencies of pituitary hormones in the case of hypopituitarism.

In the case of diagnosis of GH deficiency, the physician should complete the "Application form for qualification for rhGH treatment in a patient with growth hormone deficiency" (Appendix 3) and submit it to the Coordination Team for consideration.

After obtaining approval of GH therapy in the Reference Centre for the GH Treatment in Adults, patient training will be conducted on how to store the drug and administer the preparation, and an individual treatment regime and treatment control will be established.

A network of Reference Centres for Growth Hormone Treatment will be created on the base of existing Clinics and Departments, taking care of adult patients in Poland. Treatment of patients with severe GHD, who completed growth promoting therapy before the age of 18 years, will be continued in paediatric centres.

Once a year a patient's physician from the Reference Centre will have to send to the Coordination Team the "Observation chart of a patient treated with rhGH due to growth hormone deficiency" (Appendix 4), regarding the patient's health status, selected auxological, biochemical, and hormonal parameters, and the effective dose, in order to verify the demand for medicine.

4.2.3. Tasks of the Coordination Team

— coordination and substantive supervision over the implementation of the Program tasks;
— considering and approving the "Application form for qualification for rhGH treatment in patient with GH deficiency", substantive supervision over the correct qualification for treatment;
— development of criteria for excluding patients from therapy;
— constant verification of the central drug demand based on the analysis of "Observation charts of a patient treated with rhGH due to growth hormone deficiency";
— control over the proper distribution of the drug;
— creating a central patient registration system;
— organisation and coordination of educational activities.

Meetings of the Coordination Team will be held regularly at least once every three months.

For the purpose of implementing the Program, it is necessary to extend the Coordination Team for Growth Hormone Application with persons who will coordinate growth hormone therapy in adults and in adolescents with severe GHD after completion of growth-promoting therapy. In particular, it is planned to include the authors of this document.

4.3. Development of detailed guidelines

Detailed guidelines will be developed with the participation of all entities involved in the implementation of the Program (representatives of specialist supervision in the field of endocrinology, paediatric endocrinology and diabetology, paediatrics, family medicine, and representatives of academic, medical, psychological, sociological, and economic environments). The proposed set of procedures implemented in the Program is presented in the Appendix 5.

4.4. Educational materials and training

Educational materials for primary care physicians and specialists will be developed to address the problem of growth hormone deficiency in adults. They will discuss possible causes of GHD, symptoms suggestive of GHD, basic diagnostic issues, and benefits of substitution treatment. The principles of referring patients suspected of GHD to endocrinology outpatient clinics and Reference Centres will also be presented.

During the period of implementation of the Program, it is planned to prepare a series of lectures for primary care physicians and specialists dealing with growth hormone deficiency in adults.

In order to propagate knowledge about the disease and raise public health awareness in this area, it is planned to prepare brochures for patients, and to carry out an information campaign in the mass media (TV, radio, press, advertising).

4.5. Expected effects of introduction of the Program

4.5.1. The health aspect

1. Introduction of the Program assumes the development and implementation of an optimal diagnostic and therapeutic algorithm for adults with GHD throughout the country.
2. Proper treatment of GHD patients will prevent the deterioration of the quality of life and other long-term consequences of growth hormone deficiency often requiring long-term therapy and rehabilitation.

4.5.2. The cognitive aspect

1. Formation of a central registry of adult GHD patients will allow for the development of epidemiology and aetiopathogenesis data of this disease in Poland, enabling a thorough analysis of the effectiveness of the therapy.
2. Implementation of the tasks of the Program will broaden the knowledge about GHD in adults among both doctors and nurses, and will increase the level of society health education in this area.

4.5.3. The economic aspect

1. Introduction of the Program will allow for:
   - wholesale purchases of the drug, significantly reducing the cost of the transaction;
   - accurate planning and proper distribution of public funds.

2. Proper GHD therapy will help to avoid long-term consequences of the disease, eliminating the costs of long-term treatment and rehabilitation (especially treatment of heart attacks, osteoporotic fractures), as well as long-term exclusion from active working life.
3. It has been proven that the costs of treating complications of GHD and social costs resulting from the exclusion from active working life (sick leave, disability pension) outweigh the costs of using rhGH in GHD in adults.

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Appendix 1

The most commonly used tests stimulating growth hormone secretion in adults: the mechanism of action of the stimulating factors, methods of testing, side effects, contraindications, and recommended precautions.

Stimulating factor	Mechanism of action	Dosing	Time of sample collections (min)	Side effects, contraindications, and recommended precautions
Insulin	Insulin causes hypoglycaemia, which intensifies GH secretion indirectly by stimulating GHRH	0.1 U/kg IV	–30, 0, 30, 60, 90, 120 (with simultaneous serum glucose tests)	The patient must have normal glucose concentration at the beginning of the test. During the test, glucose concentration should reach values below 40 mg/dl or below 50% of the initial value The test is contraindicated in patients with epilepsy, with cardiovascular disease, and in older age During the test, glucose levels should be monitored using a glucometer. Ensure constant nurse care during the test If the symptoms of hypoglycaemia are severe, oral glucose or a highly sweetened liquid should be given. In the case of prolonged hypoglycaemic symptoms or consciousness disturbances, glucose 10–25% solution should be administered intravenously
Glucagon	Glucagon causes an increase in glucose concentration stimulating the release of endogenous insulin, which is the stimulus for GH secretion (see insulin test)	1 mg IM (in children 30 μg/kg body weight)	0, 90, 120, 150, 180 (glucose assessment every 30 minutes during the whole test)	Similar to the insulin test but usually less severe and occurring later
L-DOPA	Dopamine stimulates the secretion of GH at the level of hypothalamus	500 mg orally	–30, 0, 30, 60, 90	Side effects: often causes nausea, vomiting
Arginine	Arginine stimulates GH secretion at the level of hypothalamus, possibly by reducing secretion of somatostatin	0.5 g/kg IV for 30 minutes (maximum dose 30 g)	–30, 0, 30, 60, 90, 120	Side effects: may cause nausea, vomiting and skin irritation at the injection site Contraindications: severe liver or kidney disease, acidosis
GHRH	Directly stimulates the pituitary to release GH. It can be used to differentiate GH deficiency of pituitary and hypothalamic origin	1 μg/kg in fast IV injection	–30, –15, 0, 30, 60	Side effects: hot flashes, metallic taste or smell

Appendix 2

Stamp of the centre issuing the application:

REFERRAL CARD FOR PATIENT TREATED WITH rhGH DUE TO GROWTH HORMONE DEFICIENCY FROM THE PAEDIATRIC ENDOCRINOLOGY CENTRE TO THE REFERENCE CENTRE FOR GH TREATMENT IN ADULTS

1. Patient personal data

First name and last name: ....
Place of residence of the patient:
City: ..... No. ..... Postal code ..... Mail ....
Street ....No. ..... Apartment number .....
Voivodeship: .....
Phone number: ...…….
Number of the department of the National Health Foundation: ☐☐☐
Date of birth: ☐☐-☐☐-☐☐☐☐ day — month — year
Personal identity number ☐☐☐☐☐☐☐☐☐☐☐
Ethnic origin: ☐ C — Caucasian O — other, describe .....
Gender: ☐ F — female ☐ M — male

2. Medical history

a) Perinatal data:

body weight at birth: ☐☐☐☐ g body length at birth: ☐☐.☐ cm
head circumference: ☐☐.☐ cm
childbirth no.: ☐☐ pregnancy no.: ☐☐ duration of pregnancy in weeks: ☐☐
normal pregnancy: ☐ Y — yes, N — no, if not, describe .....
.....
.....
course of delivery: natural ☐, head ☐, breech ☐, other .....
caesarean section ☐, forceps delivery ☐ other .....
birth injury ☐, hypoxia and resuscitation ☐
grade according to the Apgar scale ☐
was the course of the neonatal period normal? ☐ Y — yes, N — no, if not, describe
.....
.....

b) History concerning sexual maturation:

If a man:
Beginning of puberty: ☐ early ☐ average ☐ late
☐ spontaneous
☐ induced
If a woman:
The occurrence of the first menstrual bleeding (menarche): age ☐☐ years
☐ spontaneous ☐ induced

c) Family history:

mother: height ☐☐☐.☐ cm body weight ☐☐☐.☐ kg
father: height ☐☐☐.☐ cm body weight ☐☐☐.☐ kg
target height (TH) ☐☐☐.☐ cm SDS TH (☐☐.☐☐)

d) Chronic diseases:

diabetes ☐ Y — yes, N — no
leukaemia ☐ Y — yes, N — no
irradiation ☐ Y — yes, N — no
cytostatic drugs ☐ Y — yes, N — no
other ☐ Y — yes, N — no

3. Data on the diagnosis of growth hormone deficiency (GHD)

year of diagnosis of growth hormone deficiency ☐☐☐☐

If causative morphologic lesion:

type of tumour description .....
neurosurgery description .....
radiotherapy description .....
cytostatic drugs description .....

Pituitary insufficiency status:

isolated GH deficiency ☐ panhypopituitarism ☐
TSH deficiency ☐ Y — yes N — no
year of diagnosis ☐☐☐☐ replacement therapy: ☐ Y — yes N — no
ACTH deficiency ☐ Y — yes N — no
year of diagnosis ☐☐☐☐ replacement therapy: ☐ Y — yes N — no
LH / FSH deficiency ☐ Y — yes N — no
year of diagnosis ☐☐☐☐ replacement therapy: ☐ Y — yes N — no
ADH deficiency ☐ Y — yes N — no
year of diagnosis ☐☐☐☐ replacement therapy: ☐ Y — yes N — no

GH stimulation tests

date ☐☐ - ☐☐ - ☐☐☐☐
way of stimulation .....…….. max GH ☐☐. ☐ unit .....

date ☐☐ - ☐☐ - ☐☐☐☐
way of stimulation ..... max GH ☐☐. ☐ unit .....
date ☐☐ - ☐☐ - ☐☐☐☐
way of stimulation ..... max GH ☐☐. ☐ unit .....
date ☐☐-☐☐-☐☐☐☐
diurnal/night profile of GH secretion:
maximum concentration of GH ☐☐.☐ unit ……
mean concentration of GH ☐☐.☐ unit ……
date ☐☐-☐☐-☐☐☐☐ serum IGF-I concentration ☐☐☐☐.☐ unit……
reference range…….
date ☐☐-☐☐-☐☐☐☐ serum IGFBP-3 concentration ☐☐☐☐.☐ unit……
reference range…….
Pituitary MRI Date of scan ☐☐-☐☐-☐☐☐☐
.....
.....
Pituitary CT Date of scan ☐☐-☐☐-☐☐☐☐ ……
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.....
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Confirmed diagnoses:
1 .....
2 .....
3 .....

4. Data concerning GH replacement therapy
Date of the therapy onset ☐☐-☐☐-☐☐☐☐
Treatment course without complications ☐ Y — yes, N — no If no, describe
.....
.....
.....

Date of the last injection ☐☐-☐☐-☐☐☐☐
Main reason for treatment cessation:

Patient met exclusion criteria from the drug program for children	☐	Y — yes, N — no
Reaching the target height	☐	Y — yes, N — no
Fusion of the epiphyseal cartilage	☐	Y — yes, N — no
Significant deceleration of the growth rate	☐	Y — yes, N — no
Change of diagnosis	☐	Y — yes, N — no
Patient's decision	☐	Y — yes, N — no
Other	☐	Y — yes, N — no

5. Auxological data after the end of therapy: test date ☐☐-☐☐-☐☐☐☐
height ☐☐☐.☐ cm body weight ☐☐☐.☐ kg BMI ☐☐☐ kg/m^2 WHR ☐☐☐
Psychological examination carried out after the end of treatment: ☐ Y — yes, N — no,
If yes, describe
.....
.....
Psychological test for quality of life (QoL-AGHDA test) assessment .....
.....
.....
Others .....
.....
.....
.....

6. Laboratory tests after treatment cessation:

GH secretion stimulatory tests
date ☐☐ - ☐☐ - ☐☐☐☐ way of stimulation ..... max GH ☐☐. ☐ unit .....
date ☐☐ - ☐☐ - ☐☐☐☐ way of stimulation ..... max GH ☐☐. ☐ unit .....
For the insulin test, please provide the baseline and the lowest blood glucose concentrations:
Result ☐☐☐☐.☐ unit ...., Result ☐☐☐☐.☐ unit ....
serum IGF-I concentration: date ☐☐-☐☐-☐☐☐☐ result ☐☐☐☐.☐ unit…….
reference range…….
serum IGFBP-3 concentration date ☐☐-☐☐-☐☐☐☐ result ☐☐☐☐.☐ unit…….
reference range…….

Densitometry: date of examination ☐☐-☐☐-☐☐☐☐

Method: ……

	Z-score	T-score	BMD [g/cm]	BMC [kg]	Comments
Lumbar spine					
Femoral neck					
Whole body					
Others					
Others					

Others:
.....
.....
.....

Unit/department completing the application:
Full name: .....
Address: ....
Telephone / fax: ....
Date of issue: ☐☐-☐☐-☐☐☐☐
The physician issuing the application: Signature and stamp
First name: .....
Last name: .....

Head of the unit/department issuing the application:

Signature and stamp:

Appendix 3

Stamp of the centre issuing the application:

APPLICATION FOR QUALIFICATION FOR rhGH TREATMENT IN A PATIENT WITH GROWTH HORMONE DEFICIENCY

1. Patient personal data

First name and last name: ....
Place of residence of the patient:
City: ..... No. ..... Postal code ..... Mail .....
Street ....No ..... Apartment number .....
Voivodeship: .....
Phone number: ...…….
Number of the department of the National Health Fund: ☐☐☐
Date of birth: ☐☐-☐☐-☐☐☐☐ day - month - year
Personal identity number ☐☐☐☐☐☐☐☐☐☐☐

Ethnic origin: ☐ C — Caucasian O — other, describe .....
Gender: ☐ F — female ☐ M — male

2. Professional activity of the patient:
☐ student
☐ mental worker
☐ physical worker
☐ farmer
☐ receiving a pension
☐ retired

3. Marital status:
☐ single
☐ married
☐ divorced
☐ widow / widower
Number of children ☐☐

4. Does the patient smoke?
☐ does not smoke at all
☐ smokes sometimes
☐ smokes less than 15 cigarettes a day
☐ smokes more than 15 cigarettes a day

5. Medical history concerning sexual maturation:
If a man:
Beginning of puberty: ☐ early ☐ average ☐ late
☐ spontaneous
☐ induced
If a woman:
The occurrence of the first menstrual bleeding (menarche): age ☐☐ years
☐ spontaneous ☐ induced
Age of menopause / last menstruation: ☐☐ years

6. Medical history concerning the patient's health status:
Has the patient been diagnosed with:
☐ hypertension year of diagnosis ☐☐☐☐
☐ ischemic heart disease year of diagnosis ☐☐☐☐
☐ myocardial infarction year of diagnosis ☐☐☐☐
☐ joint degeneration disease year of diagnosis ☐☐☐☐
☐ diabetes year of diagnosis ☐☐☐☐
☐ tumours (other than pituitary) year of diagnosis ☐☐☐☐
description .....
year of diagnosis ☐☐☐☐
description .....
☐ bone fracture year of diagnosis ☐☐☐☐ location ... .
year of diagnosis ☐☐☐☐ location ... .
year of diagnosis ☐☐☐☐ location ... .
Other chronic diseases: ☐Y — yes; ☐ N — no
If so, describe .....
.....
.....
.....
.....

7. Significant family history:

Were there in the closest family (parents or siblings) any cases of:

vascular and cardiac diseases ☐ Y — yes; N — no; NA — no data available
hip fracture ☐ Y — yes; N — no; NA — no data available
tumours ☐ Y — yes; N — no; NA — no data available
benign ☐ Y — yes; N — no; NA — no data available
malignant ☐ Y — yes; N — no; NA — no data available

8. Medical history regarding growth hormone deficiency:

Year of diagnosis of growth hormone deficiency ☐☐☐☐ year

<u>The primary cause of growth hormone deficiency:</u>

☐ pituitary tumour or its treatment
type of pituitary tumour: ☐ non-functioning; ☐ secreting ACTH
☐ secreting GH; ☐ secreting prolactin
☐ gonadotropin-secreting; ☐ secreting TSH
☐ unknown
☐ craniopharyngioma
☐ surgical procedures (other than pituitary surgery)
☐ irradiation (other than irradiation of the pituitary)
☐ idiopathic
☐ injuries
☐ other, describe ……
……...

Was the patient treated surgically due to a pituitary disease? ☐ Y — yes; N — no
If so, please enter the number of surgical interventions: ☐
Details of the last three operations:

year ☐☐☐☐	year ☐☐☐☐	year ☐☐☐☐	
Operation type: transcranial	☐	☐	☐
transsphenoidal	☐	☐	☐

Was the patient treated with radiotherapy due to a pituitary disease?
external: ☐ year ☐☐☐☐
stereotaxic: ☐ year ☐☐☐☐

9. Current clinical status:

<u>Clinical examination</u>:
Main symptoms:
☐ weakness, ☐ easy fatigability, ☐ constant fatigue,
☐ lowered mood, ☐ reduced life energy
☐ deterioration of social contacts with an intensified tendency to isolation
☐ disorder of emotional reactions,
☐ sense of deterioration of the quality of life
☐ no sense of health
Others, description .....
.....

<u>Psychological examination:</u>
Psychological test for quality of life (QoL-AGHDA test) assessment .....
.....
.....
.....
Others .....
.....
.....

<u>Vital signs</u> — date ☐☐-☐☐-☐☐☐☐ day - month - year
Height: ☐☐☐,☐ cm Body weight: ☐☐☐ kg BMI ☐☐,☐ kg/m^2

Waist circumference: ☐☐☐ cm Hip circumference: ☐☐☐ cm WHR ☐☐,☐
Blood pressure: ☐☐☐/☐☐☐ mmHg
Heart rate: ☐☐☐/min
Abnormalities in clinical examination:
Head: .....
Neck: .....
Chest: ……..
Circulatory system: .....
Respiratory system: .....
Abdomen: .....
Nervous system: .....
Genitals: .....
Others: .....

10. Laboratory tests:

GH secretion stimulatory tests
date ☐☐ - ☐☐ - ☐☐☐☐ way of stimulation ..... max GH ☐☐. ☐ unit .....
date ☐☐ - ☐☐ - ☐☐☐☐ way of stimulation ..... max GH ☐☐. ☐ unit .....
For the insulin test, please provide the baseline and the lowest blood glucose concentrations:
Result ☐☐☐☐.☐ unit ...., Result ☐☐☐☐.☐ unit ....
date ☐☐-☐☐-☐☐☐☐ ☐ diurnal profile max GH ☐☐.☐ unit .....
mean concentration of GH ☐☐.☐ unit .....
Has a deficiency of other pituitary hormones been diagnosed? (Y — yes, N — no)
☐ TSH deficiency year of diagnosis ☐☐☐☐ ☐ replacement therapy
☐ ACTH deficiency year of diagnosis ☐☐☐☐ ☐ replacement therapy
☐ LH / FSH deficiency year of diagnosis ☐☐☐☐ ☐ replacement therapy
☐ ADH deficiency year of diagnosis ☐☐☐☐ ☐ replacement therapy

Current laboratory results:

Test	Date	Result	Units	Reference range
TSH				
FT4				
FT3				
Cortisol				
ACTH				
Prl				
LH				
FSH				
IGF-I				
IGFBP-3				
Serum glucose				
Glycated haemoglobin concentration				

Renal function tests …….
Liver tests …….

Lipids:

Test	date	result	unit	reference range
Total cholesterol				
LDL-cholesterol				
HDL-cholesterol				
Triglycerides				
Lp(a)				

Densitometry: .....
.....date of examination ☐☐-☐☐-☐☐☐☐
Method: .....

	Z-score	T-score	BMD [g/cm]	BMC [kg]	Comments
Lumbar spine					
Femoral neck					
Whole body					
Others					
Others					

Assessment of body composition .....
.....
.....
Resting ECG.....
.....
.....
.....
.....
Cardiac stress test.....
.....
.....
.....
.....
ECHOCARDIOGRAPHY .....
.....
.....
MRI or CT scan performed within the last six months
☐ Y — yes; N — no
If so, describe .....
.....
.....
.....
.....
Others:
.....
.....
.....
.....

11. Has rhGH replacement therapy ever been used before?
☐ Y — yes; N — no
If so, was it in childhood (childhood onset GHD)? ☐ Y — yes; N — no
Or was it after 18 years of age (adult-onset GHD)? ☐ Y — yes; N — no
If in childhood:
Date of starting rhGH treatment ☐☐-☐☐☐☐ month — year
Date of cessation of rhGH treatment ☐☐-☐☐☐☐ month — year
Were there any complications during treatment with rhGH? ☐ Y — yes; N — no
If so, please describe.....
If after 18 years of age:
Beginning of treatment ☐☐ - ☐☐☐☐ month — year
Duration of treatment ☐☐ months
Is the patient still on therapy? ☐ T — yes; N — no
If not, enter the date of the last injection ☐☐ - ☐☐☐☐ month — year

If so, enter the exact date of the beginning of the current treatment period
☐☐-☐☐-☐☐☐☐ day — month — year
Were there any complications during treatment with rhGH? ☐ Y — yes; N — no
If so, describe .....
.....

12. List all the medicines currently used by the patient:
name of the drug ……..…. dose……treatment onset ☐☐-☐☐☐☐ month — year
name of the drug ……..…. dose……treatment onset ☐☐-☐☐☐☐ month — year
name of the drug ……..…. dose……treatment onset ☐☐-☐☐☐☐ month — year
name of the drug ……..…. dose……treatment onset ☐☐-☐☐☐☐ month — year
name of the drug ……..…. dose……treatment onset ☐☐-☐☐☐☐ month — year
name of the drug ……..…. dose……treatment onset ☐☐-☐☐☐☐ month — year

13. Comments:
.....
.....
Unit/department completing the application: Date of issue: ☐☐-☐☐-☐☐☐☐
Full name: .....
Address: .....
Telephone/fax: .....
The physician issuing the application:
First name and last name
.....

Signature and stamp

Head of the unit/department issuing the application:

Signature and stamp:

Appendix 4

Stamp of the centre issuing the application:

OBSERVATION CHART OF A PATIENT TREATED WITH rhGH DUE TO GROWTH HORMONE DEFICIENCY
(fill in every 12 months)

1. Patient's personal data:
Surname and first name of the patient:
.....
Date of birth: ☐☐-☐☐-☐☐☐☐ day — month — year
Personal identity number ☐☐☐☐☐☐☐☐☐☐☐
Date of patient examination: ☐☐-☐☐-☐☐☐☐ day — month — year

2. Current clinical status:
a) Clinical examination:
Main symptoms:
☐ weakness, ☐ easy fatigability, ☐ constant fatigue,
☐ lowered mood, ☐ reduced life energy
☐ deterioration of social contacts with an intensified tendency to isolation
☐ disorder of emotional reactions,
☐ sense of deterioration of the quality of life
☐ no sense of health

Others, describe .....
.....
.....

b) Psychological examination:

Psychological test for quality of life (QoL-AGHDA test) assessment .....
.....
.....
.....
Others ……
……
……...

Vital signs - date ☐☐-☐☐-☐☐☐☐ day — month — year
Height: ☐☐☐.☐ cm Body weight: ☐☐☐ kg BMI ☐☐.☐ kg/m^2
Waist circumference: ☐☐☐ cm Hip circumference: ☐☐☐ cm WHR ☐☐,☐
Blood pressure: ☐☐☐/☐☐☐ mmHg
Heart rate: ☐☐☐/min
Abnormalities in clinical examination:
Head: .....
Neck: .....
Chest: .....
Circulatory system: .....
Respiratory system: .....
Abdomen: .....
Nervous system: .....
Genitals: ……
Others: .....

c) Laboratory tests:

Test	date	result	units	reference range
IGF-I				
TSH				
FT_4				
cortisol				
Serum glucose				
Glycated haemoglobin				

Lipids:

Test	date	result	unit	reference range
Total cholesterol				
LDL-cholesterol				
HDL-cholesterol				
Triglycerides				
Lp(a)				

Renal function tests .....
Liver tests .....
Densitometry: .....
.....
Date of examination ☐☐-☐☐-☐☐☐☐
Method: ……

	Z-score	T-score	BMD g/cm	BMC kg	Comments
Lumbar spine					
Femoral neck					
Whole body					
Others					
Others					

Body composition .....
.....
.....
MRI or CT performed in the last six months
Date ☐☐-☐☐-☐☐☐☐
.....
.....
Others: .....

3. The course of therapy:
Beginning of treatment ☐☐-☐☐☐☐ month — year
Duration of treatment ☐☐ months
Have there been any interruptions in therapy since the last observation? ☐ Y — yes; N — no
Preparation ..... dose..... ...
Treatment schedule ....
Have there been any complications during treatment with rhGH? ☐ T — yes; N — no
If so, describe
……..

4. List all the medicines currently used by the patient:
name of the drug ……..…. dose……treatment onset ☐☐-☐☐☐☐ month — year
name of the drug ……..…. dose……treatment onset ☐☐-☐☐☐☐ month — year
name of the drug ……..…. dose……treatment onset ☐☐-☐☐☐☐ month — year
name of the drug ……..…. dose……treatment onset ☐☐-☐☐☐☐ month — year
name of the drug ……..…. dose……treatment onset ☐☐-☐☐☐☐ month — year
name of the drug ……..…. dose……treatment onset ☐☐-☐☐☐☐ month — year
Date of issue: ☐☐-☐☐-☐☐☐☐
Unit/department completing the application:
Full name: .....
Address: .....
Telephone / fax: .....
The physician issuing the application:
First name and last name
.....

Signature and stamp

Head of the unit/department issuing the application:

Signature and stamp:

Appendix 5

NATIONAL PROGRAM OF SEVERE GROWTH HORMONE DEFICIENCY TREATMENT IN ADULTS AND ADOLESCENTS AFTER COMPLETION OF GROWTH-PROMOTING THERAPY (ICD-10 E23.0)

BENEFICIARIES

Patients are qualified for the Program by the Growth Hormone Treatment Coordination Team.

1. Inclusion criteria

1) symptoms of growth hormone deficiency;
2) IGF-I concentration below the normal range or within lower range of normal values;
3) confirmation of severe GH deficiency on the basis of:
   a) in adults not treated in childhood due to GHD (AO-GHD) — decreased GH secretion (below 3 ng/ml) in 2 different stimulation tests in the case of isolated GHD or in 1 stimulation test in the case of multi-hormonal pituitary insufficiency (tests must be performed after proper correction of at least cortisol and L-thyroxine deficiency);
   b) in adolescents and adults previously treated for GHD (CO-GHD) — decreased GH secretion (less than 3 ng/ml) in 2 different stimulation tests in isolated GHD or in 1 stimulation test in the case of multi-hormonal pituitary insufficiency (tests must be performed after proper correction of at least cortisol and L-thyroxine deficiency);
   c) in the presence of multi-hormonal pituitary insufficiency in all axes (except prolactin) and confirmation of the morphological or genetic cause of this condition, it is possible to avoid stimulation tests and to grant rhGH treatment based on a decreased IGF-I concentration.
4) no contraindications to GH therapy, based on the results of laboratory or imaging tests (in particular contrast MRI or CT of the hypothalamic-pituitary area) in order to exclude active neoplastic process.

All the inclusion criteria must be met.

2. Determining the period of treatment in the program

Treatment lasts until the attending physician or the Coordination Team decides to exclude the beneficiary from the program, according to the exclusion criteria.

3. Exclusion criteria

1) new diagnosis or recurrence of active cancer process;
2) severe life-threatening conditions;
3) diabetes that cannot be properly compensated on the treatment with rhGH
4) persistently elevated IGF-I concentration, despite the dose reduction to the minimum (0.1 mg/day);
5) occurrence of new metabolic disorders or worsening of the existing ones and deterioration of the quality of life (assessment after 12 and 24 months);
6) lack of consent of the beneficiary to continue treatment or lack of cooperation of the beneficiary.

PRINCIPLES OF DRUG DOSING IN THE PROGRAM

1. Dosing

Somatropin injections every evening in the daily dose of: 0.1–0.8 mg

DIAGNOSTIC TESTS PERFORMED IN THE PROGRAM

1. Qualification tests:

1) assessment of body weight and waist circumference (BMI and WHR), recommended: assessment of body composition by bioimpedance method;
2) measurement of blood pressure;
3) blood count with smear;
4) serum ionogram (at least Na, K and Ca concentrations);
5) IGF-I concentration;
6) blood glucose and the percentage of glycated haemoglobin (HbA_1c) or an oral glucose tolerance test, with the assessment of glucose and insulin levels
7) triglyceride, total cholesterol, HDL-cholesterol, and LDL-cholesterol levels;
8) TSH and FT_4 levels;
9) morning cortisol;
10) evaluation of quality of life (QoL) with a special questionnaire
11) 1 or 2 GH stimulation tests;
12) hypothalamic-pituitary imaging (contrast MRI or CT);
13) abdominal US;
14) ECG, optionally echocardiography;
15) fundoscopy;
16) other tests and consultations, as needed.

2. Treatment monitoring

2.1 After 30 days from the beginning of the treatment

1) assessment of IGF-1 concentration to determine the optimal dose of the drug.

2.2. Every 180 days

1) assessment of body weight and waist circumference (BMI and WHR), recommended: assessment of body composition by bioimpedance method;
2) measurement of blood pressure;
3) serum ionogram (at least Na and Ca concentration measurements);
4) glycated haemoglobin HBA1c;
5) IGF-I concentration;
6) TSH and FT4 levels;
7) triglyceride, total cholesterol, HDL-cholesterol, and LDL-cholesterol concentrations;
8) QoL evaluation;
9) other tests and consultations depending on the need.

3. Program monitoring

1) medical documentation of the treated patient should include data regarding the treatment monitoring and should be presented on every request of the controllers of the National Health Foundation (NFZ);
2) completion of data contained in the SMPT (Therapeutic Program Monitoring System) registry available via the web application provided by the Regional Branch of the NFZ, at a frequency consistent with the description of the program and at the end of treatment;
3) providing reports and financial data to the National Health Fund (NFZ): information is provided to the NFZ by paper or electronically, in accordance with the requirements published by the NFZ.