Pharmaceuticals and Medical Devices Safety Information

No. 392

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Available information is listed here

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Pharmaceuticals and Medical Devices Safety Information

No. 392

Ministry of Health, Labour and Welfare
Pharmaceutical Safety and Environmental Health Bureau, Japan

[Outline of Information]

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E: Distribution of Dear Healthcare Professional Letters of Emergency Communications, *R:* Distribution of Dear Healthcare Professional Letters of Rapid Communications, *P*: Revision of Precautions, *C*: Case Reports

Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of medical and pharmaceutical providers.

If medical and pharmaceutical providers such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, please report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As medical and pharmaceutical providers, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Please utilize the Report Reception Site for reporting.
(This service is only available in Japanese.)
https://www.pmda.go.jp/safety/reports/hcp/0002.html

Abbreviations

ADR	Adverse drug reaction
DKA	Diabetic ketoacidosis
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal Year
GH	growth hormone
IFN	Interferon
IGF-1	Insulin-like growth factor-1
JDIIP	Japan Drug Information Institute in Pregnancy
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
NCCHD	National Center for Child Health and Development
PMDA	Pharmaceuticals and Medical Devices Agency
PSD	Pharmaceutical Safety Division
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
VEGF	vascular endothelial growth factor

1
Revision of Precautions for Somatropin (genetical recombination)

1. Introduction

Somatropin (genetical recombination) (hereinafter referred to as “somatropin”), a recombinant human growth hormone preparation, is approved for marketing in Japan with the indication for growth hormone-deficient short stature without epiphyseal closure, adult growth hormone deficiency, etc.

Recently, CONTRAINDICATIONS, etc. for somatropin have been revised based on the deliberation in the 31st Fiscal year (FY) 2021 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (hereinafter referred to as "the Subcommittee on Drug Safety") held on March 22, 2022. This section will introduce the details of the revision.

2. Background

Because growth hormone (hereinafter referred to as “GH”) has anti-insulin-like effects, administration of somatropin to patients with diabetes mellitus has been contraindicated from the time of initial approval.

In March 2021, The Japan Endocrine Society and the Japanese Society for Pediatric Endocrinology submitted a request to revise “CONTRAINDICATIONS” regarding patients with diabetes mellitus be changed to “Careful Administration” in the “Precautions” of somatropin. The main reasons for the request from the academic societies are as follows.

- It has been pointed out that treatment with somatropin may improve insulin resistance in the long term in patients with concurrent type 2 diabetes mellitus with inadequate glycaemic control. Although the US guideline states that higher doses of antidiabetic drugs may be required due to treatment with somatropin, the guideline does not contraindicate administration in patients with diabetes mellitus.
- Even in the patients with concurrent type 1 diabetes mellitus, cases have been reported that diabetes mellitus could be controlled with somatropin treatment by appropriately adjusting the dose of insulin.
- In the major nations of Europe, the US, and Australia, patients with diabetes mellitus are not contraindicated, requiring special caution instead.
- For somapacitan (genetical recombination), which is a long-acting growth hormone analogue and was approved in 2021, because no safety concerns that require contraindicating patients with diabetes mellitus were identified in the phase Ⅲ study, this drug is not contraindicated in patients with diabetes mellitus.

Taking into account the requests from the academic societies, the Subcommittee on Drug Safety has discussed revision of CONTRAINDICATIONS, etc.

3. Deliberation by the Subcommittee on Drug Safety

The statements in Japanese and overseas guidelines, overseas package inserts, the adverse reaction reports, pertinent published literature, the results of post-marketing surveillance studies, etc. are as follows.

(1) Deleting patients with diabetes mellitus from the CONTRAINDICATIONS section was considered possible for the following reasons:

- While only a limited number of drugs for diabetes mellitus were available in 1988 when

somatropin was first approved in Japan, options for diabetic treatment have increased since then at present, and it is considered that patients with diabetes mellitus under adequate control have increased. For indications such as adult growth hormone deficiency, on the other hand, no other options than GH treatment are available.

- Overseas package inserts, clinical practice guidelines and standard textbooks do not contraindicate patients with diabetes mellitus, requiring special caution instead.
- As a result of a detailed investigation of cases of adverse reactions reported in Japan, serious adverse reactions related to glucose metabolism were observed following administration of somatropin to patients with diabetes mellitus. Such serious adverse reactions have been adequately controlled by temporal discontinuation of somatropin or initiation of antidiabetic drugs.
- Several cases without serious adverse reactions related to glucose metabolism have been reported following administration of somatropin to patients with concurrent diabetes mellitus in published literature discussing the safety of administration of somatropin to patients with concurrent diabetes mellitus, as well as Japanese and overseas post-marketing surveillance.

(2) If patients with diabetes mellitus are removed from the CONTRAINDICATIONS section, it is considered that precautions be required regarding patients with diabetes mellitus for the following reasons:

- The pharmacological effects of somatropin that may elevate blood glucose levels associated with the reduction in insulin sensitivity could deteriorate conditions of diabetes mellitus.
- Cases of adverse reactions have been reported in Japan in which a causal relationship between the adverse reactions related to glucose metabolism observed following administration of somatropin to the patients with concurrent diabetes mellitus and the drug was reasonably possible.
- Clinical practice guidelines and standard textbooks overseas recommend against administering somatropin to patients with concurrent inadequately controlled diabetes mellitus, and a certain package insert of somatropin notes “patients with Prader-Willi syndrome who have inadequately controlled diabetes” as a contraindication for the drug. Therefore, adequate control and monitoring of diabetes mellitus before and after starting administration of somatropin, respectively, are considered to be important.

(3) Among the indications of somatropin, Prader-Willi syndrome and Turner’s syndrome are more likely to have diabetes mellitus concurrently than other indications because reduced glucose tolerance may occur. Therefore, it is considered that a cautionary statement is necessary for all somatropin preparations with these indications that close monitoring of the clinical course is required in the IMPORTANT PRECAUTIONS section.

(4) It is considered unnecessary that patients with diabetic retinopathy be contraindicated for the following reasons:

- Among patients with concurrent diabetes mellitus, those with proliferative or severe nonproliferative (preproliferative) diabetic retinopathy are noted as a contraindication in certain overseas package inserts, Japanese and overseas guidelines and overseas standard textbooks. However, some overseas guidelines do not contraindicate these patients, thus no consensus has been reached.
- While GH has been reported as promoting the synthesis and secretion of insulin-like growth factor-1 (hereinafter referred to as “IGF-1”) and IGF-1 has been reported as being involved in the pathogenesis and progress of diabetic retinopathy, non-involvement of GH treatment in the retinal conditions has been also reported.
- At present, it has been reported that vascular endothelial growth factor (hereinafter referred to as VEGF) is the most significant among the factors driving diabetic retinopathy, and actually, anti-VEGF agents have become the most widely adopted

treatment of diabetic retinopathy.

However, because of the possibility for somatropin, with its proliferative effect, to exacerbate conditions of diabetic retinopathy, it was considered necessary to add a cautionary statement regarding diabetic complications including diabetic retinopathy in the PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS section.

4. Closing remark

Healthcare professionals are requested to understand the gist of the revision this time and to carefully check the electronic package inserts for a careful decision on the use of somatropin. Continued cooperation by healthcare professionals for proper use of this drug would be appreciated.

[References]

- Materials 1-1 to 1-4 of the 31st FY 2021 Subcommittee on Safety Measures of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (held on March 22, 2022)
  https://www.mhlw.go.jp/stf/newpage_24579.html (only in Japanese)
- Revision of Precautions (PSEHB/PSD Notification No. 0404-1 dated April 4, 2022)
  https://www.pmda.go.jp/files/000245822.pdf (only in Japanese)
  English translation by PMDA (April 4, 2022)
  https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0010.html

2
Revisions of Precautions for Interferon Beta-1a (genetical recombination) and Interferon Beta-1b (genetical recombination)

1. Introduction

Interferon beta-1a (genetical recombination) (hereinafter referred to as "IFNβ-1a") was approved in July 2006 for the indication of "prevention of relapse in multiple sclerosis," and interferon beta-1b (genetical recombination) (hereinafter referred to as IFNβ-1b) was approved in September 2000 for the indication of "prevention of relapse and delaying the progression in multiple sclerosis."

Administration of IFNβ-1a and IFNβ-1b to pregnant women or women who may be pregnant has been contraindicated since the time of approval, and it has been stated in the Pregnant Women section that IFNβ-1a or IFNβ-1b should not be administered to pregnant women or women who may be pregnant, because spontaneous abortions have been reported as observed in an animal study (monkeys) at higher doses of IFNβ-1a and IFNβ-1b.

Recently, CONTRAINDICATIONS, etc. for IFNβ-1a and IFNβ-1b have been revised based on the deliberation in the 31st Fiscal year (FY) 2021 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (hereinafter referred to as "the Subcommittee on Drug Safety") held on March 22, 2022. This section will introduce the details of the revision.

2. Background

The marketing authorization holder of IFNβ-1a has requested a consultation for removal of the language concerning pregnant women or women who may be pregnant in the CONTRAINDICATIONS section of the Precautions of IFNβ-1a and for revision of the language in the Pregnant Women section into a precaution that the drug should be administered to pregnant women or women who may be pregnant only if the potential therapeutic benefits are considered to outweigh the potential risks, with the results of the overseas registry studies in pregnant women with multiple sclerosis treated with IFNβ-1a or IFNβ-1b (hereinafter referred to as "overseas registry studies") as the major basis.

And also, the marketing authorization holder of IFNβ-1b requested a consultation with the intention to add the summary of the results, etc. of the overseas registry studies in the Pregnant Women section.

Based on these consultations, the Subcommittee on Drug Safety has discussed revision of CONTRAINDICATIONS, etc.

3. Deliberation by the Subcommittee on Drug Safety

As a result of evaluation on the overseas registry studies, Japanese and overseas guidelines, overseas package inserts, adverse drug reactions reports, published literature, etc., it was considered possible, for the following reasons, that pregnant women or women who may be pregnant may be deleted from the CONTRAINDICATIONS section as well as specifying a cautionary statement that pregnant women or women who may be pregnant should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks.

- Taking into account that foetal deaths and spontaneous abortions were observed at 200

or more times the human clinical dose for IFNβ-1b and the exposure levels of the group in which spontaneous abortions were observed are considered comparable to 83 to 163 times the exposure level for the human clinical dose of IFNβ-1a, the blanket contraindication in pregnant women or women who may be pregnant is not considered substantially required.

- The overseas registry studies, other epidemiological studies and literature reports have not necessarily suggested the possibility of an increase in the risks of spontaneous abortions and congenital anomalies.
- The Australian package insert contraindicates administration of IFNβ-1a to pregnant women, while the US package inserts do not contraindicate but recommend administration of IFNβ-1a and IFNβ-1b with potential benefits against expected risks considered. The EU package inserts of IFNβ-1a and IFNβ-1b had initially placed at the time of initial approval but later lifted a contraindication in 2019 based on the results of the overseas registry studies. In addition, the EU guideline already stated prior to the lifting of the contraindication in the EU that administration of IFNβ-1a and IFNβ-1b may be considered as a therapeutic option in pregnant women.
- The Japanese guideline states that declined relapse rates during pregnancy or the early postpartum period have been reported in pregnant women with multiple sclerosis who continued disease-modifying drugs up to their first trimester compared with the group of pregnant women with untreated multiple sclerosis. This is considered to indicate that allowing administration of IFNβ-1a and IFNβ-1b would add a treatment option for prevention of multiple sclerosis relapse in the early postpartum period, thereby having a certain medical significance.

4. Closing remark

Healthcare professionals are requested to understand the gist of the revision this time and to carefully check the electronic package inserts for a careful decision on the use of IFNβ-1a and IFNβ-1b. Continued cooperation by healthcare professionals for proper use of these drugs would be appreciated.

[References]

- Materials 2-1 to 2-3 of the 31st FY 2021 Subcommittee on Safety Measures of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (held on March 22, 2022)
  https://www.mhlw.go.jp/stf/newpage_24579.html (only in Japanese)
- Revision of Precautions (PSEHB/PSD Notification No. 0404-2 dated April 4, 2022)
  https://www.pmda.go.jp/files/000245823.pdf (only in Japanese)
  English translation by PMDA (April 4, 2022)
  https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0010.html

3
New Project Development of the “Japan Drug Information Institute in Pregnancy”

1. Project of the Japan Drug Information Institute in Pregnancy

When drugs are used during pregnancy, attention must be paid to the effects on the fetus as well as on the mother. On the other hand, due to difficulties with obtaining safety information on drug use during pregnancy, women who are receiving drug therapy for pre-existing diseases may choose to avoid pregnancy or to discontinue taking prescribed necessary medications, which is an undesirable behavior. In addition, women who used drugs without realizing that they are pregnant become concerned about continuation of the pregnancy.

In 2005, the National Center for Child Health and Development (NCCHD) established the Japan Drug Information Institute in Pregnancy (JDIIP) on behalf of the Ministry of Health, Labour and Welfare (MHLW) to collect and assess the latest scientific evidence on the effects of drugs on mothers and fetuses. Based on these data, the JDIIP has provided consultations for approximately 20 000 women who are pregnant or who wish to become pregnant. The JDIIP conducted research by using a questionnaire among consultation clients, and reported that those clients tend to overestimate the risks of congenital anomalies in fetuses associated with drug exposure during pregnancy and that appropriate counseling decreased the overestimation of the risks and led to continued pregnancies (2018), objectively demonstrating the usefulness of this consultation project. [1)]

In addition, the JDIIP follows up consultation cases to generate new evidence. Recent results include research reports on the safety evaluation of migraine drugs, atypical antipsychotics, and antiemetics.

As well as counseling and evidence generation, the JDIIP reviews the descriptions on drug use in pregnant women in the package inserts of drugs as a project commissioned by the MHLW to promote the proper use of drugs for pregnant and breast-feeding women. In 2018, this project led to a revision in the use of tacrolimus, cyclosporine, and azathioprine, which are immunosuppressants, during pregnancy from contraindications to beneficial administration.

2. Core Hospitals

In order to strengthen the consultation system and to improve the convenience of consultation clients, the JDIIP has been conducting “Outpatient services for pregnancy and drugs” with the participation of medical institutions throughout Japan (Figure 1). In FY 2017, the assignment of ‘core’ hospitals was completed in all 47 prefectures and metropolitan areas (described in No. 343), and the number of core hospitals is 56 as of April 2022.

The JDIIP and core hospitals collaborate not only in consultation but also in research. An ongoing registry study on COVID-19 during pregnancy has enrolled approximately 150 subjects as of April 2022, and a registry study on pregnancy-associated hypertension has enrolled approximately 150 subjects, enabling the collection of registry data on a scale that could not be achieved at a single institution.

Physicians and pharmacists at core hospitals not only update their knowledge through annual training sessions but also exchange information among themselves, working together to promote and raise the awareness of proper drug use in pregnant and breast-feeding women in Japan. In addition, the JDIIP promotes collaboration between pharmacists at various core hospitals and at regional pharmacies, with core hospitals nationwide as the core.

Figure 1　List of Core Hospitals of JDIIP　≪2022≫

Core Hospitals Name

Hokkaido/Tohoku region
Hokkaido : Hokkaido University Hospital
Aomori : Hirosaki University Hospital
Iwate : Iwate Medical University Hospital
Akita : Japanese Red Cross Akita Hospital
Yamagata : Yamagata University Hospital
Miyagi : Tohoku University Hospital
Fukushima : Fukushima Medical University Hospital

Kanto region
★Tokyo : National Center for Child Health and Development
Ibaraki : University of Tsukuba Hospital
Tochigi : Saiseikai Utsunomiya Hospital
Tochigi : Jichi Medical University Hospital
Gunma : Japanese Red Cross Maebashi Hospital
Saitama : Saitama Medical University Hospital
Saitama : Jichi Medical University Saitama Medical Center
Chiba : Chiba University Hospital
Kanagawa : Yokohama City University Hospital
Tokyo : Toranomon Hospital

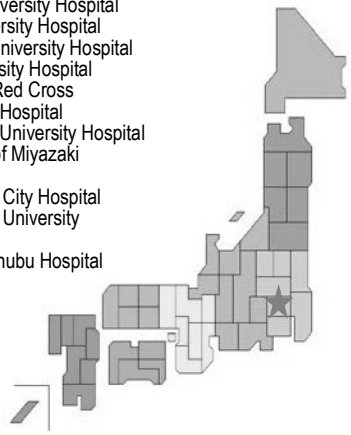
Chubu region
Yamanashi : Yamanashi Prefectural Central Hospital
Niigata : Niigata University Medical & Dental Hospital
Nagano : Shinshu University Hospital
Toyama : Toyama University Hospital
Ishikawa : National Hospital Organization Kanazawa Medical Center
Fukui : University of Fukui Hospital
Shizuoka : Hamamatsu University Hospital
Aichi : Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital
Aichi : Nagoya City University Hospital
Gifu : National Hospital Organization Nagara Medical Center
Gifu : Gifu University Hospital

Kinki region
Mie : Mie University Hospital
Shiga : Shiga University of Medical Science Hospital
Kyoto : University Hospital, Kyoto Prefectural University of Medicine
Nara : Nara Medical University Hospital
Osaka : Osaka Prefectural Hospital Organization Osaka Women's and Children's Hospital
Osaka : Osaka University Hospital
Osaka : Osaka Medical and Pharmaceutical University Hospital
Wakayama : Japanese Red Cross Wakayama Medical Center
Hyogo : Kobe University Hospital

Chugoku region
Tottori : Tottori University Hospital
Okayama : National Hospital Organization Okayama Medical Center
Okayama : Okayama University Hospital
Shimane : Shimane University Hospital
Hiroshima : Hiroshima University Hospital
Yamaguchi : Yamaguchi University Hospital

Shikoku region
Tokushima : Tokushima University Hospital
Kagawa : National Hospital Organization Shikoku Medical Center for Children and Adults
Ehime : Ehime University Hospital
Kochi : Kochi Medical School Hospital

Kyusyu/Okinawa region
Fukuoka : Kyushu University Hospital
Saga : Saga University Hospital
Nagasaki : Nagasaki University Hospital
Oita : Oita University Hospital
Kumamoto : Japanese Red Cross Kumamoto Hospital
Kumamoto : Kumamoto University Hospital
Miyazaki : University of Miyazaki Hospital
Kagoshima : Kagoshima City Hospital
Kagoshima : Kagoshima University Hospital
Okinawa : Okinawa Chubu Hospital



3. Computerization of Consultation Method

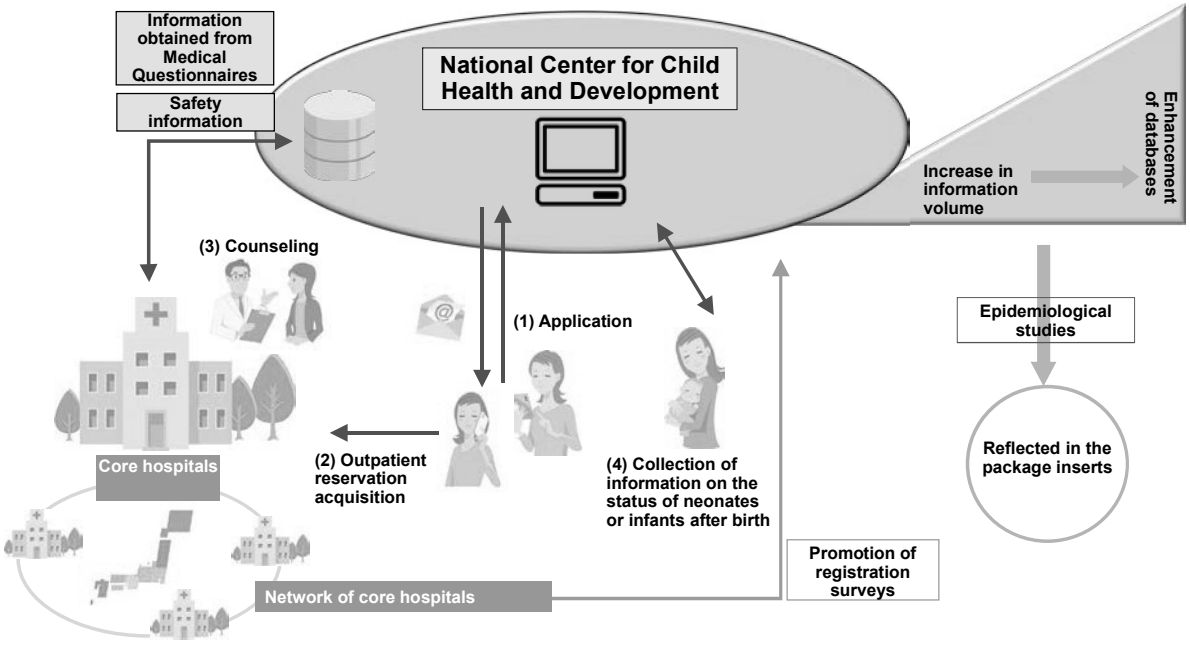
The Secretariat had previously confirmed the completed paper Medical Questionnaire sent by post from a consultation client, and adjusted the consultation method in consideration of the client's request and characteristics of the drug. In the previous method, there were problems such as that consultation clients needed to print out the Medical Questionnaire and to send it by post, and that it took time from application to counseling, which might have made it difficult for modern young women to access consultation services, and that those services might not have been adequately available for patients who had potential needs for counseling.

In terms of evidence generation, the JDIIP has conducted research analyses based on consultation cases; however, it has gradually turned out that, in order to generate evidence for drugs for chronic diseases and new drugs, not only consultation case studies but also prospective registration surveys need to be conducted proactively. The JDIIP should function as a platform for these surveys.

Therefore, through the MHLW project for the promotion of JDIIP advancement in 2021, a new system was established to create a registry as well as to computerize applications from patients and collaborations with the core hospitals, and this system was launched in May (Figure 2). Consultation clients can make simple applications from smartphones and personal computers, and at core hospitals, drug information can be accessed online immediately, which reduces the time lag from application to counseling. The manner of consultation will be integrated into counseling at core hospitals with high-level expertise to increase accuracy. Regarding registration surveys, more efficient and effective epidemiological surveys can be conducted by using the new system, in addition to recruitment using the network of core hospitals.

As described above, the new system is expected to enable core hospitals nationwide to become more active leaders in this field in their region and to form more robust networks with the JDIIP.

Figure 2



4. To Healthcare Professionals

Healthcare professionals are encouraged to introduce the consultation services of the “Japan Drug Information Institute in Pregnancy (JDIIP)” to women who are concerned about the safety of drugs during pregnancy.

If a woman visits a core hospital for the “Outpatient service for pregnancy and drugs” with an information provision document prepared by a physician, a reply will be sent to the referring physician after counseling.

For a JDIIP leaflet, please contact the JDIIP at its main number (+81-3-5494-7845) (10:00-12:00, 13:00-16:00 on weekdays).

[References]

○ Japan Drug Information Institute in Pregnancy (National Center for Child Health and Development)
https://www.ncchd.go.jp/en/center/activity/JDIIP/overview.html
https://www.ncchd.go.jp/kusuri/ (only in Japanese)

(only in Japanese)

○ Relevant Past Articles

1) Pharmaceuticals and Medical Devices Safety Information No. 343 (May 2017):
“Project of the Japan Drug Information Institute in Pregnancy”
https://www.pmda.go.jp/files/000218142.pdf

2) Pharmaceuticals and Medical Devices Safety Information No. 355 (August 2018):
“Review of Contraindications for Immunosuppressants in Pregnant Women, etc.”
https://www.pmda.go.jp/files/000225335.pdf

Reference Literature

1) Yakuwa-n et al., Perception of pregnant Japanese women regarding the teratogenic risk of medication exposure during pregnancy and the effect of counseling through the Japan drug information institute in pregnancy. Reprod Toxicol. 2018;79:66-71.

4

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated May 13, 2022, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 [1] Dexamethasone (oral dosage form) (preparations indicated for pituitary suppression tests)
[2] Dexamethasone (oral dosage form) (preparations not indicated for pituitary suppression tests)
[3] Dexamethasone sodium phosphate (injections)
[4] Dexamethasone palmitate
[5] Betamethasone (oral dosage form)
[6] Betamethasone (suppositories)
[7] Betamethasone sodium phosphate (injections)
[8] Betamethasone sodium phosphate (enemas)
[9] Betamethasone acetate/betamethasone sodium phosphate
[10] Betamethasone/d-chlorpheniramine maleate

Brand name (name of company)	[1] Decadron Tablets 0.5 mg, 4 mg, Decadron Elixir 0.01% (Nichi-Iko Pharmaceutical Co., Ltd.), and the others [2] LenaDex Tablets 2 mg, 4 mg (Bristol-Myers Squibb K.K.) [3] Decadron Phosphate Injection 1.65 mg, 3.3 mg, 6.6 mg (Sandoz Pharma K.K.), and the others [4] Limethason Intravenous Injection 2.5 mg (Mitsubishi Tanabe Pharma Corporation) [5] Rinderon Tablets 0.5 mg, Rinderon Powder 0.1%, Rinderon Syrup 0.01% (Shionogi Pharma Co., Ltd.), and the others [6] Rinderon Suppositories 0.5 mg, 1.0 mg (Shionogi Pharma Co., Ltd.) [7] Rinderon Injection 2 mg (0.4%), 4 mg (0.4%), 20 mg (0.4%), 20 mg (2%), 100 mg (2%) (Shionogi Pharma Co., Ltd.), and the others [8] Steronema Enema 3 mg, 1.5 mg (Nichi-Iko Pharmaceutical Co., Ltd.) [9] Rinderon Suspension (Shionogi Pharma Co., Ltd.) [10] Celestamine Combination Tablets, Celestamine Combination Syrup (TAKATA Pharmaceutical Co., Ltd.), and the others
Therapeutic category	Adrenal hormone preparations
Indications	Please refer to the electronic package insert of each drug.

PRECAUTIONS (revised language is underlined)

[Under old instructions]	[1] Dexamathasone (oral dosage form) (Preparations indicated for pituitary suppression tests)
(newly added)	<u>Precautions concerning Indications</u>

	Prior to conducting dexamethasone suppression tests, the presence or absence of concurrent phaeochromocytoma or paraganglioma should be confirmed. If such complications are present, treatment of phaeochromocytoma or paraganglioma should be prioritized.
Careful Administration (newly added)	Patients with phaeochromocytoma or paraganglioma and those with suspected phaeochromocytoma or paraganglioma [Phaeochromocytoma crisis may occur.]
Important Precautions (newly added)	Cases of phaeochromocytoma crisis have been reported after dexamethasone preparations (oral dosage form and injections) were administered without recognizing concurrent phaeochromocytoma. If a marked elevation in blood pressure, headache, palpitation, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possible occurrence of phaeochromocytoma crisis.
[Under new instructions] **(newly added)**	5. PRECAUTIONS CONCERNING INDICATIONS <Pituitary suppression tests> Prior to conducting dexamethasone suppression tests, the presence or absence of concurrent phaeochromocytoma or paraganglioma should be confirmed. If such complications are present, treatment of phaeochromocytoma or paraganglioma should be prioritized.
8. IMPORTANT PRECAUTIONS <Common to all indications> (newly added)	Cases of phaeochromocytoma crisis have been reported after dexamethasone preparations (oral dosage form and injections) were administered without recognizing concurrent phaeochromocytoma. If a marked elevation in blood pressure, headache, palpitation, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possible occurrence of phaeochromocytoma crisis.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.1 Patients with Complication or History of Diseases, etc. (newly added)	Patients with phaeochromocytoma or paraganglioma and those with suspected phaeochromocytoma or paraganglioma Phaeochromocytoma crisis may occur.
	[2] Dexamathasone (oral dosage form) (Preparations not indicated for pituitary suppression tests)
[Under new instructions]	[4] Dexamathasone palmitate
8. IMPORTANT PRECAUTIONS (newly added)	Cases of phaeochromocytoma crisis have been reported after dexamethasone preparations (oral dosage form and injections) were administered without recognizing concurrent phaeochromocytoma. If a marked elevation in blood pressure, headache, palpitation, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possible occurrence of phaeochromocytoma crisis.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.1 Patients with Complication or History of Diseases,	Patients with phaeochromocytoma or paraganglioma and those with suspected phaeochromocytoma or paraganglioma Phaeochromocytoma crisis may occur.

etc. **(newly added)**	
[Under old instructions]	[3] Dexamathasone sodium phosphate (injections)
Careful Administration **(newly added)**	Patients with phaeochromocytoma or paraganglioma and those with suspected phaeochromocytoma or paraganglioma [Phaeochromocytoma crisis may occur.]
Important Precautions **(newly added)**	Cases of phaeochromocytoma crisis have been reported after dexamethasone preparations (oral dosage form and injections) were administered without recognizing concurrent phaeochromocytoma. If a marked elevation in blood pressure, headache, palpitation, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possible occurrence of phaeochromocytoma crisis.
[Under new instructions]	
8. IMPORTANT PRECAUTIONS **<Common to all indications>** **(newly added)**	Cases of phaeochromocytoma crisis have been reported after dexamethasone preparations (oral dosage form and injections) were administered without recognizing concurrent phaeochromocytoma. If a marked elevation in blood pressure, headache, palpitation, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possible occurrence of phaeochromocytoma crisis.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.1 Patients with Complication or History of Diseases, etc.** **(newly added)**	Patients with phaeochromocytoma or paraganglioma and those with suspected phaeochromocytoma or paraganglioma Phaeochromocytoma crisis may occur.
[Under old instructions]	[5] Betamethasone (oral dosage form)
(newly added)	Precautions concerning Indications Prior to conducting pituitary suppression tests, the presence or absence of concurrent phaeochromocytoma or paraganglioma should be confirmed. If such complications are present, treatment of phaeochromocytoma or paraganglioma should be prioritized.
Careful Administration **(newly added)**	Patients with phaeochromocytoma or paraganglioma and those with suspected phaeochromocytoma or paraganglioma [Phaeochromocytoma crisis may occur.]
Important Precautions **(newly added)**	Cases of phaeochromocytoma crisis have been reported after betamethasone preparations (injections) were administered without recognizing concurrent phaeochromocytoma. If a marked elevation in blood pressure, headache, palpitation, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possible occurrence of phaeochromocytoma crisis.
[Under new instructions]	
(newly added)	5. PRECAUTIONS CONCERNING INDICATIONS <Pituitary suppression tests> Prior to conducting, the presence or absence of phaeochromocytoma or paraganglioma should be confirmed. If such complications are present, treatment of phaeochromocytoma or paraganglioma should be prioritized.
8. IMPORTANT PRECAUTIONS	Cases of phaeochromocytoma crisis have been reported after betamethasone preparations (injections) were administered without

<Common to all indications> **(newly added)**	recognizing concurrent phaeochromocytoma. If a marked elevation in blood pressure, headache, palpitation, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possible occurrence of phaeochromocytoma crisis.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.1 Patients with Complication or History of Diseases, etc.** **(newly added)**	Patients with phaeochromocytoma or paraganglioma and those with suspected phaeochromocytoma or paraganglioma Phaeochromocytoma crisis may occur.
[Under new instructions]	[6] Betamethasone (suppositories) [8] Betamethasone sodium phosphate (enemas) [9] Betamethasone acetate/ betamethasone sodium phosphate
8. IMPORTANT PRECAUTIONS **(newly added)**	Cases of phaeochromocytoma crisis have been reported after betamethasone preparations (injections) were administered without recognizing concurrent phaeochromocytoma. If a marked elevation in blood pressure, headache, palpitation, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possible occurrence of phaeochromocytoma crisis.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.1 Patients with Complication or History of Diseases, etc.** **(newly added)**	Patients with phaeochromocytoma or paraganglioma and those with suspected phaeochromocytoma or paraganglioma Phaeochromocytoma crisis may occur.
[Under old instructions]	[7] Betamethasone sodium phosphate (injections) [10] Betamethasone/d-cholorpheniramine maleate
Careful Administration **(newly added)**	Patients with phaeochromocytoma or paraganglioma and those with suspected phaeochromocytoma or paraganglioma [Phaeochromocytoma crisis may occur.]
Important Precautions **(newly added)**	Cases of phaeochromocytoma crisis have been reported after betamethasone preparations (injections) were administered without recognizing concurrent phaeochromocytoma. If a marked elevation in blood pressure, headache, palpitation, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possible occurrence of phaeochromocytoma crisis.
[Under new instructions]	
8. IMPORTANT PRECAUTIONS **(newly added)**	Cases of phaeochromocytoma crisis have been reported after betamethasone preparations (injections) were administered without recognizing concurrent phaeochromocytoma. If a marked elevation in blood pressure, headache, palpitation, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possible occurrence of phaeochromocytoma crisis.

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.1 Patients with Complication or History of Diseases, etc.** **(newly added)**	Patients with phaeochromocytoma or paraganglioma and those with suspected phaeochromocytoma or paraganglioma Phaeochromocytoma crisis may occur.
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) reported during the previous approximately 3-year period (April 2019 to March 2021) Cases involving phaeochromocytoma crisis: 1 (No patient mortalities) * * A case in which Rinderon Injection was administered. No cases were reported for (1), (2)-(6), (8)-(10). Number of patients using the drug as estimated by the MAH during the previous 1-year period*: *Only the numbers for Rinderon Injection described in the case summary (18 page) are shown. Rinderon Injection 2 mg (0.4%): Approximately 635 000 Rinderon Injection 4 mg (0.4%): Approximately 536 000 Rinderon Injection 20 mg (0.4%): Approximately 170 000 Rinderon Injection 20 mg (2 %): Approximately 19 700 Rinderon Injection 100 mg (2 %): Approximately 1 960 Japanese market launch* *Only the dates for Rinderon Injection described in the case summary are shown. Rinderon Injection 2 mg (0.4%), 4 mg (0.4%): August 1964 Rinderon Injection 20 mg (0.4%): August 1974 Rinderon Injection 20 mg (2 %), 100 mg (2 %): July 1985

Case summary

Product: Rinderon Injection 2 mg (0.4%)

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/ administration duration</th><th>Adverse reaction</th></tr>
<tr><th>Sex/ age</th><th>Reason for use (complication)</th><th>Clinical course and treatment</th></tr>
<tr><td>1</td><td>Male
40s</td><td>Joint pain
(hypertension)</td><td>2 mg
Unknown</td><td>Phaeochromocytoma crisis
The patient's blood pressure has been controlled with Lisinopril, and there was no other significant medical or family history or accidental headache. Smoker (approx. 20 years, 20 cigarettes/day)

Day 1 of administration: Betamethasone sodium phosphate 2 mg was administered intra-articularly for right elbow joint pain.

2 days after administration (Day of hospitalization): General malaise developed, and 2 hours later, the patient was taken to the emergency department due to sudden severe headache. On examination, blood pressure 240/126 mmHg, pulse 120 beats/min, temperature 37.6°C, respiratory rate 25 breaths/min. An imaging test and lumbar puncture ruled out the possibility of a cerebrovascular event. A blood test showed severe hyperglycaemia and metabolic acidosis.

After hospitalization: Diabetic ketoacidosis (DKA) due to fulminant type 1 diabetes mellitus was suspected, and standard DKA treatment including insulin administration was initiated. Plasma glucose levels rapidly decreased and were normal within 2 hours. At the same time, it was found that basal insulin secretion was normal and plasma ketone levels were not elevated, ruling out the possibility of fulminant type 1 diabetes. Subsequently, during screening for secondary diabetes mellitus, an abdominal CT scan revealed a left adrenal tumor. Although elevated serum catecholamine and urinary catecholamine metabolite concentrations were noted, other hormone levels were normal. Serum catecholamine concentration levels did not decrease after a clonidine test. An adrenal function scintigraphy using iodine-131 meta-iodobenzylguanidine showed strong uptake in the left adrenal region. The patient was diagnosed with phaeochromocytoma.

85 days after hospitalization: After blood pressure control with doxazosin 12 mg/day, left adrenalectomy was performed. During 28 months of postoperative follow-up, no symptoms or signs suggesting recurrence of phaeochromocytoma were noted.</td></tr>
</table>

Laboratory test value

	2 days after administration
Fasting blood glucose (mg/dL)	523
HbA1c (%)	5.7
pH	7.21
Anion gap (mEq/L)	26.2
Lactic acid (mmol/L)	11.75
Total ketone bodies (μmoL/L)	289

Suspected concomitant drugs: None
Concomitant drugs: Lisinopril

5
Revision of Precautions (No.332)

This section presents details of revisions to the Precautions of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated March 23, April 4, April 25, and May 13, 2022.

1 Vaccines
Coronavirus modified uridine RNA vaccine (SARS-CoV-2)

Brand name	Comirnaty intramuscular injection (Pfizer Japan Inc.)
[Under New instructions]	
7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION Booster dose Individuals who receive vaccinations	Individuals 12 years of age and older. The necessity of a booster dose should be judged based on the benefit/risk balance, the prevalence status of SARS-CoV-2, and the characteristics of each person.

2 Pituitary hormone preparations
Somatropin (genetical recombination) (preparations indicated for growth hormone-deficient short stature without epiphyseal closure, short stature without epiphyseal closure associated with Turner's syndrome, adult growth hormone deficiency (only in severe cases), and short stature without epiphyseal closure in patients born SGA (small-for-gestational age))

Brand name	Growject Subcutaneous injection 6 mg, 12 mg, Growject for Injection 8 mg, Growject BC for injection 8 mg (JCR Pharmaceuticals Co., Ltd.)
[Under Old instructions]	
Contraindications	(deleted)
Precautions Concerning Dosage and Administration	(deleted)
Careful Administration (newly added)	Patients with diabetes mellitus, glucose intolerance, or risk factors of diabetes mellitus (In patients with diabetes mellitus, blood glucose (levels of blood glucose, HbA1c, etc.) and diabetic complications (such as diabetic retinopathy) should be controlled before initiation of administration. After initiation, levels of blood glucose, HbA1c, etc. should be measured periodically and conditions of patients be closely monitored including diabetic complications (such as diabetic retinopathy). Doses of antidiabetic drugs should be adjusted when required. If symptoms of diabetes mellitus become apparent or exacerbated after initiation of administration, appropriate measures should be taken, such as dose reduction or temporal discontinuation of this drug. Patients with glucose intolerance or with risk factors of diabetes mellitus (such as obesity and a family history of diabetes mellitus) should be closely monitored. Diabetes mellitus may become apparent.)
Important Precautions (newly added)	<Common to all indications> Because growth hormone reduces insulin sensitivity, levels of blood glucose and HbA1c may rise with administration of this drug. Levels of

blood glucose, HbA1c, etc. should be measured periodically and if any abnormalities are observed, appropriate measures should be taken, such as dose reduction or temporal discontinuation of this drug.
Particularly in patients with Turner's syndrome, patients may become complicated with reduced glucose tolerance. The clinical course of patients should be closely monitored.

<Adult growth hormone deficiency>
(deleted)

Drug Interactions Precautions for Co-Administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Antidiabetic drugs (insulin preparations, biguanides, sulfonylureas, rapid-acting insulin secretion stimulators, α-glucosidase inhibitors, thiazolidines, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, etc.)	Blood glucose levels may rise with administration of this drug. Levels of blood glucose, HbA1c, etc. should be measured periodically and doses of these drugs should be adjusted.	Growth hormone reduces insulin sensitivity.

[Under New instructions]

2. CONTRAINDICATIONS
(deleted)

8. IMPORTANT PRECAUTIONS (newly added)
<Common to all indications>
Because growth hormone reduces insulin sensitivity, levels of blood glucose and HbA1c may rise with administration of this drug. Levels of blood glucose, HbA1c, etc. should be measured periodically and if any abnormalities are observed, appropriate measures should be taken, such as dose reduction or temporal discontinuation of this drug.
Particularly when associated with Turner's syndrome, patients may become complicated with reduced glucose tolerance. Conditions of patients should be closely monitored.

<Short stature without epiphyseal closure associated with Turner's syndrome>
(deleted)

<Adult growth hormone deficiency (only in severe cases)>
(deleted)

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS
9.1 Patients with Complication or History of Diseases, etc. (newly added)
Patients with diabetes mellitus, glucose intolerance, or risk factors of diabetes mellitus
In patients with diabetes mellitus, blood glucose (levels of blood glucose, HbA1c, etc.) and diabetic complications (such as diabetic retinopathy) should be controlled before initiation of administration. After initiation, levels of blood glucose, HbA1c, etc. should be measured periodically and conditions of patients be closely monitored including diabetic complications (such as diabetic retinopathy). Doses of antidiabetic drugs should be adjusted when required. If symptoms of diabetes mellitus become apparent or exacerbated after initiation of administration, appropriate measures should be taken, such as dose reduction or temporal discontinuation of this drug.
Patients with glucose intolerance or with risk factors of diabetes

mellitus (such as obesity and a family history of diabetes mellitus) should be closely monitored. Diabetes mellitus may become apparent.

10. INTERACTIONS
10.2 Precautions for Co-Administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Antidiabetic drugs (insulin preparations, biguanides, sulfonylureas, rapid-acting insulin secretion stimulators, α-glucosidase inhibitors, thiazolidines, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, etc.)	Blood glucose levels may rise with administration of this drug. Levels of blood glucose, HbA1c, etc. should be measured periodically and doses of these drugs should be adjusted.	Growth hormone reduces insulin sensitivity.

3 Pituitary hormone preparations

Somatropin (genetical recombination) (preparations indicated for growth hormone-deficient short stature without epiphyseal closure, short stature without epiphyseal closure associated with Turner's syndrome/chronic renal failure/Prader-Willi syndrome, adult growth hormone deficiency (only in severe cases), and short stature without epiphyseal closure in patients born SGA (small-for-gestational age))

Brand name
Genotropin TC Inj. 5.3 mg, 12 mg, Genotropin GoQuick Inj. 5.3 mg, 12 mg, and the others (Pfizer Japan Inc.)

[Under Old instructions]
Contraindications
(deleted)

Careful Administration (newly added)
Patients with diabetes mellitus, glucose intolerance, or risk factors of diabetes mellitus (In patients with diabetes mellitus, blood glucose (levels of blood glucose, HbA1c, etc.) and diabetic complications (such as diabetic retinopathy) should be controlled before initiation of administration. After initiation, levels of blood glucose, HbA1c, etc. should be measured periodically and conditions of patients be closely monitored including diabetic complications (such as diabetic retinopathy). Doses of antidiabetic drugs should be adjusted when required. If symptoms of diabetes mellitus become apparent or exacerbated after initiation of administration, appropriate measures should be taken, such as dose reduction or temporal discontinuation of this drug. Patients with glucose intolerance or with risk factors of diabetes mellitus (such as obesity and a family history of diabetes mellitus) should be closely monitored. Diabetes mellitus may become apparent.)

Important Precautions (newly added)
Because growth hormone reduces insulin sensitivity, levels of blood glucose and HbA1c may rise with administration of this drug. Levels of blood glucose, HbA1c, etc. should be measured periodically and if any abnormalities are observed, appropriate measures should be taken such as dose reduction or temporal discontinuation of this drug. Particularly in patients with Prader-Willi syndrome or Turner's

syndrome, patients may become complicated with reduced glucose tolerance. Conditions of patients should be closely monitored.
When this drug is administered to patients with short stature associated with Prader-Willi syndrome, spinal deformity (scoliosis) may progress excessively. Patients should be carefully monitored through periodic physical and x-ray examinations, etc.

Drug Interactions Precautions for Co-Administration

(deleted)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Antidiabetic drugs (insulin preparations, biguanides, sulfonylureas, rapid-acting insulin secretion stimulators, α-glucosidase inhibitors, thiazolidines, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, etc.)	Blood glucose levels may rise with administration of this drug. Levels of blood glucose, HbA1c, etc. should be measured periodically and doses of these drugs should be adjusted.	Growth hormone reduces insulin sensitivity.

Adverse Reactions Other Adverse Reactions

<Growth hormone-deficient short stature without epiphyseal closure, short stature without epiphyseal closure associated with the following diseases (Turner's syndrome, chronic renal failure, Prader-Willi syndrome), short stature without epiphyseal closure in patients born SGA (small-for-gestational age)>

Site	Adverse reactions
Endocrine system	Hypothyroidism, decreased TSH, reduced glucose tolerance

(deleted)

<Adult growth hormone deficiency (only in severe cases)>

Site	Adverse reactions
Endocrine system	Hypothyroidism, reduced glucose tolerance, dysmenorrhoea

(deleted)

[Under New instructions]

2. CONTRAINDICATIONS <Common to all indications>

(deleted)

8. IMPORTANT PRECAUTIONS <Common to all indications>

Because growth hormone reduces insulin sensitivity, levels of blood glucose and HbA1c may rise with administration of this drug. Levels of blood glucose, HbA1c, etc. should be measured periodically and if any abnormalities are observed, appropriate measures should be taken, such as dose reduction or temporal discontinuation of this drug. Particularly in patients with Prader-Willi syndrome or Turner's syndrome, patients may become complicated with reduced glucose tolerance. The clinical course of patients should be closely monitored.

<Short stature without epiphyseal closure associated with Prader-Willi syndrome>

Spinal deformity (scoliosis) may progress excessively. Patients should be carefully monitored through periodic physical and x-ray examinations, etc.

<Adult growth hormone deficiency (only in severe cases)>

(deleted)

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS
9.1 Patients with Complication or History of Diseases, etc. (newly added)

Patients with diabetes mellitus, glucose intolerance, or risk factors of diabetes mellitus
In patients with diabetes mellitus, blood glucose (levels of blood glucose, HbA1c, etc.) and diabetic complications (such as diabetic retinopathy) should be controlled before initiation of administration. After initiation, levels of blood glucose, HbA1c, etc. should be measured periodically and conditions of patients be closely monitored including diabetic complications (such as diabetic retinopathy). Doses of antidiabetic drugs should be adjusted when required. If symptoms of diabetes mellitus become apparent or exacerbated after initiation of administration, appropriate measures should be taken, such as dose reduction or temporal discontinuation of this drug.
Patients with glucose intolerance or with risk factors of diabetes mellitus (such as obesity and a family history of diabetes mellitus) should be closely monitored. Diabetes mellitus may become apparent.

10. INTERACTIONS
10.2 Precautions for Co-Administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Antidiabetic drugs (insulin preparations, biguanides, sulfonylureas, rapid-acting insulin secretion stimulators, α-glucosidase inhibitors, thiazolidines, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, etc.)	Blood glucose levels may rise with administration of this drug. Levels of blood glucose, HbA1c, etc. should be measured periodically and doses of these drugs should be adjusted.	Growth hormone reduces insulin sensitivity.

4 Pituitary hormone preparations

Somatropin (genetical recombination) (preparations indicated for growth hormone-deficient short stature without epiphyseal closure, short stature without epiphyseal closure associated with Turner's syndrome, short stature without epiphyseal closure associated with chondrodystrophy, adult growth hormone deficiency (only in severe cases), short stature without epiphyseal closure in patients born SGA (small-for-gestational age), and short stature without epiphyseal closure associated with Noonan syndrome))

Brand name
Norditropin FlexPro 5 mg, 10 mg, 15 mg (Novo Nordisk Pharma Ltd.)

[Under Old instructions]
Contraindications
(deleted)
Careful Administration (newly added)
Patients with diabetes mellitus, glucose intolerance, or risk factors of diabetes mellitus (In patients with diabetes mellitus, blood glucose (levels of blood glucose, HbA1c, etc.) and diabetic complications (such as diabetic retinopathy) should be controlled before initiation of administration. After initiation, levels of blood glucose, HbA1c, etc. should be measured periodically and conditions of patients be closely monitored including diabetic complications (such as diabetic retinopathy). Doses of antidiabetic drugs should be adjusted when

required. If symptoms of diabetes mellitus become apparent or exacerbated after initiation of administration, appropriate measures should be taken, such as dose reduction or temporal discontinuation of this drug. Patients with glucose intolerance or with risk factors of diabetes mellitus (such as obesity and a family history of diabetes mellitus) should be closely monitored. Diabetes mellitus may become apparent.)

Important Precautions (newly added)

<Common to all indications>
Because growth hormone reduces insulin sensitivity, levels of blood glucose and HbA1c may rise with administration of this drug. Levels of blood glucose, HbA1c, etc. should be measured periodically and if any abnormalities are observed, appropriate measures should be taken, such as dose reduction or temporal discontinuation of this drug. Particularly in patients with Turner's syndrome, patients may become complicated with reduced glucose tolerance. Conditions of patients should be closely monitored.

<Adult growth hormone deficiency>

(deleted)

Drug Interactions
Precautions for Co-Administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Antidiabetic drugs (insulin preparations, biguanides, sulfonylureas, rapid-acting insulin secretion stimulators, α-glucosidase inhibitors, thiazolidines, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, etc.)	Blood glucose levels may rise with administration of this drug. Levels of blood glucose, HbA1c, etc. should be measured periodically and doses of these drugs should be adjusted.	Growth hormone reduces insulin sensitivity.

Adverse Reactions
Other Adverse Reactions

Site	Adverse reactions
Endocrine system	Reduced glucose tolerance, increased or decreased T_3 values, increased or reduced T_4 values, elevated or declined TSH, hypothyroidism

(deleted)

[Under New instructions]

2. CONTRAINDICATIONS

(deleted)

8. IMPORTANT PRECAUTIONS
<Common to all indications>

Because growth hormone reduces insulin sensitivity, levels of blood glucose and HbA1c may rise with administration of this drug. Levels of blood glucose, HbA1c, etc. should be measured periodically and if any abnormalities are observed, appropriate measures should be taken, such as dose reduction or temporal discontinuation of this drug. Particularly in patients with Turner's syndrome, patients may become complicated with reduced glucose tolerance. The clinical course of patients should be monitored closely.

<Adult growth hormone deficiency>

(deleted)

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS

Patients with diabetes mellitus, glucose intolerance, or risk factors of diabetes mellitus
In patients with diabetes mellitus, blood glucose (levels of blood glucose, HbA1c, etc.) and diabetic complications (such as diabetic retinopathy) should be controlled before initiation of administration.

9.1 Patients with Complication or History of Diseases, etc. (newly added)

After initiation, levels of blood glucose, HbA1c, etc. should be measured periodically and conditions of patients be closely monitored including diabetic complications (such as diabetic retinopathy). Doses of antidiabetic drugs should be adjusted when required. If symptoms of diabetes mellitus become apparent or exacerbated after initiation of administration, appropriate measures should be taken, such as dose reduction or temporal discontinuation of this drug.
Patients with glucose intolerance or with risk factors of diabetes mellitus (such as obesity and a family history of diabetes mellitus) should be closely monitored. Diabetes mellitus may become apparent.

10. INTERACTIONS
10.2 Precautions for Co-Administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Antidiabetic drugs (insulin preparations, biguanides, sulfonylureas, rapid-acting insulin secretion stimulators, α-glucosidase inhibitors, thiazolidines, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, etc.)	Blood glucose levels may rise with administration of this drug. Levels of blood glucose, HbA1c, etc. should be measured periodically and doses of these drugs should be adjusted.	Growth hormone reduces insulin sensitivity.

5 Pituitary hormone preparations

Somatropin (genetical recombination) (preparations indicated for growth hormone-deficient short stature without epiphyseal closure, short stature without epiphyseal closure associated with Turner's syndrome, short stature without epiphyseal closure associated with chondrodystrophy (achondroplasia, hypochondroplasia), and adult growth hormone deficiency (only in severe cases))

Brand name
[Under Old instructions]
Humatrope for injection 6 mg, 12 mg (Eli Lilly Japan K.K.)

Contraindications
(deleted)

Careful Administration (newly added)
Patients with diabetes mellitus, glucose intolerance, or risk factors of diabetes mellitus (In patients with diabetes mellitus, blood glucose (levels of blood glucose, HbA1c, etc.) and diabetic complications (such as diabetic retinopathy) should be controlled before initiation of administration. After initiation, levels of blood glucose, HbA1c, etc. should be measured periodically and conditions of patients be closely monitored including diabetic complications (such as diabetic retinopathy). Doses of antidiabetic drugs should be adjusted when required. If symptoms of diabetes mellitus become apparent or exacerbated after initiation of administration, appropriate measures should be taken such as dose reduction or temporal discontinuation of this drug. Patients with glucose intolerance or with risk factors of diabetes mellitus (such as obesity and a family history of diabetes mellitus) should be closely monitored. Diabetes mellitus may become apparent.)

Important Precautions
<Common to all indications>

(newly added)

Because growth hormone reduces insulin sensitivity, levels of blood glucose and HbA1c may rise with administration of this drug. Levels of blood glucose, HbA1c, etc. should be measured periodically and if any abnormalities are observed, appropriate measures should be taken such as dose reduction or temporal discontinuation of this drug. Particularly in patients with Turner's syndrome, patients may become complicated with reduced glucose tolerance. The clinical course of patients should be monitored closely.

<Adult growth hormone deficiency>

(deleted)

Drug Interactions
Precautions for Co-Administration

Drugs	Signs, Symptoms, and Treatment	Mechanism of action
Antidiabetic drugs (insulin preparations, biguanides, sulfonylureas, rapid-acting insulin secretion stimulators, α-glucosidase inhibitors, thiazolidines, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, etc.)	Blood glucose levels may rise with administration of this drug. Levels of blood glucose, HbA1c, etc. should be measured periodically and doses of these drugs should be adjusted.	Growth hormone reduces insulin sensitivity.

Adverse Reactions
Other Adverse Reactions

Site	Adverse reactions
Endocrine system	Hypothyroidism[Note2], reduced glucose tolerance

Note 2: Hypothyroidism may occur or become exacerbated thereby may reduce the treatment effectiveness of this drug. Thyroid function should be tested periodically, and appropriate treatment should preferably be provided in such case. Particularly in patients with Turner's syndrome, patients may become complicated with thyroid diseases. The clinical course of patients should be closely monitored.

[Under New instructions]

2. CONTRAINDICATIONS

(deleted)

8. IMPORTANT PRECAUTIONS
<Common to all indications>

<Common to all indications>
Hypothyroidism may occur or become exacerbate thereby reduce the treatment effectiveness of this drug. Thyroid function should be tested periodically, and appropriate treatment should preferably be provided in such case. Particularly in patients with Turner's syndrome, patients may become complicated with thyroid diseases. The clinical course of patients should be monitored closely.

(newly added)

Because growth hormone reduces insulin sensitivity, levels of blood glucose and HbA1c may rise with administration of this drug. Levels of blood glucose, HbA1c, etc. should be measured periodically and if any abnormalities are observed, appropriate measures should be taken such as dose reduction or temporal discontinuation of this drug. Particularly in patients with Turner's syndrome, patients may become complicated with reduced glucose tolerance. The clinical course of patients should be monitored closely.

<Adult growth hormone deficiency (only in severe cases)>

(deleted)

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS
9.1 Patients with Complication or History of Diseases, etc. (newly added)

Patients with diabetes mellitus, glucose intolerance, or risk factors of diabetes mellitus
In patients with diabetes mellitus, blood glucose (levels of blood glucose, HbA1c, etc.) and diabetic complications (such as diabetic retinopathy) should be controlled before initiation of administration. After initiation, levels of blood glucose, HbA1c, etc. should be measured periodically and conditions of patients be closely monitored including diabetic complications (such as diabetic retinopathy). Doses of antidiabetic drugs should be adjusted when required. If symptoms of diabetes mellitus become apparent or exacerbated after initiation of administration, appropriate measures should be taken such as dose reduction or temporal discontinuation of this drug.
Patients with glucose intolerance or with risk factors of diabetes mellitus (such as obesity and a family history of diabetes mellitus) should be closely monitored. Diabetes mellitus may become apparent.

10. INTERACTIONS
10.2 Precautions for Co-Administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Antidiabetic drugs (insulin preparations, biguanides, sulfonylureas, rapid-acting insulin secretion stimulators, α-glucosidase inhibitors, thiazolidines, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, etc.)	Blood glucose levels may rise with administration of this drug. Levels of blood glucose, HbA1c, etc. should be measured periodically and doses of these drugs should be adjusted.	Growth hormone reduces insulin sensitivity.

6 Other biological preparations

Interferon beta-1a (genetical recombination)

Brand name: Avonex IM Injection PEN 30 μg, Avonex IM Injection Syringe 30 μg (Biogen Japan Ltd.)

[Under New instructions]

2. CONTRAINDICATIONS: (deleted)

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS
9.5 Pregnant Women: This drug should be administered to pregnant women or women who may be pregnant only if the potential therapeutic benefits are considered to outweigh the potential risks. Spontaneous abortions have been reported as observed in an animal study (monkeys) at higher doses of this drug.

7 Other biological preparations

Interferon beta-1b (genetical recombination)

Brand name: Betaferon for SC injection 960 IU (Bayer Yakuhin, Ltd.)

[Under New instructions]

2. CONTRAINDICATIONS: (deleted)

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS
9.5 Pregnant Women: This drug should be administered to pregnant women or women who may be pregnant only if the potential therapeutic benefits are considered to outweigh the potential risks. Foetal deaths and spontaneous abortions have been reported as observed in an animal study (monkeys) at higher doses of this drug.

8 Vaccines

Coronavirus modified uridine RNA vaccine (SARS-CoV-2)

Brand name	Comirnaty intramuscular injection (Pfizer Japan Inc.)
[Under New instructions]	
7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION	The third dose may be administered as a booster dose at least 5 months after the second dose.
Booster dose	For the fourth dose, the vaccination may be considered in elderly people, etc. based on the benefit/risk balance at least 5 months after the third dose.
Timing of vaccination	The effectiveness and safety on the booster dose of this vaccine in people who have received other SARS-CoV-2 vaccines have not been established.

9 Vaccines

Coronavirus modified uridine RNA vaccine (SARS-CoV-2)

Brand name	Spikevax Intramuscular Injection (Takeda Pharmaceutical Company Limited.)
[Under New instructions]	
7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION	The third dose may be administered as a booster dose at least 5 months after the second dose.
Booster dose	For the fourth dose, the vaccination may be considered in elderly people, etc. based on the benefit/risk balance at least 5 months after the third dose.
Timing of vaccination	The effectiveness and safety on the booster dose (0.25 mL) of this vaccine in people who have received other SARS-CoV-2 vaccines have not been established.

10 Adrenal hormone preparations

Dexamethasone (oral dosage form) (preparations indicated for pituitary suppression tests)

Brand name	Decadron Tablets 0.5 mg, 4 mg, Decadron Elixir 0.01% (Nichi-Iko Pharmaceutical Co., Ltd.), and the others
[Under Old instructions]	
(newly added)	Precautions concerning Indications Prior to conducting dexamethasone suppression tests, the presence or absence of concurrent phaeochromocytoma or paraganglioma should be confirmed. If such complications are present, treatment of phaeochromocytoma or paraganglioma should be prioritized.
Careful Administration (newly added)	Patients with phaeochromocytoma or paraganglioma and those with suspected phaeochromocytoma or paraganglioma [Phaeochromocytoma crisis may occur.]
Important Precautions (newly added)	Cases of phaeochromocytoma crisis have been reported after dexamethasone preparations (oral dosage form and injections) were administered without recognizing concurrent phaeochromocytoma. If a marked elevation in blood pressure, headache, palpitation, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possible occurrence of phaeochromocytoma crisis.
[Under New instructions]	
(newly added)	5. PRECAUTIONS CONCERNING INDICATIONS <Pituitary suppression tests> Prior to conducting dexamethasone suppression tests, the presence or absence of concurrent phaeochromocytoma or paraganglioma should be confirmed. If such complications are present, treatment of

	phaeochromocytoma or paraganglioma should be prioritized.
8. IMPORTANT PRECAUTIONS <Common to all indications> (newly added)	Cases of phaeochromocytoma crisis have been reported after dexamethasone preparations (oral dosage form and injections) were administered without recognizing concurrent phaeochromocytoma. If a marked elevation in blood pressure, headache, palpitation, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possible occurrence of phaeochromocytoma crisis.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.1 Patients with Complication or History of Diseases, etc. (newly added)	Patients with phaeochromocytoma or paraganglioma and those with suspected phaeochromocytoma or paraganglioma Phaeochromocytoma crisis may occur.

11 Adrenal hormone preparations

[1] Dexamethasone (oral dosage form) (preparations not indicated for pituitary suppression tests)
[2] Dexamethasone palmitate

Brand name	[1] LenaDex Tablets 2 mg, 4 mg (Bristol-Myers Squibb K.K.) [2] Limethason Intravenous Injection 2.5 mg (Mitsubishi Tanabe Pharma Corporation)
[Under New instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	Cases of phaeochromocytoma crisis have been reported after dexamethasone preparations (oral dosage form and injections) were administered without recognizing concurrent phaeochromocytoma. If a marked elevation in blood pressure, headache, palpitation, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possible occurrence of phaeochromocytoma crisis.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.1 Patients with Complication or History of Diseases, etc. (newly added)	Patients with phaeochromocytoma or paraganglioma and those with suspected phaeochromocytoma or paraganglioma Phaeochromocytoma crisis may occur.

12 Adrenal hormone preparations

Dexamethasone sodium phosphate (injections)

Brand name	Decadron Phosphate Injection 1.65 mg, 3.3 mg, 6.6 mg (Sandoz Pharma K.K.), and the others
[Under Old instructions]	
Careful Administration (newly added)	Patients with phaeochromocytoma or paraganglioma and those with suspected phaeochromocytoma or paraganglioma [Phaeochromocytoma crisis may occur.]
Important Precautions (newly added)	Cases of phaeochromocytoma crisis have been reported after dexamethasone preparations (oral dosage form and injections) were administered without recognizing concurrent phaeochromocytoma. If a marked elevation in blood pressure, headache, palpitation, etc. are observed after administration of this drug, appropriate measures

	should be taken with consideration given to the possible occurrence of phaeochromocytoma crisis.
[Under New instructions]	
8. IMPORTANT PRECAUTIONS <Common to all indications> (newly added)	Cases of phaeochromocytoma crisis have been reported after dexamethasone preparations (oral dosage form and injections) were administered without recognizing concurrent phaeochromocytoma. If a marked elevation in blood pressure, headache, palpitation, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possible occurrence of phaeochromocytoma crisis.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.1 Patients with Complication or History of Diseases, etc. (newly added)	Patients with phaeochromocytoma or paraganglioma and those with suspected phaeochromocytoma or paraganglioma Phaeochromocytoma crisis may occur.

13 Adrenal hormone preparations

Betamethasone (oral dosage form)

Brand name	Rinderon Tablets 0.5 mg, Rinderon Powder 0.1%, Rinderon Syrup 0.01% (Shionogi Pharma Co., Ltd.), and the others
[Under Old instructions]	
(newly added)	Precautions concerning Indications Prior to conducting pituitary suppression tests, the presence or absence of concurrent phaeochromocytoma or paraganglioma should be confirmed. If such complications are present, treatment of phaeochromocytoma or paraganglioma should be prioritized.
Careful Administration (newly added)	Patients with phaeochromocytoma or paraganglioma and those with suspected phaeochromocytoma or paraganglioma [Phaeochromocytoma crisis may occur.]
Important Precautions (newly added)	Cases of phaeochromocytoma crisis have been reported after betamethasone preparations (injections) were administered without recognizing concurrent phaeochromocytoma. If a marked elevation in blood pressure, headache, palpitation, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possible occurrence of phaeochromocytoma crisis.
[Under New instructions]	
(newly added)	5. PRECAUTIONS CONCERNING INDICATIONS <Pituitary suppression tests> Prior to conducting, the presence or absence of phaeochromocytoma or paraganglioma should be confirmed. If such complications are present, treatment of phaeochromocytoma or paraganglioma should be prioritized.
8. IMPORTANT PRECAUTIONS <Common to all indications> (newly added)	Cases of phaeochromocytoma crisis have been reported after betamethasone preparations (injections) were administered without recognizing concurrent phaeochromocytoma. If a marked elevation in blood pressure, headache, palpitation, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possible occurrence of phaeochromocytoma crisis.
9. PRECAUTIONS CONCERNING	Patients with phaeochromocytoma or paraganglioma and those with suspected phaeochromocytoma or paraganglioma

PATIENTS WITH SPECIFIC BACKGROUNDS 9.1 Patients with Complication or History of Diseases, etc. (newly added)	Phaeochromocytoma crisis may occur.

14 Adrenal hormone preparations

[1] Betamethasone (suppositories)
[2] Betamethasone acetate/betamethasone sodium phosphate
[3] Betamethasone sodium phosphate (enemas)

Brand name	[1] Rinderon Suppositories 0.5 mg, 1.0 mg (Shionogi Pharma Co., Ltd.) [2] Rinderon Suspension (Shionogi Pharma Co., Ltd.) [3] Steronema Enema 3 mg, 1.5 mg (Nichi-Iko Pharmaceutical Co., Ltd.)
[Under New instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	Cases of phaeochromocytoma crisis have been reported after betamethasone preparations (injections) were administered without recognizing concurrent phaeochromocytoma. If a marked elevation in blood pressure, headache, palpitation, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possible occurrence of phaeochromocytoma crisis.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.1 Patients with Complication or History of Diseases, etc. (newly added)	Patients with phaeochromocytoma or paraganglioma and those with suspected phaeochromocytoma or paraganglioma Phaeochromocytoma crisis may occur.

15 Adrenal hormone preparations

Betamethasone/d-chlorpheniramine maleate
Betamethasone sodium phosphate (injections)

Brand name	[1] Celestamine Combination Tablets, Celestamine Combination Syrup (TAKATA Pharmaceutical Co., Ltd.), and the others [2] Rinderon Injection 2 mg (0.4%), 4 mg (0.4%), 20 mg (0.4%), 20 mg (2%), 100 mg (2%) (Shionogi Pharma Co., Ltd.), and the others
[Under Old instructions]	
Careful Administration (newly added)	Patients with phaeochromocytoma or paraganglioma and those with suspected phaeochromocytoma or paraganglioma [Phaeochromocytoma crisis may occur.]
Important Precautions (newly added)	Cases of phaeochromocytoma crisis have been reported after betamethasone preparations (injections) were administered without recognizing concurrent phaeochromocytoma. If a marked elevation in blood pressure, headache, palpitation, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possible occurrence of phaeochromocytoma crisis.
[Under New instructions]	

8. IMPORTANT PRECAUTIONS (newly added)	Cases of phaeochromocytoma crisis have been reported after betamethasone preparations (injections) were administered without recognizing concurrent phaeochromocytoma. If a marked elevation in blood pressure, headache, palpitation, etc. are observed after administration of this drug, appropriate measures should be taken with consideration given to the possible occurrence of phaeochromocytoma crisis.
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.1 Patients with Complication or History of Diseases, etc. (newly added)**	Patients with phaeochromocytoma or paraganglioma and those with suspected phaeochromocytoma or paraganglioma Phaeochromocytoma crisis may occur.

16 Antibiotic preparations acting mainly on gram-positive bacteria

Teicoplanin

Brand name	Targocid 200 mg for Injection (Sanofi K.K.), and the others
[Under Old instructions]	
Adverse Reactions Clinically Significant Adverse Reactions	Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute generalised exanthematous pustulosis, erythroderma (exfoliative dermatitis): Toxic epidermal necrolysis, oculomucocutaneous syndrome, acute generalised exanthematous pustulosis, or erythroderma (exfoliative dermatitis) may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.
[Under New instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), acute generalised exanthematous pustulosis, erythroderma (exfoliative dermatitis)

6

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for newly-approved drug products refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. The MAH responsible for a new drug in the EPPV period is required to collect adverse drug reactions (ADRs) data from all medical institutions where the drug is used and to take safety measures as appropriate. The aim of EPPV is to promote the rational and appropriate use of drugs in medical treatments and to facilitate prompt action for the prevention of serious ADRs. EPPV is specified as a condition of product approval.

(As of 30 April 2022)
◎: Products for which EPPV was initiated after April 1, 2022

	Nonproprietary name / Brand name	Name of the MAH	Date of EPPV initiate
◎	Somatrogon (genetical recombination) Ngenla Inj. 24 mg Pens, 60 mg Pens	Pfizer Japan Inc.	April 27, 2022
◎	Gefapixant citrate Lyfnua Tablets 45 mg	MSD K.K.	April 21, 2022
◎	Sotorasib Lumakras Tablets 120 mg	Amgen K.K.	April 20, 2022
◎	Clazosentan sodium Pivlaz I.V. Infusion liquid 150 mg	Idorsia Pharmaceuticals Japan Ltd.	April 20, 2022
◎	Bimekizumab (genetical recombination) Bimzelx Syringe for S.C injection 160 mg, Bimzelx Autoinjector for S.C injection 160 mg	UCB Japan Co. Ltd.	April 20, 2022
	Filgotinib maleate[*1] Jyseleca Tablets 100 mg, 200 mg	Gilead Sciences K.K.	March 28, 2022
	Selpercatinib[*2] Retevmo Capsules 40 mg, 80 mg	Eli Lilly Japan K.K.	February 25, 2022
	Pegfilgrastim (genetical recombination)[*3] G-Lasta Subcutaneous Injection 3.6 mg	Kyowa Kirin Co., Ltd.	February 25, 2022
	Coronavirus modified uridine RNA vaccine (SARS-CoV-2) Comirnaty intramuscular injection for 5 to 11 years old	Pfizer Japan Inc.	February 22, 2022
	Nirmatrelvir/ritonavir Paxlovid Pack	Pfizer Japan Inc.	February 14, 2022
	Tocilizumab (genetical recombination) [*4] Actemra for Intravenous Infusion 80 mg, 200 mg, 400 mg	Chugai Pharmaceutical Co., Ltd.	January 21, 2022
	3-Iodobenzylguanidine (^{131}I) Raiatt MIBG-I 131 Injection	FUJIFILM Toyama Chemical Co., Ltd.	January 18, 2022

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
	Molnupiravir Lagevrio Capsules 200 mg	MSD K.K.	December 24, 2021
	Prasugrel hydrochloride*5 Efient Tablets 2.5 mg, 3.75 mg	Daiichi Sankyo Co., Ltd.	December 24, 2021
	Azilsartan Azilva Granules 1%, Azilva Tablets 10 mg, 20 mg, 40 mg	Takeda Pharmaceutical Company Limited.	December 16, 2021
	Abrocitinib Cibinqo Tablets 50 mg, 100 mg, 200 mg	Pfizer Japan Inc.	December 13, 2021
	Selpercatinib Retevmo Capsules 40 mg, 80 mg	Eli Lilly Japan K.K.	December 13, 2021
	Somapacitan (genetical recombination) Sogroya Subcutaneous Injection 5 mg, 10 mg	Novo Nordisk Pharma Ltd.	December 10, 2021
	Enfortumab vedotin (genetical recombination) Padcev for I.V. infusion 30 mg	Astellas Pharma Inc.	November 30, 2021
	Progesterone F-meno capsules 100 mg	Fuji Pharma Co., Ltd.	November 29, 2021
	Avalglucosidase alfa (genetical recombination) Nexviazyme for I.V. Infusion 100 mg	Sanofi K.K.	November 26, 2021
	Tucidinostat*6 Hiyasta tablets 10 mg	Huya Japan G.K.	November 25, 2021
	Empagliflozin*7 Jardiance Tablets 10 mg	Boehringer Ingelheim Japan, Inc.	November 25, 2021
	Anifrolumab (genetical recombination) Saphnelo for I.V. infusion 300 mg	AstraZeneca K.K.	November 25, 2021
	Relebactam hydrate/imipenem hydrate/cilastatin sodium Recarbrio Combination for Intravenous Drip Infusion	MSD K.K.	November 9, 2021
	Casirivimab (genetical recombination), Imdevimab (genetical recombination) Ronapreve Injection Set 300, 1332	Chugai Pharmaceutical Co., Ltd.	November 5, 2021

*1 Treatment and maintenance therapy for moderately to severely active ulcerative colitis (limited to patients who have had an inadequate response with, lost response to, or were intolerant to conventional therapies)

*2 Radically unresectable RET fusion-positive thyroid cancer, radically unresectable RET-mutant medullary thyroid cancer

*3 Mobilization of haematopoietic stem cells into peripheral blood for allogeneic blood stem cell transplantation

*4 SARS-CoV-2 pneumonia (limited to patients requiring oxygen intervention)

*5 Prevention of recurrence of ischaemic cerebrovascular disease following the former appearance of ischaemic cerebrovascular disease (associated with large-artery atherosclerosis or small-vessel occlusion) (restricted to cases with a high risk of ischaemic stroke).

*6 Relapsed or refractory peripheral T-cell lymphoma
*7 Chronic heart failure (only in patients who are receiving standard of care for chronic heart failure)