Pharmaceuticals and Medical Devices Safety Information

No. 406 December 2023

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* publication is issued reflective of safety information collected by the Ministry of Health, Labour and Welfare (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) web page (https://www.pmda.go.jp/english/) and on the MHLW website (https://www.mhlw.go.jp/, only available in Japanese language).

Available information is listed here

Access to the latest safety information is available via the PMDA Medi-navi.

The PMDA Medi-navi is an e-mail mailing list service that serves to provide essential safety information released by the MHLW and PMDA. Subscribing to the Medi-navi will allow you to receive this information on the day of its release.

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Pharmaceuticals and Medical Devices Safety Information

No. 406 December 2023

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

[Outline of Information]

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 healthcare professionals.

If healthcare professionals such as physicians, dentists, and pharmacists detect adverse reactions, infections, or malfunctions associated with drugs, medical devices, or regenerative medical products, please report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As healthcare professionals, drugstore and pharmacy personnel are also required to report adverse reactions, etc.

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
EPPV	Early Post-marketing Phase Vigilance
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
PMDA	Pharmaceuticals and Medical Devices Agency
PSB	Pharmaceutical Safety Bureau
PSD	Pharmaceutical Safety Division

1
Revisions of PRECAUTIONS for Oral Anticoagulants (Acute Kidney Injury)

1. Introduction

The MHLW issued a notification instructing the addition of “acute kidney injury” to the Clinically Significant Adverse Reactions section in the PRECAUTIONS of oral anticoagulants (apixaban, edoxaban tosilate hydrate, dabigatran etexilate methanesulfonate, rivaroxaban, warfarin potassium) on November 21, 2023.[1)] The notification was in response to the cases reported in Japan for which a causal relationship between oral anticoagulants and acute kidney injury including anticoagulant-related nephropathy was reasonably possible.

No definitions or explanations, etc. on anticoagulant-related nephropathy are available in the guidelines by related academic societies in Japan, and the disease is not considered to be generally well recognized. Therefore, this article introduces the diseases concept, etc. of anticoagulant-related nephropathy by referring to the information on currently available published articles, etc. as well as the details of the review for this revision.

Please refer to 3. Important Safety Information in this publication for the details of the revision and clinical courses of the cases.

2. Anticoagulant-related nephropathy

(1) Disease concept

Anticoagulant-related nephropathy is considered to be a form of acute kidney injury induced by an excessive anticoagulant effect, which is observed in patients receiving oral anticoagulants.[2-4)] The event was reported in the literature in 2009 as acute kidney injury during administration of warfarin, and it was initially called warfarin-related nephropathy. Since acute kidney injury with the same characteristics (haematuria, numerous red cell casts in the renal tubules manifested on renal biopsy, etc.) as those for warfarin has been reported for other oral anticoagulants thereafter, it has been collectively called anticoagulant-related nephropathy in recent years.

(2) Epidemiology

The incidence of anticoagulant-related nephropathy is not known. In addition to the poor awareness of anticoagulant-related nephropathy in clinical practice, the difficulty of diagnosis due to the fact that a kidney biopsy cannot be performed in many cases because of the patients’ tendency to bleed during anticoagulant therapy is considered to be a contributing factor to this.[3)]

The possibility that anticoagulant-related nephropathy may contribute to deterioration of life prognosis and/or renal outcome was suggested, and the importance of managing antianticoagulant-related nephropathy appropriately was pointed out.[2, 5)]

(3) Causes

The mechanism of onset of anticoagulant-related nephropathy has not been clarified yet. It is inferred, based on the kidney biopsy results in humans and the results of animal studies, that glomerular haemorrhage occurs by an anticoagulant effect, resulting in the tubular obstruction by intratubular red cell casts and tubular epithelial cell injury [2, 3)].

In addition, chronic kidney disease (especially in patients with IgA nephropathy as underlying disease), older age, diabetes mellitus, cardiac failure, hypertension, etc. have been reported as risk factors for anticoagulant-related nephropathy.[3, 6)]

(4) Diagnosis

There are no established diagnostic criteria for anticoagulant-related nephropathy. It has

been reported in the literature that anticoagulant-related nephropathy would be suspected when acute kidney injury occurs in patients receiving oral anticoagulants with no other etiologies of acute kidney injury specified.[4] The presence of haematuria (gross or microscopic) in the absence of a clear etiology for the acute kidney injury makes the diagnosis of anticoagulant-related nephropathy highly likely. However, even when haematuria is not observed, the possibility of anticoagulant-related nephropathy should not be excluded.[4] For anticoagulant-related nephropathy caused by warfarin, PT-INR above the therapeutic range (many reported cases of PT-INR beyond 3) is also considered to be a finding suggestive of anticoagulant-related nephropathy. However, cases considered to be anticoagulant-related nephropathy with PT-INR within the therapeutic range have also been reported.[7] Therefore, it is necessary to carefully diagnose anticoagulant-related nephropathy even when PT-INR is within the therapeutic range.

In addition, a kidney biopsy is required for a definitive diagnosis of anticoagulant-related nephropathy, and the tubular obstruction by red cell casts, etc. are observed as histological characteristics of anticoagulant-related nephropathy. However, whether or not to perform a kidney biopsy should be carefully determined based on the benefit/risk balance taking into account the risk of haemorrhage, etc. in patients receiving oral anticoagulants.[8]

(5) Treatment

There is no established treatment for anticoagulant-related nephropathy. To correct the conditions of overanticoagulation, dose reduction and discontinuation of the suspected oral anticoagulants and the use of antagonists, etc. are advocated in the literature.[2, 3]

3. Details of the review

Cases of acute kidney injury including anticoagulant-related nephropathy were evaluated to determine the necessity of the revision. As a result of consultation with experts regarding the causality assessment of the cases and the necessity of revision of PRECAUTIONS, the MHLW/PMDA considered it appropriate to revise PRECAUTIONS of all oral anticoagulants and add “acute kidney injury” to the Clinically Significant Adverse Reactions section based on the following reason[9].

- Among oral anticoagulants, cases for which a causal relationship of warfarin potassium and multiple direct oral anticoagulants (edoxaban tosilate hydrate, dabigatran etexilate methanesulfonate, rivaroxaban) to acute kidney injury including anticoagulant-related nephropathy was reasonably possible have been reported in Japan. (See 3. Important Safety Information in this issue.)

For apixaban, although no cases for which a causal relationship to acute kidney injury including anticoagulant-related nephropathy was reasonably possible have been reported in Japan, cases of anticoagulant-related nephropathy possibly related to apixaban have been reported in the literature published overseas.[10]

Since anticoagulant-related nephropathy is not considered to be generally well recognized, it was decided to use “acute kidney injury” for the name of the adverse reactions in the Clinically Significant Adverse Reactions and to describe the findings characteristic to anticoagulant-related nephropathy (haematuria, red cell casts in the renal tubules, etc.) reported in the published literature and case reports of adverse drug reactions. (See 3. Important Safety Information in this issue.)

4. Closing remark

Healthcare professionals are requested to pay sufficient attention to the onset of acute kidney injury related to the administration of oral anticoagulants as well as to take appropriate measures considering the possibility of anticoagulant-related nephropathy when acute kidney injury is noted in patients treated with oral anticoagulants.

[References]

1) Revisions of Precautions (PSB/PSD 1121 No.1 dated November 21, 2023)
https://www.mhlw.go.jp/content/11120000/001169267.pdf (in Japanese)

English translation by the PMDA (November 21, 2023)
https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0011.html
2) Brodsky S, et al.: J Am Soc Nephrol. 2018; 29: 2787-2793
3) Zakrocka I, et al.: Adv Clin Exp Med. 2022; 31: 165-173
4) Wheeler D, et al.: J Thromb Haemost. 2016; 14: 461-467
5) Brodsky S, et al.: Kidney Int. 2011; 80: 181-189
6) Trujillo H, et al.: Kidney Int Rep. 2022; 7: 831-840
7) Brodsky S, et al.: Kidney Res Clin Pract. 2014; 33: 174-180
8) Hirano, et. al.: J Jpn Soc Int Med. 2021; 110: 2593-2600
9) PMDA investigation report
https://www.pmda.go.jp/files/000265464.pdf (in Japanese)
English translation by the PMDA
https://www.pmda.go.jp/files/000265504.pdf
10) Brodsky S, et al.: Kidney Res Clin Pract. 2017; 36: 387-392

2
Proper Use of GLP-1 Receptor Agonists and GIP/GLP-1 Receptor Agonists

1. Introduction

Recently, it has been pointed out that GLP-1 receptor agonists and GIP/GLP-1 receptor agonists (hereinafter simply referred to as “GLP-1 receptor agonists”), which are approved for marketing for the treatment of type 2 diabetes mellitus, are actually being used for cosmetic and slimming purposes other than for the treatment of type 2 diabetes mellitus by some medical institutions. The safety and efficacy when used off-label have not been confirmed, and it is necessary to take sufficient precautions for such reasons as it may lead to health damage due to unexpected adverse drug reactions. It has also been pointed out that the increasing demand for GLP-1 receptor agonists exceeding the supply has resulted in limited shipments of some of the drugs, and there is a concern that this may hinder the supply of them for the intended purpose of treatment of type 2 diabetes mellitus. For this reason, relevant information has been summarized here.

2. Proper use of GLP-1 receptor agonists

For GLP-1 receptor agonists approved for marketing for the treatment of type 2 diabetes mellitus, recently, it has been pointed out that advertisements, etc. which can be perceived as recommending their use for the purpose of cosmetic treatment, slimming, weight loss, etc. have been found on some websites, etc. and that they are actually being used for purposes other than for the treatment of type 2 diabetes mellitus. GLP-1 receptor agonists marketed in Japan, which are shown in the attached table, are currently approved for the indication of type 2 diabetes mellitus only, and their safety and efficacy when used for off-label indications have not been confirmed. Wegovy® Subcutaneous Injections SD, which was approved for marketing this March, is also a GLP-1 receptor agonist. It is indicated for the treatment of obesity, and it cannot be used for slimming and weight loss purposes other than for the treatment of obesity. For more information, please refer to the electronic package insert for Wegovy® Subcutaneous Injections SD and the Optimal Clinical Use Guidelines.

Precautions are included in the electronic package insert stating that clinically significant adverse drug reactions such as hypoglycaemic symptoms (feeling of weakness, severe hunger, cold sweat, facial pallor, palpitations, tremor, headache, dizziness, nausea, abnormal vision, etc.) and acute pancreatitis may occur when GLP-1 receptor agonists are used, and that relatively frequent adverse drug reactions such as nausea, vomiting, diarrhoea, constipation, abdominal pain, and other gastrointestinal symptoms have been observed. These adverse drug reactions may occur even when the drugs are used off-label. Furthermore, the possibility cannot be ruled out that this could lead to unprecedented and unexpected adverse drug reactions.

As for the off-label uses, the Japan Diabetes Society and related pharmaceutical companies have issued documents on the proper use, and the PMDA has also posted them on its website to promote proper use. In addition, the Japan Society for the Study of Obesity has released a “Statement on the Safe and Proper Use of Drugs for the Treatment of Obesity” as of November 25, 2023, and the PMDA has posted it on its website as well.

There is the Relief System for Sufferers from Adverse Drug Reactions, a public system that provides medical expenses, pensions, and other benefits when adverse drug reactions cause health damage which is serious enough to require hospitalization for the treatment. However, the relief system is applicable only to health damage caused by adverse drug reactions in cases where the drugs are used in an appropriate manner for proper purposes. Therefore, please note that it is highly unlikely that the relief system will be applied to those sufferers of serious health damage by GLP-1 receptor agonists to whom these drugs were used for off-label indications such

as cosmetic treatment, slimming, and weight loss despite the fact that they do not fall under intended patients listed in the package inserts, since it will not be considered that they have used the drugs properly.

3. Request for cooperation due to tight inventory

Limited shipments of some of the GLP-1 receptor agonists have occurred due to increased demand exceeding supply. In November 2023, the Policy Planning Division for Pharmaceutical Industry Promotion and Medical Information Management, the Health Policy Bureau, the MHLW issued an administrative notice requesting cooperation from medical institutions, pharmacies, etc. until a stable supply of GLP-1 receptor agonists can be secured. A similar administrative notice was issued in July this year. However, some medical institutions still use the drugs for purposes other than for the treatment of patients with type 2 diabetes mellitus (mainly for cosmetic treatment and slimming). Therefore, we would like to request medical institutions, pharmacies, and wholesale distributors of pharmaceuticals for their cooperation in this matter once again.

1. Medical institutions and pharmacies are requested to strictly refrain from stocking up on GLP-1 receptor agonists and to purchase them only in the necessary quantity to meet immediate needs in order to avoid any returns.
2. Medical institutions and pharmacies should make sure to use GLP-1 receptor agonists properly in order to ensure that the supply to patients with type 2 diabetes mellitus who truly need them is not disrupted.
3. Upon understanding the purpose of the above requests, when wholesale distributors of pharmaceuticals receive orders from medical institutions and pharmacies, please confirm whether the orders are for the treatments within the scope of regulatory approval and deliver GLP-1 receptor agonists to the medical institutions and pharmacies that provide treatments for diabetes mellitus, refraining from delivering them when it is clear that their uses are for the treatments outside the scope of regulatory approval.

4. Reminder to consumers regarding cosmetic medicine

The MHLW and the Consumer Affairs Agency have jointly prepared “Check Once Again Before Receiving Cosmetic Medicine Services” as an explanatory material for informed consent to prevent consumer problems. Efforts are being made to inform local residents about it, so that patients will be encouraged to use the explanatory material for informed consent, etc. and to ask healthcare professionals and others for additional explanations, etc.

In addition, regarding advertisements related to medical care, from the perspective of protection of patients and other users, advertisements on medical treatments not covered by health insurance where domestically unapproved drugs are used or drugs are used for off-label indications are prohibited in principle except for those items that are allowed to be advertised. Please note that the following, for example, are considered as exaggerated advertisements and prohibited, even in cases where certain conditions are met and advertising is permissible.

- Those that have discrepancies between the “impression” or “expectation” that the general public perceives from the advertisement content and the actual content
- Those that emphasize the effectiveness of particular surgeries, procedures, etc. and lead people to take the surgeries, etc., despite the fact that the information has little scientific basis

5. Conclusion

As stated in “2. Proper use of GLP-1 receptor agonists,” the efficacy and safety of GLP-1 receptor agonists currently marketed have not been confirmed for off-label uses such as cosmetic treatment, slimming, and weight loss. The possibility cannot be ruled out that when the drugs are not used properly following the electronic package insert it may lead to unexpected health damage. In addition, there is also a concern that the current tight inventory may result in the lack

of drugs necessary for patients with diabetes mellitus who need the treatment. We would appreciate healthcare professionals' cooperation in the proper use of drugs.

This article was prepared jointly by the Pharmaceutical Safety Division, the Pharmaceutical Evaluation Division, the Office of Drug Induced Damages of the General Affairs Division of the Pharmaceutical Safety Bureau of the MHLW, the Policy Planning Division for Pharmaceutical Industry Promotion and Medical Information Management, the General Affairs Division of the Health Policy Bureau of the MHLW, and the Policy Planning Division of the Consumer Affairs Agency.

[References]

<Proper use>

- Notices from relevant societies, etc. on the proper use of drugs (PMDA website) https://www.pmda.go.jp/safety/info-services/drugs/calling-attention/properly-use-alert/0001.html (only in Japanese)
- Notices from pharmaceutical companies on the proper use, etc. (PMDA website) https://www.pmda.go.jp/safety/info-services/drugs/calling-attention/properly-use-alert/0004.html (only in Japanese)
- Optimal Clinical Use Guidelines, Semaglutide (genetical recombination) (Brand name: Wegovy Subcutaneous Injection 0.25 mg SD, 0.5 mg SD, 1.0 mg SD, 1.7 mg SD, 2.4 mg SD) https://www.pmda.go.jp/files/000265450.pdf (only in Japanese)

- Relief System for Adverse Drug Reactions (for healthcare professionals) (PMDA website) https://www.pmda.go.jp/kenkouhigai_camp/index_medical.html

<Measures to address tight inventory>

- Request for Cooperation Due to Tight Inventory of GLP-1 Receptor Agonists (administrative notice from the Policy Planning Division for Pharmaceutical Industry Promotion and Medical Information Management, the Health Policy Bureau, the MHLW, dated July 28, 2023) https://www.mhlw.go.jp/content/001126638.pdf (only in Japanese)
- Request for Cooperation Due to Tight Inventory of GLP-1 Receptor Agonists (Part 2) (administrative notice from the Policy Planning Division for Pharmaceutical Industry Promotion and Medical Information Management, the Health Policy Bureau, the MHLW, dated November 9, 2023) https://www.mhlw.go.jp/content/001165743.pdf (only in Japanese)

<Informed consent>

- Revision of Explanatory Materials for Informed Consent in Medical Treatments not Covered by Health Insurance including Cosmetic Medicine Services (administrative notice from the General Affairs Division, the Health Policy Bureau, the MHLW, dated November 12, 2020) https://www.mhlw.go.jp/content/000694623.pdf (only in Japanese)
- "Check Once Again Before Receiving Cosmetic Medicine Services (detailed version)" (November 2020) (Consumer Affairs Agency website) https://www.caa.go.jp/policies/policy/consumer_policy/information/information_002/pdf/consumer_policy_cms102_201127_02.pdf (only in Japanese)

Attached table <List of MAHs and products of GLP-1 receptor agonists for type 2 diabetes mellitus>

Novo Nordisk Pharma Ltd.	AstraZeneca K.K.	Sanofi K.K.	Eli Lilly Japan K.K.
Victoza Subcutaneous Injection 18 mg	Byetta Subcutaneous Injection 5 μg Pen 300	Lyxumia S.C. Injection 300 μg	Trulicity Subcutaneous Injection 0.75 mg Ateos
Ozempic Subcutaneous Injection 0.25 mg SD	Byetta Subcutaneous Injection 10 μg Pen 300		Mounjaro Subcutaneous Injection 2.5 mg Ateos (marketed by: Mitsubishi Tanabe Pharma Corporation)
Ozempic Subcutaneous Injection 0.5 mg SD			Mounjaro Subcutaneous Injection 5 mg Ateos (marketed by: Mitsubishi Tanabe Pharma Corporation)
Ozempic Subcutaneous Injection 1.0 mg SD			Mounjaro Subcutaneous Injection 7.5 mg Ateos (marketed by: Mitsubishi Tanabe Pharma Corporation)
Ozempic Subcutaneous Injection 2 mg			Mounjaro Subcutaneous Injection 10 mg Ateos (marketed by: Mitsubishi Tanabe Pharma Corporation)
Rybelsus tablets 3 mg (marketing collaboration: MSD K.K.)			Mounjaro Subcutaneous Injection 12.5 mg Ateos (marketed by: Mitsubishi Tanabe Pharma Corporation)
Rybelsus tablets 7 mg (marketing collaboration: MSD K.K.)			Mounjaro Subcutaneous Injection 15 mg Ateos (marketed by: Mitsubishi Tanabe Pharma Corporation)
Rybelsus tablets 14 mg (marketing collaboration: MSD K.K.)			

3

Important Safety Information

Regarding the revision of the PRECAUTIONS of package inserts of drugs in accordance with the Notification dated November 21 and 24, 2023, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 Metyrapone

Brand name (name of company)	Metopiron Capsules 250 mg (Ceolia Pharma Co., Ltd.)
Therapeutic category	Other hormone preparations (including antihormone preparations) Reagents for various function tests
Indications	•Measurement of pituitary ACTH secretory reserve capacity •Cushing's syndrome

PRECAUTIONS (Revised language is underlined.)

[Under new instructions]

8. IMPORTANT PRECAUTIONS (newly added)

<Cushing's syndrome>
Prolonged QT may occur. An electrocardiogram test should be performed as necessary.
Hypokalaemia may occur. Patients should be carefully monitored through methods such as performing tests.

11. ADVERSE REACTIONS
11.2 Other Adverse Reactions

Circulation	Hypotension, hypertension, prolonged QT
Metabolism	Hypokalaemia

Reference information

Number of cases (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports

<Cases involving prolonged QT>
No cases have been reported in Japan to date.
No cases have been reported overseas to date.

<Cases involving hypokalaemia>
One case has been reported in Japan to date. (No patient mortalities)
No cases have been reported overseas to date.

Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 1 738
Japanese market launch: September 1965

Case summary

<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
50s</td><td>Increased blood cortisol (hypertension, hyperlipidaemia, diabetes mellitus)</td><td>750 mg
Approximately 11 months</td><td>Hypokalaemia
Day 1 of administration: The administration of metyrapone was initiated to control hypercortisolaemia.
Approximately month 11 of administration: The patient had hypokalaemia. Deoxycorticosterone increased. Spironolactone was administered concomitantly.
Approximately month 12 of administration: Hypokalaemia improved.
3 years and 4 months after the start of administration: While continuing administration of metyrapone, no adverse events were noted.</td></tr>
<tr><td colspan="5">Laboratory test value
<table>
<tr><th></th><th>Before initiation of administration</th><th>Around the initiation of administration</th><th>Approximately month 1 of administration</th><th>Approximately month 5 of administration</th><th>Approximately month 6 of administration</th><th>Approximately month 9 of administration</th><th>Approximately month 12 of administration</th></tr>
<tr><td>K (mEq/L)</td><td>4.2</td><td>3.1</td><td>3.1</td><td>2.7</td><td>2.9</td><td>2.7</td><td>3.5</td></tr>
</table>
</td></tr>
<tr><td colspan="5">Suspected concomitant drugs: None
Concomitant drugs: Gliclazide, amlodipine besilate, simvastatin, rebamipide</td></tr>
</table>

2 [1] Apixaban, [2] Edoxaban tosilate hydrate, [3] Dabigatran etexilate methanesulfonate, [4] Rivaroxaban, [5] Warfarin potassium

Brand name (name of company)	[1] Eliquis tablets 2.5 mg, 5 mg (Bristol-Myers Squibb K.K.) [2] Lixiana Tablets 15 mg, 30 mg, 60 mg, Lixiana OD Tablets 15 mg, 30 mg, 60 mg (Daiichi Sankyo Co., Ltd.) [3] Prazaxa Capsules 75 mg, 110 mg (Boehringer Ingelheim Japan, Inc.) [4] Xarelto tablets 2.5 mg, 10 mg, 15 mg, Xarelto OD tablets 10 mg, 15 mg, Xarelto fine granules 10 mg, 15 mg, Xarelto dry syrup for pediatric 51.7 mg, 103.4 mg (Bayer Yakuhin Ltd.) [5] Warfarin tablets 0.5 mg, 1 mg, 5 mg, Warfarin granules 0.2% (Eisai Co., Ltd.), and the others
Therapeutic category	Anticoagulants
Indications	[1] •Prevention of ischaemic stroke and systemic embolism in patients with non-valvular atrial fibrillation •Treatment and prevention of the relapse of venous thromboembolism (deep vein thrombosis and pulmonary thromboembolism) [2] •Prevention of ischaemic stroke and systemic embolism in patients with non-valvular atrial fibrillation •Treatment and prevention of the relapse of venous thromboembolism (deep vein thrombosis and pulmonary thromboembolism) •Prevention of venous thromboembolism in patients undergoing any of the following orthopedic surgeries for the lower limbs <excluding 60 mg> Total knee replacement, total hip replacement, and hip fracture surgery [3] Prevention of ischaemic stroke and systemic embolism in patients with non-valvular atrial fibrillation [4] <tablets 2.5 mg> Prevention of thrombus/embolization formation in patients with peripheral arterial disease after lower limb revascularization surgery <tablets 10 mg, 15 mg, OD tablets 10 mg, 15 mg, fine granules> Adults •Prevention of ischaemic stroke and systemic embolism in patients with non-valvular atrial fibrillation •Treatment and prevention of the relapse of venous thromboembolism (deep vein thrombosis and pulmonary thromboembolism) Children •Treatment and prevention of the relapse of venous thromboembolism. <dry syrup> Treatment and prevention of the relapse of venous thromboembolism [5] •Treatment and prevention of thromboembolism (venous thrombosis, myocardial infarction, pulmonary embolism, cerebral embolism, slowly progressive cerebral thrombosis,

	etc.)

PRECAUTIONS (Revised language is underlined.)

[1]-[4]

[Under new instructions]

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **(newly added)**	Acute kidney injury Acute kidney injury may occur after administration of oral anticoagulants. Among cases of acute kidney injury after administration of oral anticoagulants, cases in which haematuria was noted or a renal biopsy showed numerous red cell casts in the renal tubules have been reported.

[5]

[Under old instructions]

Adverse Reactions **Clinically Significant Adverse Reactions** **(newly added)**	Acute kidney injury: Acute kidney injury may occur after administration of oral anticoagulants. Among cases of acute kidney injury after administration of warfarin, cases in which haematuria and/or supratherapeutic INR were noted or a renal biopsy showed numerous red cell casts in the renal tubules have been reported.

[Under new instructions]

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **(newly added)**	Acute kidney injury Acute kidney injury may occur after administration of oral anticoagulants. Among cases of acute kidney injury after administration of warfarin, cases in which haematuria and/or supratherapeutic INR were noted or a renal biopsy showed numerous red cell casts in the renal tubules have been reported.
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) falling under both of the conditions described below among the cases retrieved for adverse reactions (PT) of “anticoagulant-related nephropathy” or “acute kidney injury” from the PMDA's database for adverse drug reactions, etc. reports 1) Information on renal function values (serum creatinine levels, etc. at baseline and onset) required for the diagnosis of acute kidney injury in Clinical Practice Guideline for Acute Kidney Injury 2016 (the committee for preparation of Clinical Practice Guideline for Acute Kidney Injury, edited by Japanese Society of Nephrology, the Japanese Society of Intensive Care Medicine, the Japanese Society for Dialysis Therapy, Japan Society for Blood Purification in Critical Care, the Japanese Society for Pediatric Nephrology) is available, and it satisfies the diagnostic criteria for acute kidney injury. 2) Information on outcomes after the onset of adverse reactions (including information in the column of clinical course and laboratory tests) necessary for the assessment of a causal relationship is available. [1] 0 [2] 4 (No patient mortalities) [3] 7 (No patient mortalities) [4] 3 (No patient mortalities) [5] 4 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: [1] Approximately 579 182

[2] Approximately 934 000
[3] Approximately 103 000
[4] Approximately 499 284
[5] Approximately 390 000 to 460 000
Japanese market launch:
[1] Eliquis tablets: February 2013
[2] Lixiana Tablets: July 2011
Lixiana OD Tablets: November 2017
[3] Prazaxa Capsules: March 2011
[4] Xarelto tablets 2.5 mg: October 2022
Xarelto tablets 10 mg, 15 mg: April 2012
Xarelto OD tablets 10 mg, 15 mg: January 2021
Xarelto fine granules: December 2015
Xarelto dry syrup for pediatric: July 2021
[5] Warfarin tablets 0.5 mg: May 2004
Warfarin tablets 1 mg: May 1962
Warfarin tablets 5 mg: December 1976
Warfarin granules 0.2%: December 2011

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/
administration
duration</th><th colspan="2">Adverse reaction</th></tr>
<tr><th>Sex/
age</th><th>Reason for use
(complication)</th><th colspan="2">Clinical course and treatment</th></tr>
<tr><td>1</td><td>Male
50s</td><td>Deep vein thrombosis
(none)</td><td>30 mg
for 22 days
↓
15 mg
for 7 days</td><td colspan="2">Anticoagulant-related nephropathy
Day 1 of administration: Administration of rivaroxaban 30 mg was initiated for the treatment of deep venous thrombosis. Renal function was normal.
Day 23 of administration: The dose of rivaroxaban was decreased to 15 mg.
Day 29 of administration: Renal impairment was noted with a serum creatinine value of 2.38 mg/dL. Administration of rivaroxaban was discontinued on the next day.
Date unknown: Renal function was further exacerbated.
Date unknown: The patient was admitted to a hospital. Polyuria and polydipsia were observed. It was confirmed by a medical interview that he had had such symptoms since his 40s. He was diagnosed with central diabetes insipidus based on loading tests with hypertonic saline and vasopressin. Microscopic haematuria and increased renal tubule marker were noted. Proteinuria was 4.25g/gCr, antinuclear antibody (speckled type) was 80 times, and anti-neutrophil cytoplasmic antibody was negative.
14 days after discontinuation: The patient was diagnosed with anticoagulant-related nephropathy based on the result of a renal biopsy. In glomerulus, partial intraductal proliferative lesions and narrowing of loop lumen accompanying segmental collapse were observed. Obstruction by red cell casts was observed in renal tubules. The fluorescent antibody method revealed no significant findings.
Approximately 4 months after discontinuation: Serum creatinine value became normal. Urinary findings persisted with proteinuria and occult blood predominantly (+).</td></tr>
<tr><td></td><td colspan="5">Laboratory test value
<table>
<tr><th></th><th>Day 1 of administration</th><th>Day 29 of administration</th><th>After discontinuation:
Approximately 4 months after</th></tr>
<tr><td>Renal function</td><td>Normal</td><td>Serum creatinine value
2.38 mg/dL</td><td>Serum creatinine value became normal.
Urinary findings persisted with proteinuria and occult blood around (+).</td></tr>
</table></td></tr>
<tr><td></td><td colspan="5">Concomitant drugs: None</td></tr>
</table>

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
2	Female 80s	Paroxysmal atrial fibrillation (hypertension, chronic myeloid leukaemia, IgA nephropathy, sick sinus syndrome, epistaxis, epigastric discomfort, impaired appetite, lower limb oedema, pain of lower extremities, hand swelling)	Unknown for 3 days	**Anticoagulant-related nephropathy**	
				Date unknown	Dabigatran etexilate methanesulfonate was administered for paroxysmal atrial fibrillation.
				3 weeks before administration	The patient had epistaxis repeatedly.
				2 weeks before administration	The patient had epigastric discomfort and impaired appetite.
				1 week before administration	Right lower limb oedema with pain was noted.
				Approximately 2 days before administration	The patient had swelling of the right hand.
				Day 1 of administration	Dabigatran etexilate methanesulfonate was switched to edoxaban tosilate hydrate.
				Day 2 of administration	The patient visited the hospital because of stronger oedema and pain in the lower limb resulting in difficulty in walking. Symptoms such as muscle haematoma in the right lower leg, renal impairment, anaemia, coagulopathy were noted, and she had difficulty walking. She was admitted to the hospital for a detailed examination of the cause. Blood transfusion was performed to treat anaemia, and she was followed-up conservatively. Serum creatinine value was 5.12 mg/dL at the time of admission.
				Day 3 of administration (day of discontinuation)	Edoxaban tosilate hydrate was discontinued.
				3 days after discontinuation	Serum creatinine value was 5.58 mg/dL.
				Date unknown	While swelling and haematoma improved and frank haematuria disappeared, the serum creatinine value was elevated up to 5.6 mg/dL.
				14 days after discontinuation	A renal biopsy was performed. Red cell casts and neutrophil infiltration were observed in renal tubules. Findings of anticoagulant-related nephropathy (renal injury due to renal tubular obstruction by haematuria) were noted with IgA nephropathy as a background. Conservative treatment was continued under the policy of follow-up with administration of edoxaban tosilate hydrate kept discontinued.
				16 days after discontinuation	The patient was discharged from the hospital. Anticoagulant-related nephropathy was resolving. Serum creatinine value was 4.95 mg/dL before the hospital discharge.

Laboratory test value

	5 months before administration	1 month before administration	Day 2 of administration	3 days after discontinuation	Before hospital discharge	2 months after discontinuation	Half a year after discontinuation
BUN (mg/dL)	15.2	–	51.4	50.3	–	24.4	19.2
Serum creatinine (mg/dL)	0.87	1.19	5.12	5.58	4.95	1.76	1.33
Prothrombin time (seconds)	12.7	–	43.1	15.0	–	–	–
Prothrombin (%)	88	–	20.0	68	–	–	–
Activated partial thromboplastin time (seconds)	55.8	–	104	55.6	–	–	–
International normalized ratio for prothrombin time	1.08	–	3.52	1.28	–	–	–

Concomitant drugs: Nilotinib hydrochloride hydrate, amlodipine besilate

3 Technetium (^{99m}Tc) galactosyl human serum albumin diethylenetriamine pentaacetic acid

Brand name (name of company)	Asialoscinti Injection (Nihon Medi-Physics Co., Ltd.)
Therapeutic category	Radioactive medicines
Indications	Diagnosis of the function and form of the liver based on scintigraphy

PRECAUTIONS (Revised language is underlined.)

[Under new instructions]

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.) (newly added)	Patients with a history of hypersensitivity to any of the ingredients of this drug
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Shock, anaphylaxis
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports Cases involving shock, anaphylaxis reported in Japan: 4 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 8 000 Japanese market launch: August 1992

Case summary

<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>Female 60s</td><td>To assess the hepatic functional reserve [Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis]</td><td>185MBq Single dose</td><td>
Anaphylactic shock
Primary disease: Intrahepatic bile duct cancer
Medical history: Appendicitis
The patient had no history of adverse drug reaction or allergy.
The patient had no history of administration of this drug.
<table>
<tr><td>Day 1 of administration (day of termination)</td><td>185 MBq of technetium (^{99m}Tc) galactosyl human serum albumin diethylenetriamine pentaacetic acid was administered as an intravenous infusion.</td></tr>
<tr><td>8 minutes after termination of administration</td><td>Marked generalised sweating and mild cyanosis were noted. The patient’s eyes were open, and she responded to the calling of her name. Her blood pressure and SpO_2 could not be measured. Her carotid pulse was impalpable. Breath and heart sounds could not be heard by auscultation. Cardiac massage was initiated on the examination table. Ventilation was initiated using bag-valve-mask (10L/min of oxygen). Generalised redness was noted.</td></tr>
<tr><td>18 minutes after termination of administration</td><td>After the infusion of 1 ample of adrenaline by intravenous hyperalimentation (IVH), the catheter was flushed with 20 mL of normal saline solution. Immediately after that, generalised convulsion occurred. Administration of 500 mL of lactate Ringer's solution was initiated from the side tube.</td></tr>
<tr><td>23 minutes after termination of administration</td><td>Spontaneous breathing was resumed. The patient was fitted with an oxygen mask. She responded to the calling of her name.</td></tr>
<tr><td>25 minutes after termination of administration</td><td>Administration of 10 mL/h of dopamine hydrochloride was initiated.</td></tr>
<tr><td>30 minutes after termination of administration</td><td>After the patient was moved to the stretcher, her blood pressure could not be measured. Cardiac massage was performed, and her body movement and voice were noted.</td></tr>
<tr><td>31 minutes after termination of administration</td><td>The catheter was flushed with 2 mL of dopamine hydrochloride. The patient responded to the calling of her name.</td></tr>
<tr><td>35 minutes after termination of administration</td><td>The dose of dopamine hydrochloride was reduced to 5 mL/h. The patient was admitted to the intensive care unit.</td></tr>
<tr><td>45 minutes after termination of administration</td><td>Anaphylactic shock was resolving.</td></tr>
</table>
Laboratory test value
<table>
<tr><th>Test item (unit)</th><th>Before initiation of administration:</th><th>23 minutes after termination of administration</th><th>27 minutes after termination of administration</th><th>35 minutes after termination of administration</th></tr>
<tr><td>Blood pressure (mmHg)</td><td>–</td><td>57*</td><td>42*</td><td>220/170</td></tr>
</table>
*Unknown whether it is systolic or diastolic blood pressure
Concomitant drugs: Pregabalin, pancrelipase, esomeprazole magnesium hydrate, amino acid/glucose/electrolytes/ vitamins (2-4) kit, bifidobacterial preparation (4), camostat mesilate
</td></tr>
</table>

4
Revision of PRECAUTIONS (No.346)

This section presents details of revisions to the PRECAUTIONS and brand names of drugs that have been revised in accordance with the Notifications dated November 21 and 24, 2023.

1 Other hormone preparations (including antihormone preparations), reagents for various function tests

Metyrapone

Brand name Metopiron Capsules 250 mg (Ceolia Pharma Co., Ltd.)

[Under new instructions]

8. IMPORTANT PRECAUTIONS (newly added)

<Cushing's syndrome>
Prolonged QT may occur. An electrocardiogram test should be performed as necessary.
Hypokalaemia may occur. Patients should be carefully monitored through methods such as performing tests.

11. ADVERSE REACTIONS
11.2 Other Adverse Reactions

Circulation	Hypotension, hypertension, prolonged QT
Metabolism	Hypokalaemia

2 Anticoagulants

[1] Apixaban
[2] Edoxaban tosilate hydrate
[3] Dabigatran etexilate methanesulfonate
[4] Rivaroxaban

Brand name
[1] Eliquis tablets 2.5 mg, 5 mg (Bristol-Myers Squibb K.K.)
[2] Lixiana Tablets 15 mg, 30 mg, 60 mg, Lixiana OD Tablets 15 mg, 30 mg, 60 mg (Daiichi Sankyo Co., Ltd.)
[3] Prazaxa Capsules 75 mg, 110 mg (Boehringer Ingelheim Japan, Inc.)
[4] Xarelto tablets 2.5 mg, 10 mg, 15 mg, Xarelto OD tablets 10 mg, 15 mg, Xarelto fine granules 10 mg, 15 mg, Xarelto dry syrup for pediatric 51.7 mg, 103.4 mg (Bayer Yakuhin Ltd.)

[Under new instructions]

11. ADVERSE REACTIONS
11.1 Clinically Significant Adverse Reactions (newly added)

Acute kidney injury
Acute kidney injury may occur after administration of oral anticoagulants. Among cases of acute kidney injury after administration of oral anticoagulants, cases in which haematuria was noted or a renal biopsy showed numerous red cell casts in the renal tubules have been reported.

3 Anticoagulants

Warfarin potassium

Brand name Warfarin tablets 0.5 mg, 1 mg, 5 mg, Warfarin granules 0.2% (Eisai Co., Ltd.,), and the others

[Under old instructions]

Adverse Reactions
Clinically Significant Adverse Reactions

Acute kidney injury:
Acute kidney injury may occur after administration of oral anticoagulants. Among cases of acute kidney injury after

(newly added)	administration of warfarin, cases in which haematuria and/or supratherapeutic INR were noted or a renal biopsy showed numerous red cell casts in the renal tubules have been reported.
[Under new instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **(newly added)**	Acute kidney injury Acute kidney injury may occur after administration of oral anticoagulants. Among cases of acute kidney injury after administration of warfarin, cases in which haematuria and/or supratherapeutic INR were noted or a renal biopsy showed numerous red cell casts in the renal tubules have been reported.

4 Radioactive medicines

Technetium (^{99m}Tc) galactosyl human serum albumin diethylenetriamine pentaacetic acid

Brand name	Asialoscinti Injection (Nihon Medi-Physics Co., Ltd.)
[Under new instructions]	
2.CONTRAINDICATIONS **(This drug is contraindicated to the following patients.)** **(newly added)**	Patients with a history of hypersensitivity to any of the ingredients of this drug
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions** **(newly added)**	Shock, anaphylaxis

5 Other antitumor agents

Nivolumab (genetical recombination)

Brand name	Opdivo I.V. Infusion 20 mg, 100 mg, 120 mg, 240 mg (Ono Pharmaceutical Co., Ltd.)
[Under new instructions]	
7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION	<Unresectable, advanced or recurrent non-small cell lung cancer> When this drug is co-administered with other antineoplastic drugs, the other antineoplastic drugs to be administered should be selected with sufficient understanding of the contents of the 17.CLINICAL STUDIES section and with reference to the latest Japanese and overseas guidelines or other relevant sources as well as with consideration for the incidence of PD-L1 expression in the patients investigated in the clinical studies. <Neoadjuvant therapy for non-small cell lung cancer> Other antineoplastic drugs to be administered should be selected with sufficient understanding of the contents of the 17.CLINICAL STUDIES section and with reference to the latest Japanese and overseas guidelines or other relevant sources. <Unresectable, advanced or recurrent gastric cancer> When this drug is co-administered with other antineoplastic drugs, the other antineoplastic drugs to be administered should be selected with sufficient understanding of the contents of the 17.CLINICAL STUDIES section and with reference to the latest Japanese and overseas guidelines or other relevant sources. <Radically unresectable, advanced or recurrent oesophageal carcinoma>

When this drug is co-administered with other antineoplastic drugs, the other antineoplastic drugs to be administered should be selected with sufficient understanding of the contents of the 17.CLINICAL STUDIES section and with reference to the latest Japanese and overseas guidelines or other relevant sources.

5

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 October 31, 2023)
◎: Products for which EPPV was initiated after October 1, 2023

	Nonproprietary name / Brand name	Name of the MAH	Date of EPPV initiate
◎	Pegaspargase Oncaspar I.V. Infusion 3750	Nihon Servier Co. Ltd.	October 2, 2023
	Ritlecitinib tosilate Litfulo Capsules 50 mg	Pfizer Japan Inc.	September 27, 2023
	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) Comirnaty intramuscular injection for 6 months to 4 years old	Pfizer Japan Inc.	September 26, 2023
	Tralokinumab (genetical recombination) Adtralza S.C. Injection 150 mg Syringe	LEO Pharma K.K.	September 26, 2023
	Dupilumab (genetical recombination) [1] Dupixent S.C. Injection 200 mg Syringe, [2] Dupixent S.C. Injection 300 mg Syringe, [3] Dupixent S.C. Injection 300 mg Pen	Sanofi K.K.	September 25, 2023
	Lenacapavir sodium Sunlenca Subcutaneous Injection 463.5 mg, Sunlenca Tablets 300 mg	Gilead Sciences K.K.	September 13, 2023
	Futibatinib Lytgobi tablets 4 mg	TAIHO Pharmaceutical Co., Ltd.	September 7, 2023
	Pegcetacoplan Empaveli for Subcutaneous Injection 1080 mg	Swedish Orphan Biovitrum Japan Co., Ltd.	September 4, 2023
	Eculizumab (genetical recombination) Soliris for Intravenous Infusion 300 mg	Alexion Pharma Godo Kaisha	August 23, 2023
	Ruxolitinib phosphate[*1] Jakavi Tablets 5 mg, 10 mg	Novartis Pharma K.K.	August 23, 2023
	Coronavirus modified uridine RNA vaccine (SARS-CoV-2)	Moderna Japan Co.,	August 2,

Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
Spikevax Intramuscular Injection	Ltd.	2023
Purified pineapple stem juice NexoBrid gel 5 g	Kaken Pharmaceutical Co., Ltd.	August 1, 2023
Foslevodopa/foscarbidopa hydrate Vyalev combination subcutaneous infusion	AbbVie GK	July 26, 2023
Anti-human thymocyte immunoglobulin, equine Atgam Intravenous Infusion 250 mg	Pfizer Japan Inc.	July 24, 2023
Pneumococcal 15-valent conjugate vaccine, adsorbed (conjugate with a non toxic variant of diphtheria toxin) (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) [*2] Vaxneuvance Aqueous Suspension Syringes	MSD K.K.	June 26, 2023
Febuxostat Feburic Tablets 10 mg, 20 mg, 40 mg	Teijin Pharma Limited.	June 26, 2023
Somapacitan (genetical recombination) [*3] Sogroya Subcutaneous Injection 5 mg, 10 mg, 15 mg	Novo Nordisk Pharma Ltd.	June 26, 2023
Mirikizumab (genetical recombination) Omvoh Intravenous Infusion 300 mg, Omvoh Subcutaneous Injection 100 mg Autoinjectors, Omvoh Subcutaneous Injection 100 mg Syringes	Eli Lilly Japan K.K.	June 21, 2023
Cholic acid Orphacol Capsules 50 mg	ReqMed Company, Ltd.	June 19, 2023
Vedolizumab (genetical recombination) Entyvio Pens for S.C. Injection 108 mg, Entyvio Syringes for S.C. Injection 108 mg	Takeda Pharmaceutical Company Limited.	June 19, 2023
Crisantaspase Erwinase for intramuscular injection 10000	Ohara Pharmaceutical Co., Ltd.	June 14, 2023
Tirzepatide Mounjaro Subcutaneous Injection Ateos, 7.5 mg Ateos, 10 mg Ateos, 12.5 mg Ateos, 15 mg Ateos	Eli Lilly Japan K.K.	June 12, 2023
Ropeginterferon alfa-2b (genetical recombination) *Besremi* Subcutaneous Injection Syringes 250 μg, 500 μg	PharmaEssentia Japan KK	June 1, 2023
Oxybutynin hydrochloride [*4]	Hisamitsu	June 1,

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
	Apohide Lotion 20%	Pharmaceutical Co., Inc.	2023
	Avatrombopag maleate Doptelet tablets 20 mg	Swedish Orphan Biovitrum Japan Co., Ltd.	June 1, 2023
	Pegvaliase (genetical recombination) Palynziq Subcutaneous Injection 2.5 mg, 10 mg, 20 mg	BioMarin Pharmaceutical Japan K.K.	May 24, 2023
	Mifepristone/misoprostol Mefeego Pack	Linepharma KK	May 16, 2023
	Treprostinil Treprost Inhalation Solution 1.74 mg	Mochida Pharmaceutical Co., Ltd.	May 16, 2023

*1 Graft versus host disease after haematopoietic stem cell transplant (when steroids are not sufficiently effective)

*2 Prevention of invasive disease caused by *Streptococcus pneumoniae* (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) in children

*3 Growth hormone-deficient short stature without epiphyseal closure

*4 Primary palmar hyperhidrosis