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Report on Investigation Results

May 21, 2019

Pharmaceuticals and Medical Devices Agency

I. Summary of the item

[Brand name]	Refer to Appendix 1
[Non-proprietary name]	Refer to Appendix 1
[Marketing authorization holder]	Refer to Appendix 1
[Indications]	Refer to Appendix 1
[Dosage and administration]	Refer to Appendix 1
[Remarks]	Not remarkable
[Investigating office]	Office of Pharmacovigilance I

II. Investigation background

Metformin hydrochloride (metformin) is a biguanide antidiabetic agent, which has been approved for marketing in 100 or more countries including the United States and the EU as of the end of 2018 since it was approved for marketing in France in 1959. In Japan, since Melbin Tablets, etc. were approved for marketing in January 1961 as a drug containing metformin, multiple drugs have been used in the clinical settings. Since multiple cases of death from lactic acidosis induced by phenformin hydrochloride, or a biguanide drug, were reported overseas in 1970s, the package inserts* of metformin in Japan and overseas have provided a precaution to restrict the patient use, the dosage, etc. in order to minimize the risk of lactic acidosis. In the process of package-insert revision regarding lactic acidosis in Japan, there was a concern that patients with renal impairment would be at a higher risk of lactic acidosis because the blood concentration of metformin was increased due to delay in its excretion in those patients. Consequently, the use in patients with renal impairment was more tightly restricted in May 1977, for example, by revising the description of patients with renal impairment to whom the drug should be contraindicated from “patients with serious renal impairment” to “patients with mild or more severe renal impairment.”

* In this article, the “package insert” basically means information intended for the use of health care professionals.

In recent years, the restriction on metformin’s use in patients with renal impairment has been reviewed overseas based on the updated scientific findings on metformin’s safety in patients with renal impairment. The Food and Drug Administration (FDA) and the European Medicines Agency

(EMA) reviewed published papers and other sources and both concluded that metformin may be used in patients with mild to moderate renal impairment. Then, in April and October 2016, respectively, FDA and EMA announced that they would limit the contraindication only to patients with estimated Glomerular Filtration Rate (eGFR[1]) <30 mL/min/1.73 m^2 and that they would revise the package insert in order to add precautions for the use in patients with mild to moderate renal impairment. Based on the announcement, the package inserts of all metformin-containing preparations were revised in Europe and the US.

Based on the above European and US situation, the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare asked the Pharmaceuticals and Medical Devices Agency (PMDA) to conduct “an investigation regarding the revision of the Precautions of the package inserts of preparations containing metformin hydrochloride with respect to lactic acidosis” as of December 14, 2018. The PMDA accordingly conducted the investigation and discussed whether the package inserts should be revised.

PMDA held an Expert Discussion as part of its investigation. The expert advisors present at the Expert Discussion were nominated based on their conflict of interest declarations concerning the relevant products (See Appendix 1), pursuant to the Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

III. PMDA Investigation

1. Measures taken in Europe and the US

The main views/actions of FDA and EMA based on their review of published literature are as follows: Moreover, the description in the European and US package inserts of preparations containing metformin based on the review is provided in Appendix 2.

1.1 Main view/actions of FDA [2]

- To revise the labeling of metformin-containing preparations to indicate that these products may be safely used in patients with mild to moderate renal impairment.
- To revise the labeling to recommend that the measure of kidney function used to determine

1 EMA’s Assessment Report (EMA/867221/2016) provides descriptions in GFR (mL/min), all of which are annotated that GFR levels are adjusted by the mean body surface area of 1.73 m^2.
2 FDA Drug Safety Communications (https://www.fda.gov/downloads/Drugs/DrugSafety/UCM494140.pdf (The last confirmation date: April 1, 2019))

whether a patient can receive metformin be changed from one based on a single laboratory parameter (blood creatinine concentration) to one that provides a better estimate of renal function (i.e., glomerular filtration rate estimating equation (eGFR)). This is because in addition to blood creatinine concentration, the glomerular filtration rate takes into account additional parameters that are important, such as the patient's age, gender, race and/or weight.

- The labeling recommendations on how and when kidney function is measured in patients receiving metformin will include the following information:
  - Before starting metformin, obtain the patient's eGFR.
  - Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m^2.
  - Starting metformin in patients with an eGFR between 30–45 mL/minute/1.73 m^2 is not recommended.
  - Obtain an eGFR at least annually in all patients taking metformin. In patients at increased risk for the development of renal impairment such as the elderly, renal function should be assessed more frequently.
  - In patients taking metformin whose eGFR later falls below 45 mL/minute/1.73 m^2, assess the benefits and risks of continuing treatment. Discontinue metformin if the patient's eGFR later falls below 30 mL/minute/1.73 m^2.
  - Discontinue metformin at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/minute/1.73 m^2; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is stable.

1.2 Main view/actions of EMA [3]

- Metformin-containing medicines can now be used in patients with moderately reduced kidney function (GFR=30–59 mL/min). Use in patients with GFR<30 mL/min is still contraindicated. GFR should be assessed before initiation of treatment and at least annually thereafter.
- Reduced doses should be considered for patients with moderate reduction of kidney function according to dosage recommendations provided in the updated product information. The product information also details risk factors for lactic acidosis, which

3 EMA/868987/2016 (https://www.ema.europa.eu/en/documents/referral/metformin-article-31-referral-use-metformin-treat-diabetes-now-expanded-patients-moderately-reduced_en.pdf (The last confirmation date: April 1, 2019))

should be reviewed prior to and during treatment.

- If fixed-dose combination products containing metformin products are used in patients with reduced kidney function, restrictions and efficacy regarding the other active substance in the combination, the feasibility of dose adjustment and the alternative of using individual tablets should be considered.

2. Description in the package inserts in Japan

In Japan, preparations with a maximum daily dose of 750 mg (branded name: Glycoran Tablets 250 mg and the others, “low-dose preparations”), preparations with a maximum daily dose of 2 250 mg (branded name: Metgluco Tablets 250 mg and “high-dose preparations”), and combination drugs with other antidiabetic agents are marketed as drugs containing metformin (refer to Appendix 1). The description related to lactic acidosis in the package inserts of metformin is provided in Appendix 3.

For the use in patients with renal impairment, the contraindication applies to patients with mild to severe renal impairment for low-dose preparations and to patients with moderate and more severe renal impairment for high-dose preparations. The difference in contraindication between low-dose and high-dose preparations derives from the judgment at the review for marketing approval that Metgluco Tablets 250 mg (approved in January 2010), which had been filed for marketing approval after a low-dose preparation (approved in January, 1961), might be used in patients with mild renal impairment based on clinical studies conducted in Japan (refer to the review report[4] on Metgluco Tablets 250 mg). Of note, for the use in patients with hepatic impairment and elderly patients as well, the contraindication applies to patients with mild to severe hepatic impairment and elderly patients for low-dose preparations and to patients with severe hepatic impairment for high-dose preparations. Thus, the use is restricted more tightly for low-dose preparations than for high-dose preparations for the same reason.

3. Pharmacokinetics of metformin in patients with renal impairment

An investigation was conducted to examine the effect of renal impairment on pharmacokinetics of metformin since metformin is cleared by the kidneys.

(1) Pharmacokinetics in patients with renal impairment (J. Clin. Pharmacol. 1995; 35:1094-102)

The pharmacokinetics of metformin was examined by age category when metformin 850 mg

4 http://www.pmda.go.jp/drugs/2010/P201000009/40009300_22200AMX00234_A100_1.pdf (The final confirmation date: April 1, 2019)

was administered orally as a single dose in non-Japanese subjects with normal renal function or renal impairment. The demographic characteristics (age, renal function) and pharmacokinetic parameter estimates related to plasma metformin are provided in Table 1. In patients with mild and moderate renal impairment, the clearance of metformin decreased and C_{max} and AUC_{inf} increased according to the degree of renal impairment.

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Table 1 Demographic Characteristics and Pharmacokinetic Parameter Estimates Related to Plasma Metformin after a Single 850-mg Dose of Metformin

Renal function category [a] (Age category [b])	Normal renal function (Age category A)	Normal renal function (Age category B)	Mild renal impairment (Age category B)	Moderate renal impairment (Age category B)	Severe renal impairment (Age category B)
Sample size	6	3	5	4	6
Aged (years old)	27.5 ± 4.8	42.7 ± 9.1	42.0 ± 11.0	45.5 ± 6.1	38.3 ± 13.6
CCr (mL/min)	111.5 ± 8.1	101.6 ± 1.2	73.0 ± 6.8	41.4 ± 9.4	21.8 ± 5.8
C_{max} (mg/L)	1.39 ± 0.33	1.64 ± 0.50	1.86 ± 0.52	4.12 ± 1.83	3.93 ± 0.92
AUC_{inf} (μg•h/mL)	9.98 ± 2.12	11.22 ± 3.19	13.22 ± 2.00	58.30 ± 36.58	52.84 ± 29.60
CL_R (mL/min)	636 ± 84	394.7 ± 83.8	383.6 ± 122.3	108.3 ± 57.2	129.5 ± 90.3
CL/F (mL/min)	1155 ± 273	1031.7 ± 251.8	852.4 ± 144.6	238.3 ± 109.9	259.3 ± 129.0
$t_{1/2}$ (h)	6.9 ± 4.2	11.2 ± 5.2	17.3 ± 21.2	16.2 ± 7.6	17.2 ± 9.1

The mean ± standard deviation

CCr: Creatinine clearance, C_{max}: Peak plasma concentration, AUC_{inf}: Area under the plasma concentration-time curve (extrapolated value to the infinity), CL_R: Renal clearance, CL/F: Apparent total body clearance, $t_{1/2}$: Elimination half life

a) CCr-based categorization of renal functions: Normal, CCr >90; mild renal impairment, CCr 61-90; moderate renal impairment, CCr 31-60; and severe renal impairment, CCr 10-30

b) Age category A refers to 18 to 40 years while age category B refers to 21 to 60 years

(2) Pharmacokinetics in type-2-diabetes mellitus patients with renal impairment (EMR200084-622 Study, EMA/867221/2016[5])

The pharmacokinetics of metformin was examined in non-Japanese patients with type 2 diabetes mellitus and different degrees of renal function in a study where the dose of metformin was titrated up at 500 mg/day in Phase 1, 1 000 mg/day in Phase 2, 2 000/day in Phase 3, and 3 000 mg/day in Phase 4 with repeated oral dosing for a week. The metformin plasma trough concentration and lactate levels in a steady state at different CKD classification stages[6] are provided in Table 2. The metformin plasma trough concentrations in patients at Stage 3A and 3B in the CKD Classification were higher by 3.7-fold and 4.2-fold for 500 mg/day, 2.2-fold and 2.5-fold for 1 000 mg/day, and 2.7-fold and 4.2-fold for 2 000 mg/day, respectively, compared with those of the patients at Stage 1 after the drug was administered. There were no subjects whose plasma lactate level reached 5 mmol/L, or the diagnostic criteria of lactic acidosis.

5 EMA Assessment report (https://www.ema.europa.eu/en/documents/referral/metformin-article-31-referral-chmp-assessment-report_en.pdf (The final confirmation date: April 1, 2019))

6 GFR Classification (mL/min/1.73 m²): [Stage 1] ≥90, [Stage 2] 60–89, [Stage 3A] 45–59, [Stage 3B] 30–44, [Stage 4] 15–29, [Stage 5] <15 (Kidney Int. 2005; 67: 2089-100, Evidence-based Clinical Practice Guideline for CKD 2018. Japanese Society of Nephrology; 2018.)

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Table 2 Metformin Plasma Trough Concentration and Lactate Levels Following Repeated Oral Dosing of Metformin for One Week in Patients with Renal Impairment[a)]

CKD Stage		1	2	3A	3B	4	5
Phase 1 [b)] 500 mg/day (500 mg once in the evening)	Sample size	17	11	14	16	12	6
	eGFR (mL/min[e)])	121.2 ± 20.1	77.7 ± 9.7	55.9 ± 6	37.8 ± 5.4	22.6 ± 4.7	12.7 ± 1
	Metformin trough concentration (mg/L)	0.23 ± 0.11 (0.10, 0.44)	0.46 ± 0.26 (0.10, 1.03)	0.86 ± 0.54[c)] (0.10, 2.11)	0.97 ± 0.52 (0.33, 2.0)	1.44 ± 1.13[d)] (0.29, 4.17)	1.38 ± 0.57 (0.83, 2.44)
	Lactate (mmol/L)	-	-	1.34 ± 0.55	1.12 ± 0.37	1.18 ± 0.43	0.73 ± 0.52
Phase 2 [b)] 1000 mg/day (500 mg twice: In the morning and evening)	Sample size	17	11	14	15	12	5
	eGFR (mL/min[e)])	123.3 ± 18	78.5 ± 11.9	53.5 ± 6.2	35.7 ± 6.3	22.3 ± 5.5	11.8 ± 2.6
	Metformin trough concentration (mg/L)	0.50 ± 0.51 (0.10, 2.18)	0.66 ± 0.36 (0.32,1.45)	1.09 ± 0.51 (0.31, 1.82)	1.24 ± 0.50 (0.5, 2.07)	2.28 ± 1.16 (0.89, 4.9)	1.92 ± 0.95 (1.03, 3.53)
	Lactate (mmol/L)	-	-	1.34 ± 0.68	1.31 ± 0.56	1.16 ± 0.38	0.44 ± 0.17
Phase 3 [b)] 2000 mg/day (1000 mg twice: In the morning and evening)	Sample size	15	11	13	13	11	5
	eGFR (mL/min[e)])	121.7 ± 22.3	80.3 ± 7.5	55.3 ± 8.1	37.3 ± 5.5	22.5 ± 3.3	12 ± 1.2
	Metformin trough concentration (mg/L)	0.49 ± 0.30 (0.10, 1.1)	0.84 ± 0.62 (0.11, 2.0)	1.31 ± 0.90 (0.48, 3.04)	2.07 ± 1.03 (0.76, 4.06)	3.09 ± 1.58 (1.55, 7.2)	4.37 ± 1.73 (3.07, 7.19)
	Lactate (mmol/L)	-	-	1.4 ± 0.56	1.21 ± 0.64	1.47 ± 0.67	0.63 ± 0.14
Phase 4 [b)] 3000 mg/day (1000 mg in the morning, 200 mg in the evening)	Sample size	10	-	-	-	-	-
	eGFR (mL/min[e)])	123.8 ± 19	-	-	-	-	-
	Metformin trough concentration (mg/L)	0.82 ± 1.09 (0.17, 3.88)	-	-	-	-	-
	Lactate (mmol/L)	-	-	-	-	-	-

The mean ± standard deviation, -: Data not available

a) Metformin plasma concentration and lactate level measured 12 hours after the last administration of repeated dosing for one week

b) A wash-out period of one week is set between each regimen c) 13 patients, d) 10 patients.

e) The study says that eGFR normalized to an average surface area (size) of 1.73 m^2 with corrected physical constitution was used.

(3) The pharmacokinetics in type 2 diabetes mellitus with renal impairment (Diabetes Care. 2010; 33: 1291-3)

Metformin plasma trough concentration was measured at week 8 of metformin administration

in 137 non-Japanese patients with type 2 diabetes mellitus and different degrees of renal function. Patients with eGFR >60 (n=107), 30–60 (n=21), and <30 (n=9) mL/min/1.73 m^2 had a median trough metformin plasma concentrations[7] (range) of 0.58 (0.01, 2.67) mg/L, 1.00 (0.02, 1.96) mg/L, and 1.15 (0.77, 2.40) mg/L, respectively. The median doses (range) of metformin were 1 500 (500, 3 000) mg for patients with eGFR >60, 1 500 (500, 3 000) mg for eGFR 30–60, and 1 500 (1 000, 3 000) mg for eGFR <30. The author said "the trough concentrations of metformin of 20 μmol/L (2.6 mg/L) may be used as preliminary upper therapeutic limit."

(4) Population pharmacokinetic analysis (Clin Pharmacokinet. 2013; 52: 373-84)

The population pharmacokinetics (PPK) was analyzed by using the metformin plasma concentration data of 4 895 samples obtained from a total of 3 studies: A study in non-Japanese patients with type 2 diabetes mellitus (Study A: 120 patients) and 2 studies (Study B: 16 patients, Study C: 169 patients) in healthy subjects (the software used: NONMEM VI). Dosing simulations revealed that to ensure the 95th percentile of metformin C_{max} is below 5 mg/L[8], maximum metformin doses of 500, 1 000, 2 000, and 3 000 mg daily should be prescribed to patients with a respective CL_{CR} of 15, 30, 60, and 120 mL/min.

4. Description status in Japanese and oversea published literature, guidelines, etc.

4.1 Published literature

The details of published literature were investigated to assess the risk of developing lactic acidosis in the patients with renal impairment on metformin. The main details[9] are as follows:

(1) Metformin in patients with type 2 diabetes and kidney disease: A systematic review (JAMA. 2014; 312: 2668-75)

A systematic review of 65 pharmacokinetic/metabolic studies, large case series, retrospective studies, meta-analyses, and a clinical trial was conducted to assess the relation between the use of metformin and lactic acidosis in type 2 diabetes patients with renal impairment. Drug levels generally remain within the therapeutic range and lactate concentrations are not

7 In the literature, the unit of metformin plasma trough concentrations was μmol/L. To use a single unit in this report, the concentration was converted to mg/L at PMDA by using the metformin's molecular weight (free base) of 129.1636.

8 The rationale was not provided in the article. It is stated that metformin plasma concentration usually exceeds 5 mg/L in patients with lactic acidosis related to metformin in the US package inserts of metformin (Glucophage, etc.).

9 The candidate literature includes 99 report references in FDA's Drug Safety Communication and the documents released by EMA (EMA/868987/2016, EMA/867221/2016 (Assessment report), including some duplications, the same hereinafter) as well as the literature without case reports among 167 pieces of literature, which contain descriptions regarding "metformin," "lactic acidosis" and "renal function," and which were retrieved by JMEDPlus and EMBASE (as of December 31, 2018). Of the 266 pieces of candidate literature, as a result of review of their abstract, the literature was selected, which was about a systematic review, meta-analysis, randomized clinical study or population-based cohort study that was conducted to examine the risks of developing lactic acidosis in patients with renal impairment on metformin. No literature about a randomized clinical study was found.

substantially increased when metformin is used in patients with mild to moderate chronic kidney disease (hereinafter referred to "CKD") (eGFR, 30–60 mL/min/1.73 m^2). The overall incidence of lactic acidosis in metformin users varies across studies from approximately 3 per 100 000 person-years to 10 per 100 000 person-years and is generally indistinguishable from the background rate in the overall population with diabetes mellitus. There are limited data indicating an increased risk of lactic acidosis in metformin users with CKD, and no randomized controlled studies have been conducted to examine the safety of metformin in patients with significantly impaired renal function. The author concludes that "available evidence supports cautious expansion of metformin use in patients with mild to moderate CKD, as defined by eGFR, with appropriate dose reductions and careful follow-up of kidney function."

(2) Effectiveness and safety of metformin in 51675 patients with type 2 diabetes and different levels of renal function: A cohort study from the Swedish National Diabetes Register (BMJ Open, 2012, 2: e001076)

The effectiveness and safety of metformin by renal function were examined in the cohort study where 51 675 patients with type 2 diabetes were registered in Swedish National Diabetes Register. A composite end point "acidosis/serious infection" defined by related diagnosis of acidosis, shock, acute renal failure and serious infections was used to evaluate the occurrence of lactic acidosis. Metformin, compared with any other treatment, showed reduced risks of "acidosis/serious infection" in patients with eGFR 45–60 mL/min/1.73 m^2 (adjusted HR 0.85, [95% CI: 0.74, 0.97]) and did not increase risks of "acidosis/serious infection" in patients with eGFR 30–45 mL/min/1.73 m^2 (adjusted HR: 0.98 [95% CI: 0.79, 1.21]).

(3) Incidence of lactic acidosis in patients with type 2 diabetes with and without renal impairment treated with metformin: A retrospective cohort study (Diabetes Care. 2014; 37: 2291-5)

A study using the patient records in the UK Clinical Practice Research Datalink was conducted. A total of 77 601 patients treated with metformin for type 2 diabetes were identified. There were 35 lactic acidosis events (10.37/100 000 person-years [95% CI: 7.22, 14.42]) as a result of a retrospective study using the patient records in the UK Clinical Practice Research Datalink. Of these, no fatal cases were found and 23 cases were associated with complications. The incidences [95% CI] of lactic acidosis per renal function are 7.6 [0.9, 27.5]/100 000 person-years for normal kidney function (CKD stage 1 diagnosis or GFR >90 mL/min/1.73 m^2, the same hereinafter 4.6 [2.00, 9.15]/100 000 person-years for mildly impaired kidney function (CKD stage

2 diagnosis or GFR >60 or ≤90), 17 [10.89, 25.79]/100 000 person-years for moderately impaired kidney function (CKD stage 3 diagnosis or GFR >30 or ≤60), and 39 [4.72, 140.89]/ 100 000 person-years for severely impaired kidney function (CKD stage 4 or stage 5, end-stage renal disease, or GFR ≤30), showing no significant difference across patient populations with different renal functions.

(4) Risk of lactic acidosis or elevated lactate concentrations in metformin users with renal impairment: A population-based cohort study (Diabetes Care. 2014; 37: 2218-24)

A cohort study was conducted in 223 968 metformin users and 34 571 metformin non-users by using the UK Clinical Practice Research Datalink in order to investigate the relation between treatment with metformin and lactic acidosis or risks of an increase in lactate level in diabetes patients with renal impairment. The crude incidence of lactic acidosis or elevated lactate concentrations in current metformin users was 7.4 per 100 000 person-years (vs. 2.2 per 100 000 person-years in non-users). Compared with non-users, risk of lactic acidosis or elevated lactate concentrations in current metformin users was significantly associated with a renal function of eGFR <60 mL/min/1.73 m^2 (adjusted HR 6.37 [95% CI: 1.48, 27.5]). An increase in the lactate level and risks of lactic acidosis were further increased by treatment with metformin ≥730 g in the preceding year (adjusted HR 11.8 [95% CI: 2.27, 61.5]) and a recent high daily dose (>2 g/day) of metformin (adjusted HR 13.0 [95% CI: 2.36, 72.0]) in the current metformin users with renal impairment. The author concludes that "the study is consistent with current recommendations that the renal function of metformin users should be adequately monitored and that the dose of metformin should be adjusted, if necessary, if renal function (eGFR) falls below 60 mL/min/1.73 m^2."

(5) Metformin use and risk of lactic acidosis in people with diabetes with and without renal impairment: A cohort study in Denmark and the UK. (Diabet Med. 2017; 34: 485-9)

A cohort study was conducted in 43 580 metformin users and 37 788 non-metformin antidiabetic agent users (metformin non-users) in northern Denmark, 102 688 metformin users and 28 788 metformin non-users in the UK, by using the Aarhus University Prescription Database in Denmark and the Clinical Practice Research Datalink in the UK. In Denmark, the incidence rates of lactic acidosis were 11.6 [95% CI: 7.0, 18.1] for metformin users and 1.8 [95% CI: 0.4, 5.4] for metformin non-users per 100 000 person-years. In the UK, the corresponding lactic acidosis incidence rates were 6.8 [95% CI: 4.6, 9.6] for metformin users and 1.0 [95% CI: 0.01,

5.7] for metformin non-users per 100 000 person-years. The incidence rates increased with decreasing baseline eGFR in both countries. The author concludes that “Risk of lactic acidosis was higher in metformin users than in metformin non-users, and increased with decreasing eGFR, although this could be attributable to surveillance bias; however, diagnosed lactic acidosis was rare and can occur regardless of renal function.”

(6) Epidemiology of lactic acidosis in type 2 diabetes patients with metformin in Japan. (Pharmacoepidemiol Drug Saf. 2016; 25: 1196-1203)

The relation between the use of metformin and lactic acidosis was examined by using the Japanese Medical Data Vision claims database. 30 patients with lactic acidosis were identified among 283 491 treated type 2 diabetes mellitus patients with 504 169 patient-years of follow-up. Crude incidence of lactic acidosis was 5.95 per 100 000 patient-years. The age-sex adjusted incidence rates in metformin users and non-users were 5.80 and 5.78/100,000 person-years, respectively (Incidence rate ratio, 1.00 [95% CI: 0.41, 2.47]). T2DM patients with chronic kidney disease (CKD) were more likely to develop lactic acidosis than those without CKD (adjusted hazard ratio (aHR), 7.33, [95% CI: 3.17, 16.96]). Use of metformin was not associated with an increase in the risk of lactic acidosis in the study population (aHR, 0.92, [95% CI: 0.33, 2.55]), and in the propensity score matched cohort (aHR, 0.90, [95% CI: 0.26, 3.11]). Even for patients with a complication of CKD, no increased risks of lactic acidosis were observed in metformin users compared with metformin non-users (HR: 0.66 [95% CI: 0.18, 2.45], propensity-score adjusted HR: 1.04 [95% CI: 0.33, 3.28]).

(7) Metformin use and mortality in patients with advanced chronic kidney disease: National, retrospective, observational, cohort study. (Lancet Diabetes Endocrinol. 2015; 3: 605-14)

We did a retrospective, observational, cohort study of type 2 diabetes patients with advanced chronic kidney disease (CKD) who were enrolled prospectively in Taiwan’s national health insurance research database. 12 350 patients with type 2 diabetes and CKD (serum creatinine concentration >530 μmol/L) were selected and 813 metformin users were matched by propensity score to 2 439 non-users. All-cause mortality was reported in 434 (53%) of 813 metformin users and in 1 012 (41%) of 2 439 non-users. After multivariate adjustment (e.g. complications, co-administered drugs, etc.), metformin use was an independent risk factor for mortality regardless of the above risks (adjusted HR: 1.35, [95% CI: 1.20, 1.51]). On the other hand, metformin use compared with no use was associated with a higher incidence of metabolic acidosis, but no

significant risks were observed (adjusted hazard ratio 1.30, [95% CI: 0.88, 1.93]). The author concludes that "Use of metformin in type 2 diabetes people with advanced CKD (roughly equivalent to Stage 5 of CKD Classification) in this study is not associated with an increased risk of metabolic acidosis, but is associated with an increased risk of all-cause mortality. Metformin use should not be encouraged in this patient group."

4.2 Guidelines, etc.

The description status of Japanese and overseas guidelines, etc. regarding administration of metformin or biguanides to patients with renal impairment is as follows:

(1) Japanese Clinical Practice Guideline for Diabetes 2016 (The Japan Diabetes Society, 2016)

The following contents are provided in the section of "20 Acute metabolic complications of diabetes, sick days, and infectious diseases."

- Lactic acid is metabolized in the process of gluconeogenesis in the liver and kidneys. However, lactic acid tends to be produced during its metabolism in the liver and kidneys in hypoxia and patients with diabetes mellitus. Biguanides are said to increase the blood lactate level due to decreased functions in the liver and kidneys because the drugs inhibit gluconeogenesis.
- There is a report that no increase in the blood lactate level is observed in patients with mild renal impairment who received oral metformin. On the other hand, a prospective study with a sample size of approximately 200 000 revealed an increased risk of lactic acidosis in patients with eGFR <60 mL/min/1.73 m^2 who received oral metformin with a dose >2 g/day. In fact, most of the lactic acidosis associated with biguanides occurs in patients with renal impairment as a comorbid disease.
- For the proper use of biguanides (including precautions for patients with renal impairment), the summary of "Recommendation for Proper Use of Biguanides (revised in 2014)" (by the Japan Diabetes Society, the Committee on the Proper Use of Biguanides) is provided.

(2) Recommendation for Proper Use of Biguanides (by the Japan Diabetes Society, the Committee on the Proper Use of Biguanides, 2016)

In May, 2016, the above "Recommendation for Proper Use of Biguanides (revised in 2014)" was revised as "Recommendation for Proper Use of Metformin." The recommendation provides the following details:

- Refrain from administering metformin to patients with poor general conditions, such as

patients with poor oral intake and bedridden patients.

- Renal function should be assessed by eGFR. Metformin is contraindicated[10] in patients with an eGFR below 30 mL/min/1.73 m^2. Metformin should be administered carefully in patients with eGFR of 30–45 mL/min/1.73 m^2 based on the benefit-risk balance.
- Attention needs to be paid to patients with dehydration, during sick days, excessive alcohol consumption, etc.
- Metformin is contraindicated in patients with severe cardiovascular/pulmonary function impairment and preoperative or postoperative patients. Metformin should be administered carefully to patients with mild to moderate hepatic impairment.
- Metformin should be administered carefully to elderly patients. Since elderly patients have often decreased renal and hepatic functional reserve, they should be carefully and regularly monitored for renal function (eGFR), liver function, and other conditions. Consider dose adjustment or whether the administration should be continued when applicable. More careful judgment is required especially for the elderly aged 75 years or older.

(3) Standards of Medical Care in Diabetes 2019 (The American Diabetes Association, 2019)

The drug is cleared by renal filtration, and very high circulating levels (e.g., as a result of overdose or acute renal failure) have been associated with lactic acidosis. However, the occurrence of this complication is now known to be very rare, and metformin may be safely used in patients with reduced estimated glomerular filtration rates (eGFR); the FDA has revised the label for metformin to reflect its safety in patients with eGFR ≥30 mL/min/1.73 m^2.

(4) Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (ESAD) (ADA/ESAD, 2018)

Metformin should not be used in patients with an eGFR, 30 mL min^{-1} [1.73 m]$^{-2}$ and dose reduction should be considered when the eGFR is 45 mL min^{-1} [1.73 m]$^{-2}$. Caution should be taken when conditions are present that may reduce eGFR.

(5) IDF Clinical Practice Recommendations for managing Type 2 Diabetes in Primary Care

[10] Metformin is contraindicated in “patients with moderate or more severe renal impairment” for high-dose drugs and “patients with renal impairment (including mild impairment)” for low-dose drugs according to the current package insert.

(International Diabetes Federation, 2017)

Metformin dose should be reduced to 1000 mg per day when renal function is in stage 3A and contraindicated when renal function is in stage 3B or above.

(6) Evidence-based Clinical Practice Guideline for CKD 2018. Japanese Society of Nephrology; 2018.)

Sulfonyl urea derivatives and biguanides have long known to be a risk of severe hypoglycemia and lactic acidosis to CKD patients and are contraindicated[11] in patients with GFR ≤30.

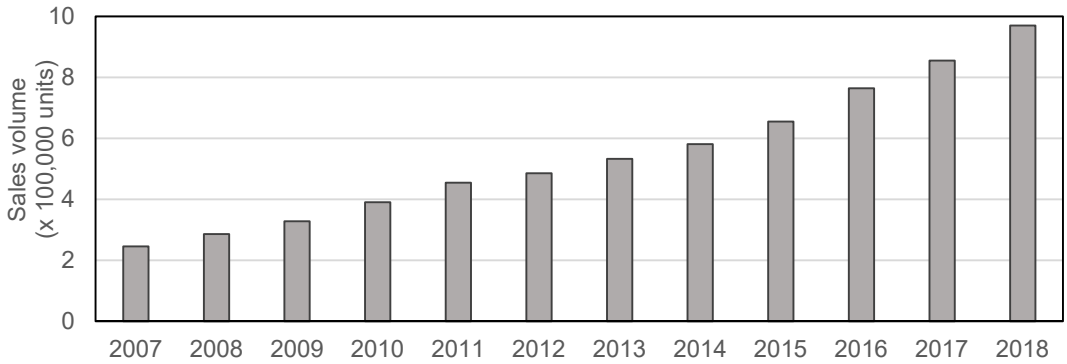
(7) Diabetic Kidney Disease– A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO) (KDIGO, 2015)

The use of metformin in CKD is restricted by FDA guidelines. Restrictions based on eGFR may be more clinically useful; however, serum creatinine concentration may reflect factors such as age, weight, or race that are unrelated to the level of metformin clearance.

The available evidence suggests that the dose of metformin should be reduced to a maximum of 1000 mg per day when the eGFR reaches 45 mL/min/1.73 m^2, and should generally be discontinued when the eGFR reaches 30 mL/min/1.73 m^2. The use of metformin may be appropriate in patients with even more advanced CKD (eGFR 15–29 mL/min/1.73 m^2) if the kidney disease is stable and if alternative treatments to manage glycemia are unavailable or produce significant side effects.

5. Actual use in Japan

Changes in sales volume of metformin-containing preparations from 2007 to 2018 in Japan are provided in Figure 1.



[11] In the current package inserts, they are contraindicated in patients with “moderate or more severe renal impairment” for high-dose drugs and patients with “renal impairment (including mild impairment)” for low-dose preparations.

Figure 1 Changes in Sales Volume* of Metformin-Containing preparations

*Copyright© 2019 IQVIA., Calculated based on JPM Dec 2007-2018 MAT, Reprinted with permission

The prescription status of metformin-containing preparations in recent years was investigated by using the third open data of National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) (the data period: April, 2016 to March, 2017)[12]. The volume of prescribed metformin in the data set is provided in Table 3, which shows that high-dose preparations accounted for 90% or more of the volume.

[12] The data are based on "the volume per therapeutic category by sex and age prescribed to outpatients (outside the hospital)," "the volume per therapeutic category by sex and age prescribed to outpatients (in the hospital)," and the volume per therapeutic category by sex and age prescribed to inpatients" in "prescribed drugs (oral/topical/injectable). (https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000177221_00002.html(The last confirmation date: April 9, 2019)

Table 3 The volume of top 100 metformin drugs that have been most commonly prescribed as an antidiabetic agent * (patients aged 18 years or older).

Classification**	Inpatient	Outpatient (in the hospital)	Outpatient (outside the hospital)
High-dose preparations	19 103 277 tablets	390 885,513 tablets	1 505 197 943 tablets
Low-dose preparations	104 239 tablets	4 542 803 tablets	17 142 28 tablets
Combination drugs	302 691 tablets	19 994 634 tablets	128 707 761 tablets

* Drugs that are applicable to Therapeutic Category 396

**They were extracted from “medical department hospitalization receipt, DPC receipt” for “inpatient”, “medical department outpatient receipt” for “outpatient (in the hospital),” and the database of preparation receipts for “outpatient (outside the hospital).”

6. Adverse reaction reports in Japan

A total of 417 cases (complete reports) of “lactic acidosis,” a preferred term, (PT) of MedDRA, as a serious adverse reaction, associated with metformin-containing preparations were reported from the marketing authorization holder of the products investigated to PMDA (the search period: April 1, 2004 to December 31, 2018). Of those, the cases that were considered to be explicitly duplicated according to patient information or other sources were removed and the remaining 347 cases were examined for the occurrence trend.

6.1 Discussion about the entire adverse reaction reports

Changes in the occurrence of lactic acidosis were examined based on the years when lactic acidosis occurred, which are written in adverse reaction case reports. The years when lactic acidosis occurred were provided for 249 of 347 cases. Figure 2 provides the number of patients by year who developed lactic acidosis. The number of cases of lactic acidosis had increased year by year until 2014 while the number was almost stable with 25 to 38 cases/year in and after 2014, showing no specific fluctuations. Given that the sales volume of metformin-containing preparations has been increased in recent years as shown in Figure 1, the incidence of lactic acidosis in metformin users does not seem to show an increasing trend, but caution is required nonetheless.

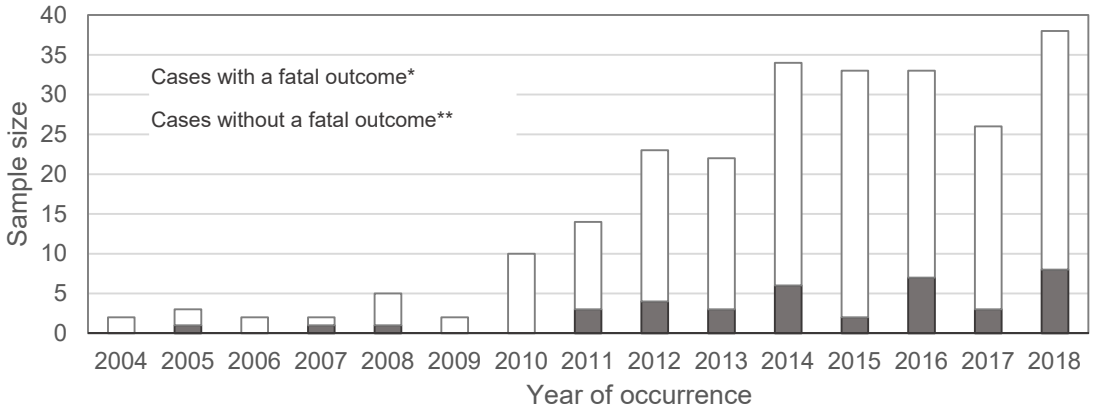


Figure 2 Number of Occurrence of Lactic Acidosis by Year collected in Japan under Serious Adverse Reaction Reports

* Causality between metformin and death was not assessed.

**The total of cases whose outcome is “recovered,” “recovering,” “recovered with sequela,” “not recovered,” and “unknown.”

Regarding background factors of cases of lactic acidosis, the presence or absence of factors that affect the occurrence of lactic acidosis stated in the package inserts was examined based on adverse reaction case reports (Table 4).

Table 4 Factors that affect the Occurrence of Lactic Acidosis (duplications included)

Background factor	Number of patients (the percentage in 347 patients)
Renal impairment (chronic)	97 (28.0%)
Renal impairment (acute deterioration at occurrence)	168 (48.4%)
Hepatic impairment (chronic)	36 (10.4%)
Hepatic impairment (acute deterioration at occurrence)	22 (6.3%)
Cardiovascular diseases	67 (19.3%)
Alcohol drinking	85 (24.5%)
Dehydration	158 (45.5%)
Poor oral intake, such as anorexia	122 (35.2%)
Co-administration of diuretics	83 (23.9%)
Infections, shock	77 (22.2%)
Iodinated contrast medium administered immediately before occurrence	17 (4.9%)
Operation performed immediately before occurrence	11 (3.2%)

The factors found in 20% or more of patients with adverse reactions (duplications included)

were "renal disorder (chronic)," "renal disorder (acute deterioration at occurrence)," "alcohol drinking," "dehydration," "poor oral intake," "co-administration of diuretics," and "infections, shock." Of the 97 cases with "renal disorder (chronic)," 77 (79%) also have other several factors ("dehydration," "poor oral intake," or "co-administration of diuretics"). For cases with renal impairment (acute deterioration at occurrence), it was difficult to distinguish between renal disorder as a background factor and deteriorated renal function due to occurrence of lactic acidosis. In multiple cases with "dehydration," "poor oral intake," or "co-administration of diuretics", patients continuously used metformin despite already being dehydrated due to co-administration of diuretics, poor oral intake, etc., and they developed lactic acidosis. For "alcohol drinking," there were patients who had a complication of alcoholic liver injury and patients who had excessive alcohol consumption and developed lactic acidosis during treatment with metformin.

Outcomes of lactic acidosis in 347 cases include “recovered” in 195, “recovering” in 74, “recovered with sequela” in 4, “not recovered” in 4, “death” in 50, and “unknown” in 20 cases. The factors (duplications included) found in 20% (10 cases) or more of the 50 cases with the outcome of death include "renal disorder (acute deterioration at occurrence)" in 24, "dehydration" in 22, "renal disorder (chronic)" in 12, and "co-administration of diuretics," "poor oral intake," and "infections, shock" in 11 cases each.

6.2 Discussion about the adverse reaction reports on patients with moderate renal impairment

The eGFR level prior to the occurrence of lactic acidosis that was recorded in the report or eGFR was calculable in 73 of 347 cases. The breakdown of eGFR (mL/min/1.73 m^2) in 73 patients is as follows: <30 in 19 patients; ≥30 and <45 in 23; ≥45 and <60 in 20; ≥60 and <90 in 10; and ≥90 in 1.

Of the 43 patients with moderate renal impairment (eGFR ≥30 and <60), the adverse reaction case reports on 21 patients stated dehydration (including the patients for whom dehydration was suspected based on the laboratory results). Of the 22 patients whose report did not mention dehydration, other factors that affect the occurrence of lactic acid acidosis were found in 14 patients (cardiovascular diseases in 7 patients, poor oral intake such poor appetite in 7, co-administration with diuretics in 6, alcohol drinking in 5, infection/shock in 4, and chronic liver disease in 4. Some are duplicated). Outcomes of lactic acidosis in 43 patients with moderate renal impairment include 'recovered' in 22 patients, 'recovering' in 15, and 'death' in 6. Of the 6 patients with the outcome of death, 1 patient may have overdosed on metformin given his/her blood concentration was extremely high (110.6 mg/L) at the occurrence of lactic acidosis while the other

5 patients may have been affected by other factors as well (alcohol drinking, dehydration, cardiac failure, peripheral circulatory failure due to shock, etc.).

IV. PMDA's judgment based on investigation results

1. Administration of metformin to patients with moderate renal impairment

1.1 Appropriateness of administration of metformin to patients with moderate renal impairment

The PMDA considers that administration of metformin may be safely used in patients with moderate renal impairment (eGFR 30–60 mL/min/1.73 m^2) if risks are minimized. The risk minimization measures include decision for initiation of treatment or its continuation based on the patient's renal function and the presence of other factors that affect renal function, as well as dose selection according to the renal function. The reasons that led to this opinion of PMDA are as follows:

- That multiple practice guidelines, etc. in Japan and overseas allow administration of metformin to patients with mild and moderate renal impairment (Refer to "III-4.2 Guidelines, etc.").
- An overseas clinical pharmacokinetics study (EMR200084-622 Study) demonstrated that the metformin trough concentration in patients at CKD stage 3A and 3B who received metformin at 2 000 mg/day and 1 000 mg/day, respectively, was within the trough concentration range (≤2 000 mg/day for 3A and ≤1 000 mg/day for 3B) in patients with normal renal function (at CKD stage 1) who received metformin at a high dose (3 000 mg/day). PPK analysis estimated that the steady state C_{max} of metformin would be comparable to the one measured when the renal function was normal if doses were reduced according to the renal function. Based on the above, it is considered possible to decrease the C_{max} and trough concentration of metformin in patients with moderate renal impairment to the levels comparable to those of patients with normal renal function if doses are appropriately adjusted according to the patient's renal function (Refer to the section of "III-3. Pharmacokinetics in patients with renal impairment").
- The serious adverse reaction reports of lactic acidosis in Japan in 347 cases include 43 with moderate renal impairment (eGFR 30–60 mL/min/1.73 m^2), of which 35 (81.4%) had risk factors other than renal function (e.g. dehydration, cardiovascular diseases). In addition, risk factors other than renal function were also found in 10 of 11 cases (90.9%) who were confirmed to have eGFR ≥60 mL/min/1.73 m^2 and in 201 of 250 patients (80.4%) who did not have "renal disorder (chronic)" in the report. Therefore, risk factors other than renal function may have affected the development of lactic acidosis (Refer to the section of "III-6. Adverse reaction reports in Japan").

In addition, PMDA considers it appropriate that metformin remains contraindicated in dialysis

patients and patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) since multiple guidelines, etc. in Japan and overseas and the package inserts in Europe and the US prohibit its use in those patients.

As for assessment for renal function, descriptions related to assessment for renal function (seriousness classification of patients with renal impairment, precautions on assessment for renal function at the start of/during administration, etc.) will be revised to provide descriptions based on eGFR in the package inserts of metformin-containing preparations in Japan, too, as in Europe and the US. This decision took into account that guidelines, etc. in Japan and overseas recommend to make assessment based on eGFR, which takes into account creatinine levels as well as other factors that affect creatinine levels (age, body weight, race, etc.) (Refer to the section of "III-4. Description in Japanese and oversea published literature, guidelines, etc.").

1.2 Doses in patients with renal impairment

The following is the explanation by the marketing authorization holder of the high-dose brand-name product (Metgluco Tablets) (Sumitomo Dainippon Pharma Co., Ltd.) regarding the necessity to provide information on approximate doses for Japanese patients with renal impairment in the package insert:

Metformin is cleared by the kidneys, and it is demonstrated that blood metformin concentration increases in patients with renal impairment compared with those with normal renal function. When a maximum daily dose of 2 250 mg is administered to a patient with moderate renal impairment without dose adjustment, the blood metformin concentration will be increased compared to a patient with normal renal function, which raises a concern that the risk of lactic acidosis, etc. will be increased in those with moderate renal impairment. This is why we consider it necessary to state dose reduction according to the renal function in the package insert.

To determine the doses in Japanese patients with renal impairment, the data from single-dose studies conducted in Japanese or in non-Japanese healthy adults have not demonstrated an evident difference in the pharmacokinetics of metformin between Japanese and non-Japanese patients. However, C_{max} and $AUC_{0\text{-}48}$ were higher by 30–55% and 22–36% in Japanese, respectively, compared with those of non-Japanese patients (the summary of application document of Metgluco 2.7.2.3.2). Therefore, it is considered to be appropriate to presume, when the safety is taken into account, that the pharmacokinetics differs between non-Japanese and Japanese patients. The approximate maximum daily dose in Japanese patients with renal impairment should be specified as in Table 5 as a result of examination on dose adjustment for patients with renal impairment in the EU, the percentage of an increase in plasma metformin

concentration when renal impairment occurred in non-Japanese patients, differences in pharmacokinetics between Japanese and non-Japanese healthy adults, etc.

Table 5 Dose Adjustment of Metformin in Japanese Patients with Renal Impairment

Renal function	eGFR (mL/min/1.73 m^2)	Approximate maximum daily dose	(Reference) The maximum daily dose in EU
Normal	90≤ eGFR	2 250 mg	3 000 mg
Mild impairment	60≤ eGFR <90	2 250 mg	3 000 mg
Moderate impairment	45≤ eGFR <60	1 500 mg	2 000 mg
	30≤ eGFR <45	750 mg	1 000 mg
Severe impairment	eGFR <30	Contraindicated	Contraindicated

PMDA's view is as follows: In view of reduction in risks associated with increased exposure to metformin in patients with moderate renal impairment, it is considered useful to provide medical institutions with the approximate maximum daily dose in patients with moderate renal impairment proposed by the marketing authorization holder. Given that the current package inserts of metformin caution to start treatment with the drug at a low dose and to determine the maintenance dose while monitoring the effect, in patients with moderate renal impairment, administration of metformin would start at a low dose and an appropriate dose specific to individual patients would be given, too. However, the presentation of the approximate maximum daily dose in patients with moderate renal impairment can lead to a misunderstanding that the stated maximum daily dose should be selected. Therefore, it is necessary to caution more thoroughly to start metformin at a low dose and adjust the subsequent doses depending on the patient's condition to avoid the misunderstanding. In this regard, it is considered appropriate that this precaution accompanies the suggested approximate maximum daily dose in Japanese patients with renal impairment in the package inserts. After the revision of precaution decided this time is adopted for safe use of metformin in patients with moderate renal impairment, PMDA and the MAH will collect information regarding the doses administered to patients with moderate renal impairment in the clinical settings and the safety at the occurrence of lactic acidosis, etc. to review the effects of actions taken this time.

2. Patient background factors related to lactic acidosis except renal impairment

Expected risk factors that had been cautioned in the package inserts were found in approximately 60% of the cases of serious lactic acidosis reported in Japan (Refer to the section of "III-6. Adverse reaction reports in Japan"). Particularly, multiple patients experienced a sudden change in their condition due to dehydration, etc. caused by poor oral intake like anorexia as well as excessive alcohol consumption, etc., which resulted in occurrence of lactic acidosis. To avoid/reduce the risks that a sudden change in a patient's condition may induce lactic acidosis, it is considered important to educate patients properly at the start of treatment with metformin and

thereafter on prevention of lactic acidosis, its initial symptoms, and initial actions to be taken. Therefore, the educational descriptions provided in the Important Precautions section in the current package inserts ("Patients should avoid excessive alcohol consumption," "When there is a concern about a state of dehydration, the patient should discontinue the drug and consult with a physician," and "When an initial symptom of lactic acidosis appears, the patient should consult with a physician immediately") should be revised to "The patient and their family should be fully and properly instructed at the start of and during treatment with metformin."

3. Differences in the package insert language between low-dose and high-dose preparations (Refer to the section of "III-2. Description status in the package inserts in Japan")

A review of the contents in Japanese and overseas published literature, guidelines, etc. did not reveal any statement that the risk of lactic acidosis in patients with moderate renal impairment varies depending on the preparation. Although multiple metformin products have been approved for marketing in Europe and the US, the precautions related to lactic acidosis are the same for patients with renal or hepatic impairment and the elderly, etc., regardless of the preparations. Moreover, given that no specific problems have been observed regarding the safety and effectiveness in patients with renal or hepatic impairment and the elderly as a result of re-examination[13] of a high-dose preparation (Metgluco Tablets), PMDA considers it appropriate to provide the same precautions including contraindications as with high-dose preparations in the package insert for low-dose preparations.

V. Expert meetings

1. Administration to patients with moderate renal impairment

1.1 Acceptance of administration to patients with moderate renal impairment

The expert committee members agreed with the PMDA's decision that metformin may be administered safely to patients with moderate renal impairment (eGFR 30–60 mL/min/1.73 m^2) on the grounds that risk minimization actions be taken.

1.2 Doses in patients with renal impairment

The expert committee members agreed with the PMDA's decision that precautions regarding

[13] Re-examination report (http://www.pmda.go.jp/drugs_reexam/2015/P20151222001/400093000_22200AMX00234_A100_1.pdf(The last confirmation date: April 9, 2019))

the initiation of treatment at a low dose and subsequent dose adjustment depending on the patient's condition should accompany the approximate maximum daily dose in the package insert. Meanwhile, the committee members expressed the following opinions regarding descriptions in the package insert:

- Although there is no substantial difference in renal function between eGFR 44 mL/min/1.73 m^2 and eGFR 45 mL/min/1.73 m^2, a 2-fold difference is indicated between the doses according to Table 5 "IV-1.2 Doses in patients with renal impairment." The maximum daily dose is just a reference and a precaution should be included that doses should be adjusted according to the patient's condition.
- For patients with moderate renal impairment, a precaution should be provided to regularly check whether the current metformin dose is appropriate for the patient through more frequent follow-ups of renal function.

Based on the opinions from the committee members, PMDA concluded that when the maximum daily dose is stated in a package insert for patients with moderate renal impairment, a statement that the dose is a reference should be included, and that a precaution should be added to perform a careful follow-up, such as frequent checks of the renal function.

2. Patient background factors related to lactic acidosis except renal impairment

The expert committee members agreed with the PMDA's conclusion that a revision should be made for the educational descriptions regarding lactic acidosis to patients, which is provided in the current "Important Precautions."

3. Differences in the package insert language between low-dose and high-dose preparations

The expert committee members agreed with the PMDA's conclusion that the same precaution should be issued for both low-dose and high-dose preparations.

VI. Overall assessment

PMDA concluded based on the above discussions that metformin may be safely used in patients with moderate renal impairment (eGFR 30–60 mL/min/1.73 m^2) if risks are minimized. PMDA decided that it is appropriate to include, in the package insert, the initiation of treatment at a low dose, dose adjustment depending on the patient's condition, careful follow-up, and other required precautions to accompany the approximate maximum daily dose in patients with renal impairment. PMDA decided that the precaution for low-dose preparations should be the same as

the one for high-dose preparations.

In addition, PMDA concluded that the Precautions should be revised in the package inserts of metformin-containing preparations as mentioned below. (English translated revisions of precautions were not attached here. Please refer to the Revision of Precaution of each drug.)

Appendix 1 List of metformin containing drugs* (as of March 31, 2019)

No	Branded Name	Nonproprietary Name	MARKETING AUTHORIZATION HOLDER	INDICATIONS	DOSAGE AND ADMINISTRATION
1	Metgluco Tablets 250 mg, 500 mg	Metformin Hydrochloride	Sumitomo Dainippon Pharma Co., Ltd.	Type 2 diabetes mellitus Only for patients who did not adequately respond to any of the following therapies: (1) Diet and exercise therapies only (2) Use of sulfonylureas in addition to diet/exercise therapies	Start with the usual adult dosage of 500 mg of metformin hydrochloride per day, and the daily dose is divided into two to three portions for oral administration either just before or after a meal. Determine the maintenance dosage usually in the 750 mg to 1,500 mg per day range while observing the effect; the dose may be tapered up or down according to the conditions of the patient but never exceeding 2,250 mg daily. Start with the usual dosage of 500 mg of metformin hydrochloride per day in children
2	Metformin Hydrochloride Tablets 250 mg MT [DSEP], 500 mg MT [DSEP]		Daiichi Sankyo Espha Co., Ltd.		
3	Metformin Hydrochloride Tablets 250 mg MT [JG], 500 mg MT [JG]		Nihon Generic Co., Ltd.		
4	Metformin Hydrochloride Tablets 250 mg [TCK], 500 mg MT [TCK]		Tatsumi Kagaku Co., Ltd.		

No	Branded Name	Nonproprietary Name	MARKETING AUTHORIZATION HOLDER	INDICATIONS	DOSAGE AND ADMINISTRATION
5	Metformin Hydrochloride Tablets 250 mg MT [TE], 500 mg MT [TE]		Toa Eiyo Ltd.		aged ≥10 years, and the daily dose is divided into two to three portions for oral administration either just before or after a meal. Determine the maintenance dosage while observing the effect usually in the range 500 mg to 1,500 mg per day. The dose may be tapered up or down according to the conditions of the patient but never exceeding 2,200 mg a day.
6	Metformin Hydrochloride Tablets 250 mg MT [Sanwa], 500 mg MT [Sanwa]		Sanwa Kagaku Kenkyusho Co., Ltd.		
7	Metformin Hydrochloride Tablets 250 mg MT [Towa], 500 mg MT [Towa]		Towa Pharmacutical Co., Ltd.		
8	Metformin Hydrochloride Tablets 250 mg MT [Nichiiko],		Nichi-Iko Pharmaceutical Co., Ltd.		

No	Branded Name	Nonproprietary Name	MARKETING AUTHORIZATION HOLDER	INDICATIONS	DOSAGE AND ADMINISTRATION
	500 mg MT [Nichiiko]				
9	Metformin Hydrochloride Tablets 250 mg MT [Nipro], 500 mg MT [Nipro]		NIPRO CORPORATION		
10	Metformin Hydrochloride Tablets 250 mg MT [Pfizer], 500 mg MT [Pfizer]		Pfizer Japan Inc.		
11	Glycoran Tablets 250 mg	Metformin Hydrochloride	Nippon Shinyaku Co., Ltd.	Type 2 diabetes mellitus Only for patients who did not adequately respond to any of the following therapies: (1) Diet and exercise therapies only	Start with the usual adult dosage of 500 mg of metformin hydrochloride per day, and the daily dose is divided into two to three portions for oral administration either just before or
12	Metformin Hydrochloride Tablets 250 mg MT [Towa]		Towa Pharmaceutical Co.,		
13	Metformin		Shiono Chemical		

No	Branded Name	Nonproprietary Name	MARKETING AUTHORIZATION HOLDER	INDICATIONS	DOSAGE AND ADMINISTRATION
	Hydrochloride Tablets 250 mg MT [SN]		Co., Ltd.	(2) Use of sulfonylureas in addition to diet/exercise therapies	after a meal. Determine the usual maintenance dosage while observing its effect; keep the highest dosage at 750 mg or lower.
14	Metact Combination Tablets LD, HD	Pioglitazone Hydrochloride/ Metformin Hydrochloride	Teva Takeda Pharma Ltd.	Type 2 diabetes mellitus Only when co-administration of Pioglitazone hydrochloride and Metformin hydrochloride is determined necessary.	The usual adult dosage 1 tablet per day (15 mg/500 mg or 30 mg/500 mg of Pioglitazone hydrochloride/metformin hydrochloride) for oral administration after a meal in the morning.
15	Equmet Combination Tablets LD, HD	Vildagliptin /Metformin Hydrochloride	Novartis Pharma K.K.	Type 2 diabetes mellitus Only when co-administration of vildagliptin and metformin hydrochloride is determined necessary.	The usual adult dosage 1 tablet twice a day (50 mg/250 mg or 50 mg/500 mg of vildagliptin/ metformin hydrochloride) for oral administration after a meal in the morning and afternoon.

No	Branded Name	Nonproprietary Name	MARKETING AUTHORIZATION HOLDER	INDICATIONS	DOSAGE AND ADMINISTRATION
16	Inisync Combination Tablets	Alogliptin Benzoat /Metformin Hydrochloride	Takeda Pharmaceutical Company Limited.	Type 2 diabetes mellitus Only when co-administration of alogliptin benzoat and metformin hydrochloride is determined necessary.	The usual adult dosage 1 tablet per day (25 mg/500 mg of Alogliptin benzoate/metformin hydrochloride) for oral administration just before or after a meal.
17	Metoana Combination Tablets LD, HD	Anagliptin/Metformin Hydrochloride	Sanwa Kagaku Kenkyusho Co., Ltd.	Type 2 diabetes mellitus Only when co-administration of anagliptin and metformin hydrochloride is determined necessary	The usual adult dosage 1 tablet twice a day (100 mg/250 mg or 100 mg/500 mg of anagliptin/metformin hydrochloride) for oral administration after a meal in the morning and afternoon

*In the Investigation report drugs were state as , No.1 to 10: “High-dose preparations”, No.11 to 13: “Low-dose preparations” and No.14 to 17: Combination drugs.

Appendix 2 Lactate acidosis related information in package inset of overseas

(1) Metformin Hydrochloride (single ingredient)

U.S.A. (USPI)	U.K. (UK SmPC)
GLUCOPHAGE/ GLUCOPHAGE XR（Bristol-Myers Squibb Company） Revision May 2018	GLUCOPHAGE（Merck Serono Ltd） Revision December 2016
WARNING:LACTIC ACIDOSIS • Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL [see Warnings and Precautions (5.1)]. • Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment. • Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided [see Dosage and Administration (2.3), (2.7), Contraindications (4), Warnings and Precautions (5.1)]. • If metformin-associated lactic acidosis is suspected, immediately discontinue GLUCOPHAGE or GLUCOPHAGE XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is	–

<table>
<tr><th>U.S.A. (USPI)</th><th>U.K. (UK SmPC)</th></tr>
<tr><td>recommended [see Warnings and Precautions (5.1)].</td><td></td></tr>
<tr><td>2 DOSAGE AND ADMINISTRATION
2.3 Recommendations for Use in Renal Impairment
• Assess renal function prior to initiation of GLUCOPHAGE/ GLUCOPHAGE XR and periodically thereafter.
• GLUCOPHAGE/GLUCOPHAGE XR is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m^2.
• Initiation of GLUCOPHAGE/GLUCOPHAGE XR in patients with an eGFR between 30 – 45 mL/minute/1.73 m^2 is not recommended.
• In patients taking GLUCOPHAGE/GLUCOPHAGE XR whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit risk of continuing therapy.
• Discontinue GLUCOPHAGE/GLUCOPHAGE XR if the patient’s eGFR later falls below 30 mL/minute/1.73 m^2 [see Warnings and Precautions (5.1)]

2.4 Discontinuation for Iodinated Contras t Imaging Procedures
Discontinue GLUCOPHAGE/GLUCOPHAGE XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2 ; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intraarterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart GLUCOPHAGE/GLUCOPHAGE XR if renal function is stable.</td><td>4. Clinical particulars
4.2 Posology and method of administration
Renal impairment
A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

<table>
<tr><th>GFR (mL/min)</th><th>Total maximum daily dose (to be divided into 2-3 daily doses)</th><th>Additional considerations</th></tr>
<tr><td>60-89</td><td>3000 mg</td><td>Dose reduction may be considered in relation to declining renal function.</td></tr>
<tr><td>45-59</td><td>2000 mg</td><td rowspan="2">Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin.
The starting dose is at most half of the maximum dose.</td></tr>
<tr><td>30-44</td><td>1000 mg</td></tr>
<tr><td><30</td><td>—</td><td>Metformin is contraindicated.</td></tr>
</table>
</td></tr>
<tr><td>4 CONTRAINDICATIONS
GLUCOPHAGE and GLUCOPHAGE XR are contraindicated in patients with:</td><td>4.3 Contraindications
• Hypersensitivity to metformin or to any of the excipients listed in section 6.1.</td></tr>
</table>

U.S.A. (USPI)	U.K. (UK SmPC)
• Severe renal impairment (eGFR below 30 mL/min/1.73 m^2) [see Warnings and Precautions (5.1)]. • Hypersensitivity to metformin. • Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.	• Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis). • Diabetic pre-coma. • Severe renal failure (GFR < 30 mL/min). • Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock. • Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock. • Hepatic insufficiency, acute alcohol intoxication, alcoholism.
5 WARNINGS AND PRECAUTIONS **5.1 Lactic Acidosis** There have been postmarketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate: pyruvate ratio; metformin plasma levels were generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk. If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of GLUCOPHAGE/GLUCOPHAGE XR. In	**4.4 Special warnings and precautions for use** Lactic acidosis Lactic acidosis, a very rare, but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended. Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see

U.S.A. (USPI)	U.K. (UK SmPC)
GLUCOPHAGE/GLUCOPHAGE XR treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery. Educate patients and their families about the symptoms of lactic acidosis and, if these symptoms occur, instruct them to discontinue GLUCOPHAGE / GLUCOPHAGE XR and report these symptoms to their healthcare provider. For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below: • *Renal impairment*—The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include [see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)] • Before initiating GLUCOPHAGE/GLUCOPHAGE XR, obtain an estimated glomerular filtration rate (eGFR). • GLUCOPHAGE/GLUCOPHAGE XR is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 [see Contraindications (4)] • Initiation of GLUCOPHAGE/GLUCOPHAGE XR is not recommended	sections 4.3 and 4.5). Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (>5 mmol/L) and an increased anion gap and lactate/pyruvate ratio. <u>Renal function</u> GFR should be assessed before treatment initiation and regularly thereafter, see section 4.2. Metformin is contraindicated in patients with GFR<30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function, see section 4.3. <u>Cardiac function</u> Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, metformin may be used with a regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, metformin is contraindicated (see section 4.3). <u>Administration of iodinated contrast agents</u> Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk

U.S.A. (USPI)	U.K. (UK SmPC)
in patients with eGFR between 30-45 mL/min/1.73 m^2. • Obtain an eGFR at least annually in all patients taking GLUCOPHAGE/ GLUCOPHAGE XR. In patients at risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently. • In patients taking GLUCOPHAGE/GLUCOPHAGE XR whose eGFR falls below 45 mL/min/1.73 m^2, assess the benefit and risk of continuing therapy. • *Drug interactions* — The concomitant use of GLUCOPHAGE/ GLUCOPHAGE XR with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance, or increase metformin accumulation. Consider more frequent monitoring of patients. • *Age 65 or greater* — The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients. • *Radiologic studies with contrast* — Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop GLUCOPHAGE/GLUCOPHAGE XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2 ; in patients with a history of hepatic impairment, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging	of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections 4.2 and 4.5. <u>Surgery</u> Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

U.S.A. (USPI)	U.K. (UK SmPC)
procedure, and restart GLUCOPHAGE/GLUCOPHAGE XR if renal function is stable. • *Surgery and other procedures* — Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension, and renal impairment. GLUCOPHAGE/GLUCOPHAGE XR should be temporarily discontinued while patients have restricted food and fluid intake. • *Hypoxic states* — Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may cause prerenal azotemia. When such an event occurs, discontinue GLUCOPHAGE/GLUCOPHAGE XR. • *Excessive alcohol intake* — Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving GLUCOPHAGE/GLUCOPHAGE XR. • *Hepatic impairment* — Patients with hepatic impairment have developed cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of GLUCOPHAGE/GLUCOPHAGE XR in patients with clinical or laboratory evidence of hepatic disease.	
7 DRUG INTERACTIONS Table 3 presents clinically significant drug interactions with GLUCOPHAGE/ GLUCOPHAGE XR. **Table 3: Clinically Significant Drug Interactions with GLUCOPHAGE/ GLUCOPHAGE XR**	**4.5 Interaction with other medicinal products and other forms of interaction** Concomitant use not recommended *Alcohol* Alcohol intoxication is associated with an increased risk of lactic acidosis,

<table>
<tr><th>U.S.A. (USPI)</th><th>U.K. (UK SmPC)</th></tr>
<tr><td>
<table>
<tr><td colspan="2">Carbonic Anhydrase Inhibitors</td></tr>
<tr><td>Clinical Impact:</td><td>Carbonic anhydrase inhibitors frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with GLUCOPHAGE/GLUCOPHAGE XR may increase the risk for lactic acidosis.</td></tr>
<tr><td>Intervention:</td><td>Consider more frequent monitoring of these patients.</td></tr>
<tr><td>Examples:</td><td>Topiramate, zonisamide, acetazolamide or dichlorphenamide.</td></tr>
<tr><td colspan="2">Drugs that Reduce GLUCOPHAGE/GLUCOPHAGE XR Clearance</td></tr>
<tr><td>Clinical Impact:</td><td>Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors) could increase systemic exposure to metformin and may increase the risk for lactic acidosis [see Clinical Pharmacology (12.3)].</td></tr>
<tr><td>Intervention:</td><td>Consider the benefits and risks of concomitant use with GLUCOPHAGE/GLUCOPHAGE XR.</td></tr>
<tr><td>Examples:</td><td>Ranolazine, vandetanib, dolutegravir, and cimetidine.</td></tr>
<tr><td colspan="2">Alcohol</td></tr>
<tr><td>Clinical Impact:</td><td>Alcohol is known to potentiate the effect of metformin on lactate metabolism.</td></tr>
<tr><td>Intervention:</td><td>Warn patients against excessive alcohol intake while receiving GLUCOPHAGE/GLUCOPHAGE XR.</td></tr>
</table>
</td><td>particularly in case of fasting, malnutrition or hepatic impairment.

Iodinated contrast agents
Metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections 4.2 and 4.4.

<u>Combinations requiring precautions for use</u>
Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics)
More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon its discontinuation.

Organic cation transporters (OCT)
Metformin is a substrate of both transporters OCT1 and OCT2.
Co-administration of metformin with
• Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
• Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.</td></tr>
</table>

U.S.A. (USPI)	U.K. (UK SmPC)
	• Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration. • Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin. Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.
6 ADVERSE REACTIONS The following adverse reactions are also discussed elsewhere in the labeling: • Lactic Acidosis [see Boxed Warning and Warnings and Precautions (5.1)]	**4.8 Undesirable effects** Metabolism and nutrition disorders Very rare • Lactic acidosis (see section 4.4).
8 USE IN SPECIFIC POPULATIONS **8.6 Renal Impairment** Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. GLUCOPHAGE/GLUCOPHAGE XR is contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2 [see Dosage and Administration (2.3), Contraindications (4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)].	—
12 CLINICAL PHARMACOLOGY **12.3 Pharmacokinetics** **Specific Populations** ***Renal Impairment***	**5. Pharmacological properties** **5.2 Pharmacokinetic properties** Renal impairment The available data in subjects with moderate renal insufficiency are scarce

U.S.A. (USPI)	U.K. (UK SmPC)
In patients with decreased renal function the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased (see Table 3) [See Dosage and Administration (2.3), Contraindications (4), Warnings and Precautions (5.1) and Use in Specific Populations (8.6)]	and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability considerations (see section 4.2).

(2) Metformin Hydrochloride/pioglitazone (Combination drug) *limited to dosage and administration for Renal impairment patients

<table>
<tr><th>U.S.A. (USPI)</th><th>Europe (EU SmPC）</th></tr>
<tr><td>ACTOPLUS MET（Takeda Pharmaceuticals America, Inc.）
Revision December 2017</td><td>Competact（Takeda Pharma A/S）
Revision January 2017</td></tr>
<tr><td>2 DOSAGE AND ADMINISTRATION
2.2 Recommendations for Us e in Renal Impairment
Assess renal function prior to initiation of ACTOPLUS MET and periodically thereafter.
ACTOPLUS MET is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2.
Initiation of ACTOPLUS MET in patients with an eGFR between 30 – 45 mL/min/1.73 m^2 is not recommended.
In patients taking ACTOPLUS MET whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit risk of continuing therapy.
Discontinue ACTOPLUS MET if the patient's eGFR later falls below 30 mL/min/1.73 m^2 [see Contraindications (4) and Warnings and Precautions (5.2)].</td><td>4. CLINICAL PARTICULARS
4.2 Posology and method of administration
Renal impairment
A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.
The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin in patients with GFR < 60 mL/min.
If no adequate strength of Competact is available, individual monocomponents should be used instead of the fixed dose combination.
<table>
<tr><th>GFR mL/min</th><th>Metformin</th><th>Pioglitazone</th></tr>
<tr><td>60-89</td><td>Maximum daily dose is 3000 mg.</td><td>No dose adjustment.
Maximum daily dose is 45 mg</td></tr>
</table>
</td></tr>
</table>

U.S.A. (USPI)	Europe (EU SmPC)
	<table><tr><td></td><td>Dose reduction may be considered in relation to declining renal function.</td></tr><tr><td>45-59</td><td>Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.</td></tr><tr><td>30-44</td><td>Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.</td></tr><tr><td><30</td><td>Metformin is contra-indicated</td></tr></table>

(3) Metformin Hydrochloride/vildagliptin (Combination drug) *limited to dosage and administration for Renal impairment patients

U.S.A.	Europe (EU SmPC)
Not marketed	Eucreas（Novartis Europharm Limited） Revision May 2018
—	**4. CLINICAL PARTICULARS** **4.2 Posology and method of administration** Renal impairment A GFR should be assessed before initiation of treatment with metformin-containing products and at least annually thereafter. In patients at increased risk

<table>
<tr><th>U.S.A.</th><th>Europe (EU SmPC)</th></tr>
<tr><td></td><td>of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.
The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin in patients with GFR<60 ml/min.
If no adequate strength of Eucreas is available, individual monocomponents should be used instead of the fixed dose combination.

<table>
<tr><th>GFR mL/min</th><th>Metformin</th><th>Vildagliptin</th></tr>
<tr><td>60-89</td><td>Maximum daily dose is 3000 mg.
Dose reduction may be considered in relation to declining renal function.</td><td>No dose adjustment.</td></tr>
<tr><td>45-59</td><td>Maximum daily dose is 2000 mg.
The starting dose is at most half of the maximum dose.</td><td rowspan="3">Maximum daily dose is 50 mg</td></tr>
<tr><td>30-44</td><td>Maximum daily dose is 1000 mg.
The starting dose is at most half of the maximum dose.</td></tr>
<tr><td><30</td><td>Metformin is contra-indicated</td></tr>
</table>
</td></tr>
</table>

(4) Metformin Hydrochloride/alogliptin (Combination drug) *limited to dosage and administration for Renal impairment patients

U.S.A (USPI)	U.K (UK SmPC
KAZANO（Takeda Pharmaceuticals America, Inc.） Revision February 2017	Vipdomet（Takeda Pharma A/S） Revision December 2018
2 DOSAGE AND ADMINISTRATION **2.2 Recommendations for Us e in Renal Impairment** Assess renal function prior to initiation of KAZANO and periodically thereafter. KAZANO is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2 [see Contraindications (4) and Warnings and Precautions (5.1)]. KAZANO is not recommended in patients with an eGFR between 30 and 60 mL/min/1.73 m^2 because these patients require a lower daily dosage of alogliptin than what is available in the fixed combination KAZANO product.	**4. CLINICAL PARTICULARS** **4.2 Posology and method of administration** Renal impairment A GFR should be assessed before initiation of treatment with metformin containing medicinal products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g every 3-6 months. The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin in patients with GFR<60 mL/min. If no adequate strength of Vipdomet is available, individual monocomponents should be used instead of the fixed dose combination.

<table>
<tr><th>U.S.A (USPI)</th><th>U.K (UK SmPC</th></tr>
<tr><td></td><td>
<table>
<tr><th>GFR mL/min</th><th>Metformin</th><th>Alogliptin*</th></tr>
<tr><td>60-89</td><td>Maximum daily dose is 3000 mg.
Dose reduction may be considered in relation to declining renal function.</td><td>No dose adjustment
Maximum daily dose is 25 mg</td></tr>
<tr><td>45-59</td><td>Maximum daily dose is 2000 mg.
The starting dose is at most half of the maximum dose.</td><td>Maximum daily dose is 12.5 mg</td></tr>
<tr><td>30-44</td><td>Maximum daily dose is 1000 mg.
The starting dose is at most half of the maximum dose.</td><td>Maximum daily dose is 12.5 mg</td></tr>
<tr><td><30</td><td>Metformin is contra-indicated</td><td>Maximum daily dose is 6.25 mg</td></tr>
</table>
* Alogliptin dose adjustment is based on a pharmacokinetic study where kidney function was assessed using creatinine clearance (CrCl) levels estimated from the Cockcroft-Gault equation.
</td></tr>
</table>

(5) Metformin Hydrochloride/anagliptin (Combination drug) *limited to dosage and administration for Renal impairment patients

U.S.A. Not marketed	Europe Not marketed

Appendix 3 Lactic acidosis related descriptions in the domestic package insert of metformin (single agent)

The difference in the description between low dose formulation and high dose formulation is underlined.

Low Dose Formulation	High Dose Formulation
Glycoran Tablets 250 mg and the others (Nippon Shinyaku Co., Ltd. and the others) Revised: February, 2018	Metgluco Tablets 250mg, 500 mgand the others (Sumitomo Dainippon Pharma Co., Ltd and the others) Revised: February, 2018
WARNINGS This drug may cause serious lactic acidosis, and some cases have been reported with deaths. Do not use this drug in patients predisposed to lactic acidosis. [See CONTRAINDICATION section.] Sever hypoglycemia may occur. Special attention to Dosage and Administration and Precautions should be paid.	WARNINGS This drug may cause serious lactic acidosis, and some cases have been reported with deaths. Do not use this drug in patients predisposed to lactic acidosis. [See CONTRAINDICATION section.] This drug should be administered in patients with renal or hepatic impairment and elderly patients with care including regular check of renal or hepatic function. Especially in elderly patients aged ≥75 years, whether the administration of this drug is appropriate or not should be carefully determined. [See careful administration, IMPORTANT PRECAUTIONS, and The elderly sections.]

CONTRAINDICATIONS (This drug is contraindicated in the following patients.)	CONTRAINDICATIONS (This drug is contraindicated in the following patients.)
1. Patients with the following conditions: [predisposed to lactic acidosis.]	1. Patients with the following conditions: [predisposed to lactic acidosis.]
(1) Patients with prior history of lactic acidosis	(1) Patients with prior history of lactic acidosis
(2) Patients with renal impairment (including mild impairment) [Renal excretion of this drug is decreased]	(2) Patients with moderate and severer renal impairment [Renal excretion of this drug is decreased. See IMPORTANT PRECAUTIONS section.]
(3) Patients undergoing dialysis (including peritoneal dialysis) [High concentration of this drug in blood may sustain.]	(3) Patients undergoing dialysis (including peritoneal dialysis) [High concentration of this drug in blood may sustain.]
(4) Patients with hepatic impairment [The ability to metabolize lactate in the liver may be impaired.]	(4) Patients with severe hepatic impairment [The ability to metabolize lactate in the liver may be impaired. See IMPORTANT PRECAUTIONS section.]
(5) Patients with advanced cardiovascular or pulmonary dysfunction including shock, heart failure, myocardial infarction and pulmonary embolism and other conditions susceptible to hypoxemia [Lactate production may be increased.]	(5) Patients with advanced cardiovascular or pulmonary dysfunction including shock, heart failure, myocardial infarction and pulmonary embolism and other conditions susceptible to hypoxemia [Lactate production may be increased.]
(6) Patients who consume excessive amount of alcohol [The ability to metabolize lactate in the liver may be impaired.]	(6) Patients who consume excessive amount of alcohol [The ability to metabolize lactate in the liver may be impaired.]
(7) Patients with gastrointestinal disorder including diarrhea and vomiting which may lead to dehydration or state of dehydration.	(7) Patients with gastrointestinal disorder including diarrhea and vomiting which may lead to dehydration or state of dehydration
(8) The elderly [See the elderly section]	
2. (Snip)	2. (Snip)
3. Patients with severe infection, preoperative or postoperative condition or	

Low Dose Formulation	High Dose Formulation
serious trauma [Administration of this drug is inappropriate as glycemic control with insulin injection is desirable. In addition, such patients are predisposed to lactic acidosis.] 4. (Snip) 5. Women who are or may be pregnant [See Pregnant women and Breast-feeding women sections] 6. (Snip)	3. Patients with severe infection, preoperative or postoperative condition or serious trauma [Administration of this drug is inappropriate as glycemic control with insulin injection is desirable. In addition, such patients are predisposed to lactic acidosis.] 4. (Snip) 5. Women who are or may be pregnant [See Pregnant women and Breast-feeding women sections] 6. (Snip)
Careful administration (Administration with care to following patients) Patients with following states (1) and (2) (Snip) (3) Infections [Lactic acidosis may occur.] (4) INTERACTIONS Co-administration with drugs shown in (1) [Lactic acidosis may occur.] (5) (Snip)	Careful administration (Administration with care to following patients) Patients with following states (1) and (2) (Snip) (3) Mild renal impairment [Lactic acidosis may occur. See IMPORTANT PEWCAUTIONS] (4) Mild to moderate hepatic impairment [Lactic acidosis may occur. See IMPORTANT PEWCAUTIONS] (5) Infections [Lactic acidosis may occur.] (6) The elderly [See the elderly section] (7) INTERACTIONS Co-administration with drugs shown in (1) [Lactic acidosis may occur.] (8) (Snip)

Low Dose Formulation	High Dose Formulation
IMPORTANT PRECAUTIONS 1. Since serious lactic acidosis may be caused infrequently, the patient and his/her family should be fully instructed on the following descriptions: (1) Avoid excessive alcohol intake. [See contraindication section.] (2) If dehydration due to fever, diarrhea, vomiting, poor food intake, etc. is a concern, stop taking the oral medication once and consult with a physician. [See contraindication section.] (3) If any early symptoms of lactic acidosis appear, consult a physician immediately. [See clinically significant adverse reactions section.] 2. Since lactic acidosis may be caused by the concomitant use of this drug in patients who undergo a test with an iodine-containing contrast agent, the administration of this drug should be temporarily discontinued before the testing (excluding the case when the testing is urgently needed). Do not resume the administration of this drug within 48 hours after administration of the iodine-containing contrast agent. Pay attention to the patient's conditions when resuming the administration of this drug. [See INTERACTIONS section.] 3. Lactic acidosis may be caused by dehydration. If any symptoms of dehydration appear, discontinue the treatment with this drug and take	IMPORTANT PRECAUTIONS 1. Since serious lactic acidosis may be caused infrequently, the patient and his/her family should be fully instructed on the following descriptions: (1) Avoid excessive alcohol intake. [See contraindication section.] (2) If dehydration due to fever, diarrhea, vomiting, poor food intake, etc. is a concern, stop taking the oral medication once and consult with a physician. [See contraindication section.] (3) If any early symptoms of lactic acidosis appear, consult a physician immediately. [See clinically significant adverse reactions section.] 2. Since lactic acidosis may be caused by the concomitant use of this drug in patients who undergo a test with an iodine-containing contrast agent, the administration of this drug should be temporarily discontinued before the testing (excluding the case when the testing is urgently needed). Do not resume the administration of this drug within 48 hours after administration of the iodine-containing contrast agent. Pay attention to the patient's conditions when resuming the administration of this drug. [See INTERACTIONS section.] 3. Lactic acidosis may be caused by dehydration. If any symptoms of dehydration appear, discontinue the treatment with this drug and take

Low Dose Formulation	High Dose Formulation
appropriate measures. When co-administration with drugs with diuretic activity (such as diuretics and SGLT2 inhibitors), special attention to dehydration should be paid. [See INTERACTIONS section.]	appropriate measures. When co-administration with drugs with diuretic activity (such as diuretics and SGLT2 inhibitors), special attention to dehydration should be paid. [See INTERACTIONS section.]
4. Renal excretion of this drug is lowered, and the drug concentrations in blood are elevated. During the treatment with this drug, renal function and patient status should be thoroughly monitored and consider the necessity of administration. Renal functions should be assessed based on eGFR, serum creatinine levels etc.	4. Renal excretion of this drug is lowered, and the drug concentrations in blood are elevated. Caution should be exerted for the following descriptions before starting administration and during administration.[See the elderly and INTERACTIONS sections.] (1) Assess whether this drug should be administered or not and dosage adjustment while paying close attention to the renal function and patient's conditions. The renal function should be assessed with reference to eGFR, serum creatinine levels, etc. (The exclusion criteria in clinical studies in Japan included serum creatinine levels of ≥1.3 mg/dL, ≥1.2 mg/dL and >1.0 mg/dL for adult male, adult female and children, respectively. [See the section 17.1.]) (2) During the treatment with this drug, renal function (eGFR, serum creatinine levels etc.) should be checked periodically, and more frequently in elderly patients, etc., who particularly need a careful follow-up. If any aggravation of renal function is confirmed, discontinuation of this drug or dose reduction should be carried out.
	5. The ability to metabolize lactate in the liver may be impaired. Hepatic

<table>
<tr><th>Low Dose Formulation</th><th>High Dose Formulation</th></tr>
<tr><td></td><td>function should be checked periodically during the treatment with this drug. [See clinical studies sections]
6 to 10 (Snip)</td></tr>
<tr><td>Precautions for co-administration (This drug should administered with care when co-administrated with the following drugs.)
<table>
<tr><th></th><th>Drug name, etc.</th><th>Clinical symptom/treatment method</th><th>Mechanism/risk factor</th></tr>
<tr><td>（1）</td><td>Iodine-containing contrast agent</td><td>Lactic acidosis may be caused by co-administration. Temporarily discontinue the treatment with this drug when performing a test with an iodine-containing contrast agent. [See IMPORTANT PRECAUTIONS section.]</td><td>Renal function is impaired, and excretion of this drug may be lowered.</td></tr>
<tr><td></td><td>Highly nephrotoxi</td><td>Lactic acidosis may be</td><td></td></tr>
</table></td><td>Precautions for co-administration (This drug should administered with care when co-administrated with the following drugs.)
<table>
<tr><th></th><th>Drug name, etc.</th><th>Clinical symptom/treatment method</th><th>Mechanism/risk factor</th></tr>
<tr><td>（1）</td><td>Iodine-containing contrast agent</td><td>Lactic acidosis may be caused by co-administration. Temporarily discontinue the treatment with this drug when performing a test with an iodine-containing contrast agent. [See IMPORTANT PRECAUTIONS section.]</td><td>Renal function is impaired, and excretion of this drug may be lowered.</td></tr>
<tr><td></td><td>Highly nephrotoxi</td><td>Lactic acidosis may be</td><td></td></tr>
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Low Dose Formulation				High Dose Formulation			
	c antibiotics Gentamicin, etc.	caused by co-administration. Take appropriate measures such as temporary dose reduction or discontinuation of the treatment with this drug when co-administrated with such antibiotics.			c antibiotics Gentamicin, etc.	caused by co-administration. Take appropriate measures such as temporary dose reduction or discontinuation of the treatment with this drug when co-administrated with such antibiotics.	
	Diuretic drugs Diuretics, SGLT2 inhibitors, etc.	Lactic acidosis may be caused by dehydration. If any symptoms of dehydration appear, discontinue the treatment with this drug and take appropriate measures. [See IMPORTANT PRECAUTIONS section.]	The body fluid volume is reduced due to a diuretic drug, and dehydration ma y occur.		Diuretic drugs Diuretics, SGLT2 inhibitors, etc.	Lactic acidosis may be caused by dehydration. If any symptoms of dehydration appear, discontinue the treatment with this drug and take appropriate measures. [See IMPORTANT PRECAUTIONS section.]	The body fluid volume is reduced due to a diuretic drug, and dehydration ma y occur.
(Snip)				(Snip)			

Low Dose Formulation	High Dose Formulation
Clinically significant adverse reactions 1. Lactic acidosis (Unknown frequency) Lactic acidosis (which exhibits elevated blood lactate levels, elevated Lactate-to-pyruvate ratio, low blood pH, etc.) is commonly associated with poor prognosis. In general, it includes various clinical symptoms, and the patients commonly develop symptoms such as gastrointestinal symptoms, malaise, muscle pain and hyperventilation. When these symptoms appear, administration of this drug should be immediately discontinued, and necessary testing should be conducted. However, if the patient is strongly suspected to have lactic acidosis, appropriate measures should be taken without waiting for lactate measurement result, etc. 2 to 4 (Snip)	Clinically significant adverse reactions 1. Lactic acidosis (Unknown frequency) Lactic acidosis (which exhibits elevated blood lactate levels, elevated Lactate-to-pyruvate ratio, low blood pH, etc.) is commonly associated with poor prognosis. In general, it includes various clinical symptoms, and the patients commonly develop symptoms such as gastrointestinal symptoms, malaise, muscle pain and hyperventilation. When these symptoms appear, administration of this drug should be immediately discontinued, and necessary testing should be conducted. However, if the patient is strongly suspected to have lactic acidosis, appropriate measures should be taken without waiting for lactate measurement result, etc. 2 to 4 (Snip)
The elderly The elderly tends to have impaired renal and/or hepatic function. Since impaired renal function by decrease in excretion of this drug and impaired hepatic function by decreased metabolism of lactose will lead to a tendency for lactate acidosis to occur and therefore, this drug should not be administered to the elderly.	The elderly The elderly tends to have impaired renal and/or hepatic function and is predisposed to dehydration. Since these conditions are more likely to cause lactic acidosis, pay attention to the following descriptions. (1) Administer this drug carefully while closely monitoring the patient by checking the renal and hepatic functions periodically before start of treatment with this drug and during the treatment, or more frequently when careful follow-up is required in particular. [This drug is metabolized little

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	and excreted into the urine as unchanged drug. (See PHARMACOKINETICS section) In addition, the ability to metabolize lactate is lowered due to hepatic impairment.] (2) Assess discontinuation of the treatment or dose reduction by adequately paying attention to the patient conditions such as renal function and dehydration. Especially in patients aged ≥75 years, carefully determine whether to administer this drug or not. Lactic acidosis has been reported frequently, and the prognosis tends to be poor. [In the clinical studies conducted before approval of this drug in Japan, use of this drug at the daily dose of >1,500 mg in the elderly aged ≥75 years is limited.] (3) Carefully monitor the patient condition by considering eGFR, etc., even when serum creatinine levels are within the normal range. Actual renal function may be impaired depending on the patient's age.
Administration to pregnant women, parturient women, and breast-feeding women (1) Do not administer this drug to women who are or may be pregnant. [Excretion into fetus has been confirmed in animal experiments (rats and rabbits), and teratogenic actions have been reported in some animal experiments (rats)). In addition, pregnant women are predisposed to lactic	Administration to pregnant women, parturient women, and breast-feeding women (1) Do not administer this drug to women who are or may be pregnant. [Excretion into fetus has been confirmed in animal experiments (rats and rabbits), and teratogenic actions have been reported in some animal experiments (rats)). In addition, pregnant women are predisposed to

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