March 3, 2026
Pharmaceuticals and Medical Devices Agency, Japan

Report on Investigation Results

I. Summary of drug

[Non-proprietary name]	Lithium carbonate
[Brand name]	See Appendix 1.
[Marketing authorization holder]	See Appendix 1.
[Indications]	See Appendix 1.
[Dosage and administration]	See Appendix 1.
[Investigating office]	Office of Pharmacovigilance I

II. Investigation background

Administration of lithium carbonate to “pregnant women or women who may be pregnant” is contraindicated. It was decided at the approval of the brand-name product of lithium carbonate (August 1979) that lithium carbonate should not be administered to pregnant women or women who may be pregnant because of the following reasons: it had been reported that teratogenicity was identified in animal studies in multiple papers; and an increase in the frequency of congenital cardiovascular anomaly even in humans had been reported in an epidemiological study[1] already during the development phase of lithium carbonate.

Recently, the Information Provision Working Group (hereinafter referred to as the “WG”) in the “Proper Use Promotion Project for Pregnant and Lactating Women”[2] of the MHLW reviewed the appropriateness of the contraindication for “pregnant women or women who may be pregnant” in the electronic package insert for the drug products shown in Appendix 1, and an evaluation report on the revision of the package insert for lithium carbonate (hereinafter referred to as the “WG report”) (Appendix 2) was prepared. Lithium carbonate has been approved for the indication of “mania or manic state of manic depressive illness”. Recently, “manic depressive illness” has been referred to as “bipolar disorder” according to the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM-5-TR). There are a certain number of patients in whom mood episodes in bipolar disorder can be clinically well controlled only with lithium carbonate (including use in the depressive state or the maintenance phase that falls under off-label use) according to the WG report. The WG report pointed out that if these patients discontinue treatment with lithium carbonate as they become pregnant, the risk of recurrence is expected to markedly increase after delivery, which may lead to significant outcomes including suicide. In response to the WG report, the Pharmaceutical Safety Division, Pharmaceutical Safety Bureau, MHLW requested the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as “PMDA”) to conduct an investigation into the revision of PRECAUTIONS of lithium carbonate regarding administration to

[1] Weinstein M.R., et al.:Am J Psychiat. 1975;132(5):529-531
[2] Web page of the MHLW (https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iyakuhin/ninshin_00002.html) (Final confirmation: January 31, 2026) (only in Japanese)

pregnant women/nursing mothers, under the “Notification on Request of Investigation Related to the Safety of Drugs, etc.” (PSB/PSD 1217 No. 2, dated December 17, 2025). The PMDA accordingly conducted an investigation into the request and discussed the necessity of a revision of the electronic package insert.

The 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, 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. Investigation by the WG

The WG report (Appendix 2), containing the items shown in Table 1, was prepared on the appropriateness of the precautions concerning “pregnant women or women who may be pregnant” in the electronic package insert of lithium carbonate.

Table 1 Table of Contents of the WG report

1. Summary of drug	6. Japanese and overseas reference texts and clinical guidelines
2. Background	7. Appropriateness of lifting the contraindications
3. Descriptions in overseas product labeling	8. Measurement of serum lithium concentration in pregnant women
4. Animal study	9. Proposed revision of package insert by the WG
5. Reports on clinical uses	

IV. Investigation by the PMDA

Taking account of the WG report, the PMDA conducted the following review.

1. Information based on nonclinical studies (Refer to “4. Animal study” in the WG report.)

1-1. Published literature

The WG evaluated a toxicity study according to OECD guidelines (OECD TG 414 and OECD TG 416)[3] in addition to reproductive and developmental toxicity studies, which were conducted during the development phase of lithium carbonate, and reported that the risk of teratogenicity is considered low based on the comprehensive assessment of the results of these studies (Refer to “4. Animal study” and “7. Appropriateness of lifting the contraindications” in the WG report).

Although it is recommended to use 2 animal species of rats (or mice) and rabbits in the re-evaluation based on the results of GLP toxicity studies in accordance with the OECD guidelines, the results of studies evaluated in the WG report were mainly results in rats, and therefore, the PMDA considers that there are limitaions in concluding that the risk of teratogenicity is low from a nonclinical viewpoint. On the other hand, cases in which lithium carbonate was used in clinical settings have been accumulated, and therefore the data from humans are considered to be more useful in the evaluation of risks of embryo-foetal toxicity than in animals.

2. Information based on clinical uses (Refer to “5. Reports on clinical uses” in the WG report.)

2-1. Published literature

The WG searched for published literature on the effects of exposure to lithium carbonate on pregnancy in pregnant women who were exposed to lithium carbonate during pregnancy and on congenital anomalies in

[3] Van Deun K et al. Toxicology. 2021;461:1–16

their children and retrieved 20 reports (searched on March 31, 2025). The WG reported that these reports suggested a potential increased risk of heart malformation to a certain extent, but there were variations in the results between the reports (Refer to “5. Reports on clinical uses” in the WG report.)

The 20 reports retrieved by the WG included 7 reports in which the effect index was not calculated (reference 3, 4, 9 to 12, 19 in the WG report), 6 case series (reference 13 to 18 in the WG report), and 1 report on methodology (reference 20 in the WG report). The PMDA focused on a total of 6 reports excluding these reports (Table 2).

In addition to the literature retrieved by the WG, 3 reports concerning lithium carbonate and pregnancy have been reported from the marketing authorization holders to the PMDA as research reports. However, these reports included 1 report that was similar to the report retrieved by the WG in the authors and the contents (reference 7 in the WG report) and 1 report each on the relationship between autism spectrum disorder or abortion and lithium carbonate, and these reports are therefore not included in Table 2.

Table 2 Outline of literature mainly evaluated by the PMDA

No	**Exposure group [number of patients]**	**Control group [number of patients]**	**Outcome definition**	**Risk ratio/odds ratio (95% CI) [number of patients with the events in the exposure group]**
1	Children born to women who have used lithium carbonate in the first pregnancy trimester [≈165]	Children born to women exposed to nonteratogenic agents during pregnancy [748]	Cardiovascular malformation	7.23 (1.97-26.53)[5] *Risk ratio
			Cardiovascular malformation (excluding malformation that spontaneously resolved)	5.78 (0.82-40.65)[3] *Risk ratio
			Overall malformation	5.37 (1.01-28.56) *Odds ratio
			Non-cardiovascular malformation	9.22 (1.55-54.77) *Odds ratio
			Cardiovascular malformation	4.75 (1.11–20.36) *Odds ratio

2	Children born to women who used lithium carbonate in the first pregnancy trimester [138]	Children born to women who received prescription of drugs whose teratogenic potential is unknown or not suspected [148]	Congenital malformation	1.2 (0.2-5.7) *Risk ratio
			Abortion (Ebstein's anomaly) is included in the above event.	1.5 (0.4-6.7) *Risk ratio
			Heart malformation	1.1 (0.1-16.6) *Risk ratio
			Ebstein's disease	3.5 (0.1-84.9) *Risk ratio
5	Children born to women exposed to lithium during the first pregnancy trimester (in 90 days from the date of last menstrual period) [663]	Children born to women without exposure to lithium or lamotrigine in 3 months before the start of pregnancy or during the first pregnancy trimester [1,322,955]	Heart malformation	1.65 (1.02-2.68)[16] *Risk ratio
			Right ventricular outflow tract stenosis	2.66 (1.00-7.06)[<11] *Risk ratio
			Cardiac disorders (other than right ventricular outflow tract stenosis)	1.46 (0.84-2.57)[12] *Risk ratio
			Non-heart malformation	1.22 (0.81-1.84)[22] *Risk ratio
		Children born to women exposed to lamotrigine in 3 months before the start of pregnancy or during the first pregnancy trimester [1,945]	Heart malformation	2.25 (1.17-4.34)[16] *Risk ratio
			Non-heart malformation	1.63 (0.96-2.78)[22] *Risk ratio
6	Children born to women exposed to lithium during the first pregnancy trimester [654]	Children born to women with a history of mood disorder (bipolar disorder or major depressive disorder) who were not exposed to lithium from 90 days before pregnancy through delivery [21,397]	Major malformation	1.71 (1.07-2.72)[47] *Odds ratio
			Common heart malformation	1.54 (0.64-3.70)[16] *Odds ratio
7	Children born to women who were exposed to lithium during pregnancy or in 3 months before pregnancy [434]	Children born to women who did not use lithium [853,583]	Congenital malformation	1.41 (0.90-2.23)[19] *Risk ratio
			Heart malformation	3.17 (1.64-6.13)[9] *Risk ratio
	Children born to women who were exposed to lithium during pregnancy or in 3 months before pregnancy [434]	Children born to women who received prescription of lithium before pregnancy but did not during pregnancy [871]	Heart malformation *Subgroup analyses	2.99 (1.10-8.10)[9] *Risk ratio
	Children born to women who were diagnosed with mental illness (bipolar disorder, schizophrenia, psychosis) and	Children born to women who were diagnosed with mental illness (bipolar disorder, schizophrenia, psychosis) but did not receive prescription of	Heart malformation *Subgroup analyses	3.01 (1.38-6.53)[8] *Risk ratio

	received prescription of lithium [412]	lithium [9,140]		
8	Children with congenital anomaly [10,698]	Children without congenital anomaly [21,546]	Use of lithium	1.3 (0.22-9.0) *Odds ratio

All of the 6 reports listed in Table 2 evaluated the relationship between exposure to lithium carbonate during pregnancy and congenital anomaly. Except for 1 report (reference 8 in the WG report) in which only the effect index for overall congenital anomaly was calculated, the effect index especially for heart malformation was calculated among congenital anomalies. Of the 5 reports in which an effect index for heart malformation was calculated, 2 reports stated that there was no increase in the risk of heart malformation associated with use of lithium carbonate during pregnancy (reference 2, 6 in the WG report), while 3 reports stated that an increase in the risk of heart malformation was noted (reference 1, 5, 7 in the WG report). In particular, the report of reference 5 indicated a dose-response relationship as well. However, of the 5 reports in which the effect index for heart malformation was calculated, 2 reports (reference 1, 2 in the WG report) have limitations such as a wide range of 95% confidence intervals and potential inadequate adjustment for confounding.

2-2. Adverse reaction report

The number of case reports of adverse reactions for lithium carbonate in Japan concerning pregnancy and neonates in the PMDA's database for adverse reactions, etc. report is shown in Appendix 3. A total of 33 events in 23 cases fell under Standardized MedDRA Query (SMQ (broad)) “pregnancy and neonatal topics.” After excluding adverse events that were not events observed in mothers or fetuses, the number of the remaining case reports was 11 events in 10 cases (data lock: January 31, 2026).

The events (PT) for which 2 or more events have been reported included 2 events each of drug withdrawal syndrome neonatal, abortion, and abortion spontaneous. Regarding events possibly related to heart malformation for which the increased risk in humans has been suggested in the current electronic package insert, 1 event of heart disease congenital has been reported. As a result of consultation with expert advisors, two cases including 1 of the 2 cases of drug withdrawal syndrome neonatal and 1 case for which neonatal asphyxia and respiratory disorder neonatal were reported were regarded as cases in which a causal relationship between lithium carbonate and the events was reasonably possible although not only lithium carbonate but also effects of high-dose intake for suicide attempt and concomitant use of multiple drugs were also considered. For 1 case for which neonatal asphyxia and respiratory disorder neonatal were reported, the events may possibly be symptoms associated with drug withdrawal syndrome neonatal although the possibility was not directly mentioned. Among the cases other than those for which the causal relationship was reasonably possible, for heart disease congenital, attention has already been called in the 9.5 Pregnant Women section in the current electronic package insert, and other events may generally occur even in children of pregnant women who are not taking lithium carbonate. In addition, each report lacked information, such as maternal primary diseases, dose and duration of administration of lithium carbonate, presence or absence of concomitant drugs, and clinical courses, making the assessment of a causal relationship difficult.

2-3. Measurement of serum lithium concentration in pregnant women

It has been instructed to measure serum lithium concentration periodically in the electronic package insert for lithium carbonate. The WG reported that attention has also been called to measurement of serum lithium

concentration in foreign countries where lithium carbonate is not contraindicated in pregnant women.

3. Guidelines (Refer to "6. Japanese and overseas reference texts and clinical guidelines " in the WG report.)

3-1. Descriptions in the guidelines regarding the use of lithium carbonate in pregnant women

The WG reviewed descriptions in Japanese and overseas guidelines regarding the use of lithium carbonate in pregnant women and the clinical positioning of lithium carbonate concerning the indicated diseases. (Refer to "6. Japanese and overseas guidelines" in the WG report.) Descriptions in the guidelines in Japan and overseas are not uniform. However, the WG reported that there are descriptions to the effect that the use of lithium carbonate is allowed in pregnant women who have difficulty in discontinuing lithium carbonate on the premise of adequate control of serum lithium concentration, etc., such as a description found in "Clinical Guide for Women with Mental Health Problems during Perinatal Period (2021) (edited by The Japanese Society of Psychiatry and Neurology and Japan Society of Obstetrics and Gynecology)": "The prescription should be avoided during pregnancy unless other drugs are not effective, and even if the prescription is necessary, the dose should be as low as possible and periodic measurement of blood concentration and dose adjustment are recommended".

In addition, in "Chapter 6: Perinatal" in "Practice Guidelines for Bipolar Disorder by Japanese Society of Mood Disorders 2023," the following description is included; "Considering the severity and the response to pharmacotherapy of the patient intending pregnancy, a treatment plan should be developed and shared with the patient and family. It is recommended that the risks and benefits of treatment be thoroughly discussed with the patient and family, and that efforts be made to reach shared decision making," and it is stated that information on the use of lithium carbonate and valproate needs to be shared with obstetricians.

4. Descriptions in overseas product labeling (Refer to "3. Descriptions in overseas product labeling" in the WG report.)

The WG reviewed descriptions in overseas product labeling (the US, the UK, Canada, Australia). (Refer to "3. Descriptions in overseas product labeling" in the WG report.) Although the use of lithium carbonate in pregnant women is not contraindicated in product labeling in these countries, there are descriptions to the effect that if lithium carbonate has to be administered, it is necessary to monitor serum lithium concentration frequently and appropriately adjust the dose during pregnancy and that symptoms such as drug withdrawal syndrome neonatal and lithium poisoning may occur in neonates born to pregnant women who have used lithium carbonate.

V. PMDA's judgment based on the WG report and "IV. Investigation by the PMDA"

1. Decision on administration to pregnant women

Based on the WG report and the results of "IV. Investigation by the PMDA," the PMDA considered that "pregnant women or women who may be pregnant" may be deleted from the CONTRAINDICATIONS section in the electronic package insert for lithium carbonate for the following reasons.

- An increase in the frequency of congenital cardiovascular anomalies in humans was reported in an epidemiological study. This study, however, only mentions that the proportion of cases of congenital cardiovascular anomaly (or congenital heart malformation) in all cases of major malformation in 143

children exposed to lithium was higher than the proportion reported in the epidemiological data in the past (the status of exposure to drugs including lithium is unknown), and this study was not intended to calculate the effect index. On the other hand, the epidemiological studies reviewed for this investigation mainly included pregnant women who used lithium carbonate in the early stage of pregnancy and calculated the effect index. In addition, the PMDA was able to examine studies that indicate the association between lithium carbonate and increased risk of congenital anomaly (especially heart malformation) (reference 1, 5, 7 in the WG report) and those that do not (reference 2, 6 in the WG report). Although increased risks of congenital anomaly due to lithium carbonate cannot be ruled out, it was considered appropriate to lift the contraindication under the appropriate precautions as a result of the consideration of the benefit of continuing lithium carbonate during pregnancy, changes in serum concentration associated with pregnancy, and the risks of drug withdrawal syndrome neonatal and teratogenicity based on the latest knowledge (Refer to "5. Reports on clinical uses" in the WG report).

- The use of lithium carbonate in pregnant women is not contraindicated in overseas product labeling (the US, the UK, Canada, and Australia), and it is stated in the guidelines in Japan and overseas that use of lithium carbonate is allowed in pregnant women who have difficulty in discontinuing lithium carbonate on the premise of adequate control of serum lithium concentration, etc. (Refer to "3. Descriptions in overseas product labeling" and "6. Japanese and overseas guidelines" in the WG report.)

2. Necessity of appropriate perinatal management

In the current electronic package insert of lithium carbonate that specifies the use of lithium carbonate in "pregnant women or women who may be pregnant" as contraindication, attention has been called so that serum lithium concentration will be measured at a certain frequency during the administration of lithium carbonate and the administration will be based on the measurement results because overdose may cause lithium poisoning. However, in the investigation conducted by the PMDA on the implementation status of measurement of serum lithium concentration using the National Database of Health Insurance Claims (NDB), it was suggested that serum lithium concentration may not be measured at all in about 54% of patients to whom lithium carbonate was newly prescribed. Therefore, the "PMDA Request for Proper Use of Drugs" has been updated (updated in September 2025)[4] to call attention so that measurement of serum lithium concentration will be followed. The PMDA considered that "pregnant women or women who may be pregnant" may be deleted from the CONTRAINDICATIONS section in the electronic package insert for lithium carbonate as described in the above "1. Decision on administration to pregnant women"; however, it is considered that administration of lithium carbonate to pregnant women should be performed under the condition that psychiatrists and physicians responsible for perinatal medicine (including obstetrics and neonatal medicine), who are able to closely collaborate with each other, for example sharing measurement results of serum lithium concentration for the evaluation, manage pregnant women who use lithium carbonate. In addition, it is considered that the appropriateness of administration of lithium carbonate to pregnant women must be determined by a physician who has knowledge and experience in the treatment of bipolar disorder and can adequately manage and explain risks of lithium carbonate, and perinatal medical institutions should be able to perform appropriate perinatal management including management of effects of lithium carbonate

[4] Pharmaceuticals and Medical Devices Agency Web page (https://www.pmda.go.jp/files/000277130.pdf) (Final confirmation: January 31, 2026)

on pregnant women, fetuses, and neonates (drug withdrawal syndrome neonatal, changes in serum lithium concentrations, etc.). (Refer to “7. Appropriateness of lifting the contraindications” and “8. Measurement of serum lithium concentration in pregnant women" in the WG report.)

3. Proposed revision

Based on “V-1. Decision on administration to pregnant women” and “V-2. Requirements for physicians/institutions,” the PMDA considered that the electronic package insert of lithium carbonate may be revised as follows: “Pregnant women or women who may be pregnant” may be deleted from 2. CONTRAINDICATIONS; a statement that “<u>This drug should not be administered to pregnant women or women who may be pregnant unless it is considered necessary for the treatment.</u>” may be added to the 9.5 Pregnant Women section in 9.

PRECAUTIONS CONCERNING PERSONS WITH SPECIFIC BACKGROUNDS. Furthermore, the PMDA considered it appropriate to add the following contents to the electronic package insert for information provision.

Of note, regarding the precautions for “9.4 Patients with Reproductive Potential” and “9.5 Pregnant Women,” it is considered appropriate to refer to descriptions in “Practice Guidelines for Bipolar Disorder by Japanese Society of Mood Disorders 2023”; the description in “Chapter 6: Perinatal” (“IV-2-1. Descriptions in the guidelines regarding the use of lithium carbonate in pregnant women”) and the description about valproate, a drug which has the same indications as that of lithium carbonate and for which teratogenicity risk has been identified. However, since the risk of teratogenicity with lithium carbonate is latent compared to that with valproate, the description was partially modified.

- Under close collaboration between psychiatrists and physicians responsible for perinatal medicine (including obstetrics and neonatal medicine), a physician who has knowledge and experience in the treatment of bipolar disorder and is able to adequately manage and explain the risks of lithium carbonate should determine the appropriateness of administration of lithium carbonate to pregnant women. In addition, it is required to collaborate with medical institutions that can perform appropriate perinatal management including management of effects of lithium carbonate on pregnant women, fetuses, and neonates (drug withdrawal syndrome neonatal, changes in serum lithium concentrations, etc.) (Refer to “7. Appropriateness of lifting the contraindications” and “8. Measurement of serum lithium concentration in pregnant women" in the WG report.)
- Based on the review of the multiple epidemiological studies shown in “IV-2-1. Published literature” in this report on investigation results, consistent results concerning the risk of teratogenicity associated with lithium carbonate including heart malformation has not been demonstrated, resulting in a failure to obtain sufficient results to rule out the risk. Taking into account that it is described in 9.5 Pregnant Women section of the current electronic package insert that occurrence of heart malformation in humans has been reported, the information provision should be performed by attaching 2 reports that were judged, by the PMDA, to have calculated the effect index for heart malformation based on the appropriate plan and have demonstrated the risk of heart malformation (reference 5, 7 in the WG report) among the 6 reports evaluated by the PMDA as references. (Refer to 5. Reports on clinical uses” in the WG report.)
- The serum concentration of lithium changes with pregnancy, which affects the treatment response.

Therefore, serum lithium concentration should be frequently measured and patients' condition should be carefully monitored. Meanwhile, as shown in "Chapter 7. Side Effects and Monitoring" of "Practice Guidelines for Bipolar Disorder by Japanese Society of Mood Disorders (bipolar disorder) 2023," the purpose of the measurement is to maintain appropriate blood concentration. Therefore, it is considered not appropriate that the electronic package insert presents the specific frequency of measurement of serum lithium concentration only for pregnant women. The current PRECAUTIONS also state that "blood lithium concentration should be measured if there is a factor that increases serum lithium concentration or if initial symptoms of lithium poisoning are observed" and a decrease in blood concentration may prevent the effective blood concentration from being maintained in pregnant women although pregnancy is one of the factors that increase serum lithium concentration. Taking this into account, it is more important to ensure evaluation by a physician who is familiar with treatment of bipolar disorder and specify that serum lithium concentration should be measured in the case where the physician judged necessary rather than simply specifying the number of times of measurement. (Refer to "5. Reports on clinical uses," "7. Appropriateness of lifting the contraindications," and "8. Measurement of serum lithium concentration in pregnant women" in the WG report.)

- In the overseas product labeling, attention is called to the possibility that effects of lithium carbonate that is transferred to the placenta may be observed in children exposed to lithium carbonate. Caution should be exercised for drug withdrawal syndrome neonatal, for which the neonatal cases suggestive of effects of lithium carbonate have been confirmed in "IV-2-2. Adverse reaction report," and lithium poisoning, for which the precaution has been provided in 11.1 Clinically Significant Adverse Reactions in the current electronic package insert. (Refer to "3. Descriptions in overseas product labeling" and "7. Appropriateness of lifting the contraindications" in the WG report.)
- Since it is considered that opportunities for lithium carbonate to be administered to women with reproductive potential increases, it should be described in 9.4 Patients with Reproductive Potential that when lithium carbonate is used in women with childbearing potential, use of lithium carbonate should be carefully determined after the risk of teratogenicity associated with lithium carbonate is explained (Refer to "9. Proposed revision of package insert by the WG" in the WG report.)

VI. Expert Discussion

The PMDA decided that "pregnant women or women who may be pregnant" may be deleted from 2. CONTRAINDICATIONS, a statement that "When this drug is used in women with childbearing potential, the teratogenicity of this drug should be adequately explained, and the appropriateness of using this drug should be carefully determined." may be added to the 9.4 Patients with Reproductive Potential section, and a precautionary statement that "This drug should not be administered to pregnant women or women who may be pregnant unless it is considered necessary for the treatment." and the relevant precautionary statements may be added to the 9.5 Pregnant Women section in 9. PRECAUTIONS CONCERNING PERSONS WITH SPECIFIC BACKGROUNDS, and the decision and the proposed revision were supported by all expert advisors. Of note, the following opinions were expressed by expert advisors.

- It is necessary to provide materials for patients and perform appropriate information provision to physicians so that physicians can adequately explain the benefit-risk of lithium carbonate to patients.
- It is necessary to adequately provide the detailed information such as related literature while

disseminating the importance of measurement of serum lithium concentration and the risk of drug withdrawal syndrome neonatal and lithium poisoning to medical practice settings and to related academic societies.

- It is also useful to provide information on the fact that there are some reports indicating that a concern about reproductive toxicity/developmental toxicity is not suggested in non-clinical studies[3] in addition to information on the clinical uses.

VII. Overall evaluation

The PMDA concluded that PRECAUTIONS may be revised according to Appendix 4 based on the above discussions.

Appendix 1

Summary of investigated drug products (as of January 31, 2026)

No.	Brand name	Marketing authorization holder	Indications/dosage and administration
1	LIMAS tablets 100, 200	Taisho Pharmaceutical Co., Ltd.	Mania or manic state of manic depressive illness The usual starting dose for adults is 400 to 600 mg of lithium carbonate orally administered in 2 to 3 divided doses per day. Thereafter, the dose should be usually escalated every 3 days or 1 week up to a therapeutic dose of 1200 mg per day. If improvement is observed, the dose should be usually tapered to the maintenance dose of 200 to 800 mg daily orally administered in 1 to 3 divided doses. The dose should be adjusted according to the patient's age and symptoms.
2	Lithium Carbonate tablets 100 mg "Taisho," 200 mg "Taisho"	TOKUHON Corporation	
3	Lithium Carbonate Tablets 100 mg "Fujinaga," 200 mg "Fujinaga"	Fujinaga pharm Co., Ltd.	

Appendix 3

Occurrence of events related to pregnancy and neonates [Note 1)]

Event (PT)	Number of events
Foetal disorders (SMQ)	
Foetal distress syndrome	1
Neonatal disorders (SMQ)	
Drug withdrawal syndrome neonatal	2
Neonatal asphyxia	1 [Note2]
Transient tachypnoea of the newborn	1
Respiratory disorder neonatal	1 [Note2]
Congenital, familial and genetic disorders (SMQ)	
Heart disease congenital	1
Termination of pregnancy and risk of abortion (SMQ)	
Abortion spontaneous	2
Abortion	2

Note 1) Cases collected in the PMDA's safety database for drugs. Of cases in which the event falls under Standardized MedDRA Query (SMQ (broad)) “Pregnancy and neonatal topics,” those in which the adverse event did not occur in the mother or fetus were excluded.

“Pregnancy and neonatal topics (SMQ (broad))” includes the following SMQs: “Congenital, familial and genetic disorders (SMQ (broad)),” “Pregnancy, labour and delivery complications and risk factors (excl abortions and stillbirth) (SMQ (broad)),” “Foetal disorders (SMQ (broad)),” “Lactation related topics (incl neonatal exposure through breast milk) (SMQ (broad)),” “Neonatal disorders (SMQ (broad)),” “Termination of pregnancy and risk of abortion (SMQ (broad)),” and “Normal pregnancy conditions and outcomes (SMQ (broad))” (MedDRA version 28.0).

Note 2) Neonatal asphyxia and respiratory disorder neonatal occurred in the same case.

Revision of PRECAUTIONS

Revised language is underlined.

Current	Revision
2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.) 2.1 to 2.3 (Omitted) 2.4.Pregnant women or women who may be pregnant [See 9.5.]	2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.) 2.1 to 2.3 (Omitted) (Deleted)
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS (N/A)	9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.4 Patients with Reproductive Potential When this drug is used in women with childbearing potential, the teratogenicity of this drug should be adequately explained, and the appropriateness of using this drug should be carefully determined. [See 9.5.1.]
9.5 Pregnant Women This drug should not be administered to pregnant women or women who may be pregnant. Teratogenic effects have been reported in animal studies (rats and mice), and an increase in the frequency of heart malformations have been reported in humans. An abnormally elevated serum concentration of lithium may occur immediately before delivery in women in late pregnancy. [See 2.4.] (N/A)	9.5 Pregnant Women 9.5.1 This drug should not be administered to pregnant women or women who may be pregnant unless it is considered necessary for the treatment. Teratogenic effects have been reported in animal studies (rats and mice), and the occurrence of heart malformations has been reported in humans[1)2)]. [See 9.4.] 9.5.2 This drug should be used only in patients for whom administration of this drug is considered appropriate, under the supervision of a physician who has knowledge and experience in the treatment of bipolar disorder and

	can adequately manage and explain the following risks, etc. of this drug, in collaboration with medical institutions that can perform appropriate perinatal management of pregnant women, fetuses, and neonates. [See 11.1.1] • The serum concentration of lithium following administration of lithium carbonate may change with pregnancy, which may affect the treatment response. When this drug is administered to pregnant women, serum lithium concentration should be frequently measured and the patients' condition, etc. should be carefully monitored. An abnormally elevated serum concentration of lithium may occur immediately before delivery in late pregnancy [3)4)]. • Neonatal drug withdrawal syndrome or lithium poisoning may occur in neonates born to pregnant women exposed to lithium [4)5)].
23. REFERENCES (N/A)	23. REFERENCES 1) Patorno E, et al.: N Engl J Med. 2017;376:2245-2254 2) Hastie R, et al.: BMC Med. 2021;19:291 3) Wesseloo R, et al.: Br J Psychiatry. 2017 Jul;211(1):31-36. 4) Molenaar NM, et al.: Bipolar Disord. 2021;23(1):49-54. 5) Newport DJ, et al.: Am J Psychiatry. 2005,162(11):2162-70.
1) to 18) (Omitted)	6) to 23) (Omitted)

N/A: Not Applicable. No corresponding language is included in the current PRECAUTIONS.