



Report on the Investigation Results

June 16, 2017

Pharmaceuticals and Medical Devices Agency

I. Overview of Product

[Non-proprietary name]	See Attachment 1
[Brand name]	See Attachment 1
[Approval holder]	See Attachment 1
[Indications]	See Attachment 1
[Dosage and administration]	See Attachment 1
[Remarks]	Nothing in particular
[Investigating office]	Office of Safety II

II. Background of the investigation

1. Status in Japan

1.1 Codeine phosphate hydrate and dihydrocodeine phosphate

Codeine phosphate hydrate and dihydrocodeine phosphate (codeines) are metabolized to morphine and dihydromorphine as active metabolites by hepatic metabolic enzyme CYP2D6, and exhibit central nervous system depressant actions such as analgesic, antitussive, as well as peripheral actions such as antidiarrheal.

As prescription drugs, codeines are available in the form of single agents and combination drugs, and they are contained in some over-the-counter (OTC) cold and antitussive and expectorant drugs. Among both prescription drugs and OTC drugs, there are some products for which pediatric dosage and administration have been approved.

Codeines are known to have the adverse drug reaction of respiratory depression, and the Contraindications, Careful Administration, Adverse Drug Reactions, Other Precautions, and other sections of the package inserts for prescription drugs currently contain precautions against respiratory depression. In addition, the Careful Administration and Pediatric Use sections contain precautions about the need for careful administration in children because they are highly susceptible to respiratory depression. The package inserts for OTC drugs do not include precautions against respiratory depression.

1.2 Tramadol hydrochloride

Tramadol hydrochloride (tramadol) is metabolized to mono-*O*-demethyl as active metabolite by hepatic metabolic enzyme CYP2D6 and exhibits central nervous system depressant actions such as analgesic.

As a prescription drug, tramadol is available in the form of single agents and in combination drugs. There are no products for which pediatric dosage and administration have been approved.

Tramadol is also known to have respiratory depression as an adverse drug reaction, and the Contraindications, Careful Administration, Clinically Significant Adverse Reactions, and other sections of the package inserts currently contain precautions against respiratory depression. Moreover, the Pediatric Use section contains a precaution to the effect that safety in children has not been established.

2. Status in other countries

2.1 Codeines



In the U.S. drug labels, the *Contraindications* section includes postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy, and the *Boxed Warning* and *Warnings and Precautions* sections state that respiratory depression and death have occurred in children who received codeine for pain relief following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers (UM) of codeine due to a CYP2D6 polymorphism.

In the package inserts for codeine phosphate (single agent) in the U.K., the *Contraindications* section includes all paediatric patients (0 to 18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome and children below the age of 12 years for the symptomatic treatment of cough due to an increased risk of developing serious and life-threatening adverse reactions. The *Therapeutic indications* section specifies acute moderate pain in patients older than 12 years of age which is not considered to be relieved by other analgesics for pain relief. The *Posology and method of administration* section states that codeine should not be used in children below the age of 12 years for pain relief or the symptomatic treatment of cough, and that codeine is not recommended for use in children aged 12 years to 18 years with compromised respiratory function for the symptomatic treatment of cough. The *Special warnings and precautions for use* section states that there have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death, and that codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. Respiratory depression in children is not mentioned in the package inserts for dihydrocodeine phosphate.

2.2 Tramadol

The *Pediatric Use* section of the U.S. drug labels states that the safety and efficacy of tramadol in patients younger than 16 years old have not been established, and the use of tramadol in children is not recommended.

Moreover, the *Posology and method of administration* section of the European package inserts states that the use of tramadol in children younger than 12 years old is not suitable.

3. Background leading up to the investigation

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In April 2017, the U.S. Food and Drug Administration (FDA) recommended that use in children younger than 12 years old be added to the *Contraindication* section, and a statement recommending against their use in patient between 12 and 18 years who are obese or have conditions such as obstructive sleep apnoea, or severe lung disease to the *Warning* section in the drug labels of products containing codeines or tramadol because there had been reports of respiratory depression with the use of codeines and tramadol in children to the FDA Adverse Event Reporting System (FAERS), specifically identifying 64 cases, including 24 deaths, with codeines (from January 1969 to May 2015), and 9 cases, including 3 deaths, with the use of tramadol (from January 1969 to March 2016)¹. For tramadol, it was also recommended to add the use in patients younger than 18 years for pain relief after tonsillectomy and/or adenoidectomy to the *Contraindications* section of the drug labels in order to reflect the content of the measures already taken with regard to the risk of respiratory depression with codeines.² The measures for OTC drugs containing codeines are now being considered.

In light of these recommendations, on May 25, 2017, the Safety Division of the Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare (MHLW) requested the Pharmaceuticals and Medical Devices Agency (PMDA) to conduct investigations on safety of drugs containing codeines, etc. Based on this request, PMDA conducted investigations regarding respiratory depression in children using drugs containing codeines or tramadol and considered whether there was a need to revise their package inserts.

PMDA has held an Expert Discussion as part of the investigations. The expert advisors for the Expert Discussion were nominated based on their declarations etc., concerning the products, in accordance with the provisions of “Rules for Convening Expert Discussions, etc., by Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

¹ FDA HP: FDA Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women (<https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm>)

² FDA HP: FDA Drug Safety Communication: Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy (<https://www.fda.gov/Drugs/DrugSafety/ucm339112.htm>)

III. Investigation by PMDA

1. Accumulated adverse drug reaction reports in Japan

The reports of serious adverse drug reactions related to respiratory depression³ in patients 18 years old and younger that were reported to the Ministry of Health, Labour and Welfare or the PMDA between April 1, 2004 and May 31, 2017 are as follows for the respective products subject to the investigation.

1.1 Codeines

Two cases were reported for prescription drugs and 2 cases for OTC drugs; there were no deaths. All of the reported cases were children younger than 12 years old. One of them was a UM of CYP2D6, took an OTC drug, and developed respiratory failure and consciousness disturbance, etc. There were no reported cases after tonsillectomy or adenoidectomy, or with obesity, obstructive sleep apnoea syndrome or serious lung disease.

1.2 Tramadol

There were no corresponding reports of adverse drug reactions.

2. Summary of Investigation at PMDA

2.1 Codeines

Reports of adverse drug reactions for codeines in Japan included a case of respiratory depression in a patient younger than 12 years old who was a UM of CYP2D6, where a causal relationship to the drug containing codeines could not be ruled out, and this case had a serious outcome. Moreover, all reported cases of serious adverse drug reactions related to respiratory depression were children younger than 12 years old. In addition, in the U.S., administration to children younger than 12 years old was restricted because of the risk of respiratory depression, and a similar recommendation was made in Europe as well.⁴

³ Cases in which respiratory depression developed were extracted from among events corresponding to Medical Dictionary for Regulatory Activities (MedDRA) High Level Terms (HLTs) “Breathing abnormalities”, “Dyspnoeas”, “Respiratory failures (excl neonatal)”, “Disturbances in consciousness NEC”, and “Poisoning and toxicity”.

⁴ EMA HP: EMA HP:

Restrictions on use of codeine for pain relief in children – CMDh endorses PRAC recommendation (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeine-containing_medicines/human_referral_prac_000008.jsp&mid=WC0b01ac05805c516f)

In light of these circumstances, PMDA deemed it necessary for Japan to take measures similar to those taken in the U.S.

However, the CYP2D6 involved in the metabolism of codeines to morphine etc. has genetic polymorphism, and in UM, who has a genetic predisposition to excessive activity of CYP2D6, it is known that adverse reaction such as respiratory depression can readily occur because of the rapid formation of active metabolite morphine and the resulting rise in the blood concentration of morphine.⁵ Moreover, there are known to be ethnic differences in the frequency with which CYP2D6 UM occurs, and the frequency of UM among the Japanese population has been reported to be lower compared to people in the U.S. and Europe (Caucasians, 1–10%; Japanese, 0.5–1%).⁶ For this reason, the risk of respiratory depression in children in Japan is presumed to be lower genetically compared to that in the U.S. and Europe. In light of the fact as well that no deaths were reported in Japan, Contraindications should not be necessary for administration to children younger than 12 years old, subject, however, to a precaution added to the package inserts for prescription drugs that codeines should not be used in children younger than 12 years old. To the package inserts for OTC drugs, a precaution against the risk of respiratory depression and a precaution that examination by a physician should always precede administration for children younger than 12 years old were considered appropriate.

In addition, in the U.S., there are restrictions on the use of codeines for postoperative pain management in patients younger than 18 years old who have undergone tonsillectomy and/or adenoidectomy, as well as in patients between 12 and 18 years old who are obese or have conditions such as obstructive sleep apnoea or severe lung disease, because there could be an increased risk of serious respiratory depression. In Japan, there have been no reports of adverse drug reactions in patients with these backgrounds. However, since the risk is not considered to differ greatly from that for children younger than 12 years old, it was deemed appropriate to add to the package inserts precautions to the effect that codeines should not be administered to patients between 12 and 18 years old who are

Codeine not to be used in children below 12 years for cough and cold

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeine_containing_medicinal_products_for_the_treatment_of_cough_and_cold_in_paediatric_patients/human_referral_prac_000039.jsp&mid=WC0b01ac05805c516f

⁵ Pediatrics 2012; 129(5): e1343-e1347

⁶ FDA HP: <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM475975.pdf>

Clinical Pharmacology & Therapeutics 2012; 91: 321-6.

obese, have obstructive sleep apnoea syndrome, or have serious lung disease. A precaution that codeines should not be used in patients younger than 18 years old for pain relief after tonsillectomy or adenoidectomy was also considered appropriate to add to those, among products containing codeines, for which use for pain relief after tonsillectomy and/or adenoidectomy is assumed judging from the indications.

2.2 Tramadol

No Japanese drugs containing tramadol have approved pediatric dosage and administration, and there has been no report of serious adverse drug reactions related to respiratory depression in patients 18 years old and younger in Japan. However, since a risk of respiratory depression similar to that with codeines exists with tramadol as well, and since the U.S. has had cases of severe respiratory depression in children and has taken measures for tramadol similar to those for codeines, it was deemed appropriate to add a precaution to the effect that, like codeines, tramadol should not be administered to children younger than 12 years old. Moreover, as was done with codeines, it was deemed necessary to add a precaution that tramadol should not be administered to patients between 12 and 18 years old who are obese, have obstructive sleep apnoea, or have serious lung disease. A precaution that tramadol should not be used in patients younger than 18 years old for pain relief after tonsillectomy or adenoidectomy was also considered appropriate to add to those, among products containing tramadol, for which use for pain relief after tonsillectomy and/or adenoidectomy is assumed judging from the indications.

The above-mentioned view of PMDA was discussed at an Expert Discussion. As a result, the proposed revision for a precaution that codeines and tramadol should not be used in children younger than 12 years old, children younger than 18 years old for pain relief after tonsillectomy or adenoidectomy, and patients who are obese or have obstructive sleep apnoea syndrome or serious lung disease was supported by the expert advisors. On the other hand, the expert advisors expressed their opinions as follows:

- Contraindications should be more appropriate when considering that respiratory depression is a potentially life-threatening complication.
- Ethnic differences in UM frequency for CYP2D6 or number of reported cases in Japan is not sufficient explanation for the decision on a precaution rather than contraindications regarding the use in children younger than 12 years old.



- Including in the contraindications could be acceptable in light of the risk for respiratory depression in children younger than 12 years old. In that case, assuming that some physicians are actually using the drugs in such patients in Japan, and considering the fact that they are available in some OTCs, a transition period would be necessary to ensure awareness that they should not be used.

Based on the opinions of expert advisors, PMDA considers as follows regarding the use of codeines and tramadol in children etc.

When considering the seriousness of respiratory depression due to codeines, Contraindications should be appropriate for prescription products containing codeines in children younger than 12 years old as well as in patients younger than 18 years old who have undergone tonsillectomy and/or adenoidectomy in line with the U.S. There should be, however, a period to ensure the awareness that prescription products containing codeines should not be administered to such patients. Moreover, the risk of respiratory depression in children in Japan is presumably lower compared with the U.S. and Europe genetically, and no fatal cases of respiratory depression have been reported so far. Considering these situations, it would be appropriate to add a precaution for a certain period of time that they should not be administered, eventually followed by Contraindications.

Including children younger than 12 years old in the When not to use the product section after a certain period of time should be also appropriate for OTC products containing codeines in line with the prescription products.

Similar measures to those in codeines should be appropriate for tramadol based on the risk of respiratory depression of tramadol and the U.S. measures taken for tramadol in line with codeines.

IV. Overall evaluation

PMDA concludes that it is appropriate to revise the precautions on the package inserts as follows (See the Detailed information on revisions of PRECAUTIONS):

Codeine phosphate hydrate and Dihydrocodeine phosphate (prescription drugs)

Non-proprietary name	Brand name	MAH	Indications	Dosage and administration
Codeine phosphate hydrate	Codeine Phosphate Powder 1% “Daiichi Sankyo”, Codeine Phosphate Powder 10% “Daiichi Sankyo”, Codeine Phosphate Hydrate Powder “Daiichi Sankyo”, Codeine Phosphate Tablets 20mg “Daiichi Sankyo”, Codeine Phosphate Tablets 5mg “Sioe”, and others	Daiichi Sankyo Co., Ltd.; Daiichi Sankyo Propharma; Sioe Pharmaceutical Co., Ltd., and others	Antitussive/sedation in various respiratory diseases, pain relief, improvement of severe diarrhea symptoms	The usual adult dose of codeine phosphate hydrate is 20 mg given orally, up to 60 mg per day. The dose may be adjusted according to the patient's age and symptoms.
Dihydrocodeine phosphate	Dihydrocodeine Phosphate Powder 1% “Daiichi Sankyo”, Dihydrocodeine Phosphate Powder 10% “Daiichi Sankyo”, Dihydrocodeine Phosphate Powder “Daiichi Sankyo”, and others	Daiichi Sankyo Co, Ltd; Daiichi Sankyo Propharma, and the others	Antitussive/sedation in various respiratory diseases, pain relief, improvement of severe diarrhea symptoms	The usual adult dose of dihydrocodeine phosphate is 10 mg given orally, up to 30 mg per day. The dose may be adjusted according to the patient's age and symptoms.
Codeine phosphate hydrate/Cherry bark extract	Salipara-Codeine Solution	Maruishi Pharmaceutical Co., Ltd.	Cough and difficult sputum expectoration in the following diseases Acute bronchitis, cold/upper respiratory inflammation, pulmonary tuberculosis	The usual adult dose is 1.5 to 2 mL diluted 2- to 3-fold in hot water or hot sugar water and given orally 3 times daily. The dose may be adjusted according to the patient's age and symptoms.

Dihydrocodeine phosphate/ <i>dl</i> -Methylephedrine hydrochloride/ Chlorpheniramine maleate	Lightgen Combination Syrup, and the others	Teijin Pharma Ltd., and the others	Cough in the following diseases Acute bronchitis, bronchitis chronic, cold/upper respiratory inflammation, pneumonia, pulmonary tuberculosis	The usual adult dose is 10 mL daily, given orally in 3 divided doses. The dose may be adjusted according to symptoms. It should be administered to infants and children as follows. ≥ 12 to < 15 years old: 2/3 of adult dosage ≥ 8 to < 12 years old: 1/2 of adult dosage ≥ 5 to < 8 years old: 1/3 of adult dosage ≥ 2 to < 5 years old: 1/5 of adult dosage < 2 years old: 1/10 of adult dosage
	Huscode Combination Tablets, and the others	Mylan EPD LLC, and the others		The usual adult dose is 9 tablets daily, given orally in 3 divided doses. The dose may be adjusted according to symptoms. It should be administered to infants and children as follows. ≥ 12 to < 15 years old: 2/3 of adult dosage ≥ 8 to < 12 years old: 1/2 of adult dosage ≥ 5 to < 8 years old: 1/3 of adult dosage ≥ 2 to < 5 years old: 1/5 of adult dosage < 2 years old: 1/10 of adult dosage

	Nichicode Combination Powder, and the others	Nichi-Iko Pharmaceutical Co., Ltd., and the others		<p>The usual adult dose is 3g daily, given orally in 3 divided doses. The dose may be adjusted according to symptoms.</p> <p>It should be administered to infants and children as follows.</p> <p>≥ 12 to < 15 years old: 2/3 of adult dosage</p> <p>≥ 8 to < 12 years old: 1/2 of adult dosage</p> <p>≥ 5 to < 8 years old: 1/3 of adult dosage</p> <p>≥ 2 to < 5 years old: 1/5 of adult dosage</p> <p>< 2 years old: 1/10 of adult dosage</p>
Dihydrocodeine phosphate/ Diprophylline/ <i>dl</i> - Methylephedrine hydrochloride/ Diphenhydramine salicylate/ Acetaminophen/Bromovalerylurea	Coughcode-N Combination Tablets	Pfizer Japan Inc.	Antitussive, pain relief, and antipyresis in common cold syndrome Antitussive in bronchitis	The usual adult dose is 2 tablets per dose, given orally 3 times daily. The dose should be reduced in children, as appropriate according to the patient's age.
Dihydrocodeine phosphate /Platycodon fluidextract/ Glycyrrhiza extract/Plantago	Opisezol Codeine Solution	Nichi-Iko Pharmaceutical Co., Ltd.	Cough and difficult sputum expectoration in the following diseases Upper respiratory inflammation, acute bronchitis	The usual adult dose is 4 to 6 mL daily, given orally in 3 divided doses. The dose may be adjusted according to the patient's age and symptoms.

herb extract/Peony root extract				
Dihydrocodeine phosphate/Ephedrine hydrochloride/Ammonium chloride	Sekicode Combination Syrup	Nichi-Iko Pharmaceutical Co., Ltd.	Cough and difficult sputum expectoration in the following diseases Acute bronchitis, chronic bronchitis, cold/upper respiratory inflammation	The usual adult dose is 3 to 5 mL per dose, given orally 3 times daily after meals or between meals as is or diluted with hot water. 11 to 14 years old: 2/3 of adult dosage 8 to 10 years old: 1/2 of adult dosage 5 to 7 years old: 1/3 of adult dosage 3 to 4 years old: 1/4 of adult dosage 1 to 2 years old: 1/5 of adult dosage 3 months to < 1 year old: 1/10 of adult dosage

Codeine phosphate hydrate and Dihydrocodeine phosphate (OTC drugs)

Non-proprietary name	Brand name	MAH	Indications	Dosage and administration
Products containing dihydrocodeine phosphate	Pabron Gold A, Shin Lulu A Tablets s, Benza Block L, and the others	Taisho Pharmaceuticals Co., Ltd., Daiichi Sankyo Healthcare Co., Ltd., Takeda Consumer Healthcare Co., Ltd., and the others	Alleviation of cold symptoms (nasal mucus, nasal congestion, sneezing, sore throat, cough, sputum, chills (from fever), fever, headache, arthralgia, myalgia) ¹⁾	Administration should be 3 times daily after meals, within 30 minutes if possible. Syrup should be administered after every meal and before bed when necessary. May be administered up to 6 times daily, depending on the patient's condition, but as a rule, a dosing interval of about 4 hours must be allowed when administering 6 times daily. ¹⁾
Products containing dihydrocodeine phosphate	New Bron Solution Ace, New Tonin Cough Syrup, Coolone Cough GX, and the others	SSP Co., Ltd., Sato Pharmaceutical Co., Ltd., Teika Pharmaceutical Co., Ltd., and the others	Cough, sputum accompanying cough, wheezing (wheezy, noisy) ²⁾	Administration should be 3 or 4 times daily and timing of doses and the dosing intervals should be clearly indicated. Troches, drops, oral liquid, and syrup may be administered up to 6 times daily, but as a rule, a dosing interval of at least 2 hours must be allowed for troches and drops and a dosing interval of about 4 hours must be allowed for oral liquid and syrup when administering 5 or 6 times daily. ²⁾
Products containing codeine phosphate hydrate	Aneton Sekidome Eki, and the others	Johnson & Johnson K.K.		

1) Excerpted from “Standards for Marketing Approval of Cold Medicines (PFSB Notification No. 0325-28, dated March 25, 2015)

- 2) Excerpted from “Partial Revision of ‘Standards for Marketing Approval of Antitussive and Expectorant Drugs’ ” (PSEHB Notification No. 0328-10, dated March 28, 2016)

Tramadol (prescription drug)

Non-proprietary name	Brand name	MAH	Indications	Dosage and administration
Tramadol hydrochloride	Tramal Injection 100	Nippon Shinyaku Co., Ltd.	Pain relief for the following diseases and conditions Cancers with pain and postoperative pain after surgery	The usual adult dose of tramadol hydrochloride is 100 mg or 150 mg injected intramuscularly. Following the initial dose, injections may be repeated every 4 to 5 hours as needed. The dose should be adjusted according to the symptoms.
	Tramal OD Tablets 25mg, 50mg	Nippon Shinyaku Co., Ltd.	Pain relief in the following diseases that cannot be managed by treatment with non-opioid analgesics Cancers associated with pain and chronic pain	The usual adult daily dose of tramadol hydrochloride is 100 to 300 mg, given orally in 4 divided doses. The dose may be adjusted according to the symptoms but should not exceed 100 mg per dose or 400 mg per day.
	Onetram Tablets 100mg	Nippon Shinyaku Co., Ltd.	Pain relief in the following diseases that cannot be managed by treatment with non-opioid analgesics Cancers associated with pain and chronic pain	The usual adult dose of tramadol hydrochloride is 100 to 300 mg, given orally once daily. The dose may be adjusted according to the symptoms but should not exceed 400 mg per day.

<p>Tramadol hydrochloride/acetaminophen</p>	<p>Tramcet Combination Tablets</p>	<p>Janssen Pharmaceutical K.K.</p>	<p>Pain relief in the following diseases that cannot be managed by treatment with non-opioid analgesics Non-cancerous chronic pain and pain after tooth extraction</p>	<p>Non-cancerous chronic pain The usual adult dose is 1 tablet, given orally 4 times daily. The interval between doses should be at least 4 hours. The dose should be adjusted according to the symptoms but should not exceed 2 tablets at a time or a total of 8 tablets per day. It is desirable to avoid administering on an empty stomach.</p> <p>Pain after tooth extraction The usual adult dose is 2 tablets, given orally. When additional doses are given, the interval between doses should be at least 4 hours. Do not exceed 2 tablets at a time or a total of 8 tablets per day. It is desirable to avoid administering on an empty stomach.</p>
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