

# Report on Investigation Results

July 10, 2023

Pharmaceuticals and Medical Devices Agency

## I. Summary of drug

[Non-proprietary name]	See Appendix 1.
[Brand name]	See Appendix 1.
[Indications]	See Appendix 1.
[Dosage and administration]	See Appendix 1.
[Marketing authorization holder]	See Appendix 1.
[Remarks]	Nothing noteworthy
[Investigating office]	Office of Pharmacovigilance II

## II. Investigation background

Acetaminophen is widely used as antipyretics and analgesics, and “patients with peptic ulcer,” “patients with serious blood abnormalities,” “patients with serious liver disorder,” “patients with serious renal disorder,” “patients with serious cardiac function failure,” “patients with a history of hypersensitivity to any of the ingredients of acetaminophen preparations,” and “patients with aspirin asthma (induction of asthmatic attack due to nonsteroidal anti-inflammatory drug) or a history of the disease” have been specified as contraindications.

Recently, Japanese Association for the Study of Musculoskeletal Pain (hereinafter referred to as “Society”) requested to lift the contraindications for “patients with serious renal disorder” and “patients with serious cardiac function failure” among the patients for whom acetaminophen is contraindicated on the basis of the reasons described below. In response to the request, the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare (hereinafter referred to as “MHLW”) requested the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as “PMDA”) to conduct an investigation on the contraindications of acetaminophen.

- Currently published standard textbooks, guidelines, etc. state that acetaminophen has less effect on renal function, fluid retention, etc. than nonsteroidal anti-inflammatory drugs (hereinafter referred to as “NSAIDs”), and that it can be a treatment option for patients in

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whom NSAIDs cannot be used.

- In actual clinical practice, cases are not rare in which acetaminophen is used in patients with renal disorder or cardiac function failure. However, specifying these patients as contraindications impedes appropriate drug therapy.

As described later, it was confirmed in related standard textbooks, guidelines, etc. that acetaminophen can be a treatment option for patients with peptic ulcer, blood abnormalities, or aspirin asthma as well (see Section III 2.3 to 2.5). Therefore, it was decided to examine whether the contraindications should be lifted for “patients with peptic ulcer,” “patients with serious blood abnormalities,” and “patients with aspirin asthma (induction of asthmatic attack due to NSAIDs) or a history of the disease” in addition to “patients with serious renal impairment” and “patients with serious cardiac function failure” for whom the lifting of the contraindication was requested. Both the single active ingredient drugs of acetaminophen and the combination drugs containing acetaminophen will be examined in this investigation. However, the following combination drugs are not included in the drug products subject to this investigation for lifting the contraindications because they contain NSAIDs.

- Salicylamide/acetaminophen/anhydrous caffeine/promethazine methylenedisalicylate combination drugs
- Salicylamide/acetaminophen/anhydrous caffeine/chlorpheniramine maleate combination drugs
- Isopropylantipyrine/acetaminophen/allylisopropylacetylurea/anhydrous caffeine combination drugs

The background for specifying the contraindications for these 5 patient populations concerning the drug products investigated is as follows.

As a result of re-evaluating indications and dosage and administration of the oral dosage forms of acetaminophen in 1994 (“Results of Re-evaluations of Drug Products in 1994 (No.2)” PAB Notification No.779 by the Director-General of Pharmaceutical Affairs Bureau (PAB), Ministry of Health and Welfare (MHW) dated September 8,1994), along with NSAIDs<sup>1</sup> that

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<sup>1</sup> Among the single active ingredient prescription drugs containing the following ingredients as active ingredients, those which have “pharyngitis,” “common cold syndrome,” “antipyresis for common cold,” “acute bronchitis,” “acute respiratory tract infection,” “acute upper respiratory inflammation,” “laryngitis,” “upper respiratory inflammation,” or “tonsillitis” as indications

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were designated as drugs that should be re-evaluated simultaneously, these 5 populations were specified in the section of “This drug is contraindicated to the following patients” (currently CONTRAINDICATIONS).

For the suppositories of acetaminophen, on the basis of “Approval Applications for Pediatric Drug Therapy of Acetaminophen That Underwent Prior Assessment at the Pharmaceutical Affairs and Food Sanitation Council” (PSFB/ELD Notification No.0328001, dated March 28, 2007), the contraindications were specified with reference to the oral dosage form in September 2007 when the partial change approval application was made to add analgesia in the field of pediatrics to the indications and dosage and administration.

At the initial marketing authorization approval review of the injections of acetaminophen, it was determined that the safety profile of the injections was not apparently different from that of the oral dosage forms of acetaminophen. Therefore, the same contraindications as those for oral dosage forms have been specified since the time of the marketing approval (June, 2013).

For tramadol hydrochloride/acetaminophen combination drugs and diprophylline/dihydrocodeine phosphate/dl-methylephedrine hydrochloride/diphenhydramine salicylate/acetaminophen/bromovalerylurea combination drugs (hereinafter referred to as diprophylline/acetaminophen, etc. combination drugs), on the basis of the fact that acetaminophen is contained, the same contraindications have been specified as those for the oral dosage forms of the single active ingredient drugs since the time of the initial marketing approval (April, 2011 and March, 2002, respectively).

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. Outline of investigation by the PMDA**

#### **1. Current descriptions of overseas product labeling**

For the overseas (the US, the EU, the UK, Germany, France, Canada, and Australia)

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Aspirin (excluding microencapsulated formulation), aspirin aluminum, acetaminophen (excluding suppository), indometacin (excluding extended-release preparations), ethenzamide, benzydamine hydrochloride, sasapyrine, choline salicylate, sulpyrine (excluding suppository), phenacetin

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product labeling of drug products investigated, the descriptions for “patients with peptic ulcer,” “patients with serious blood abnormalities,” “patients with serious renal disorder,” “patients with serious cardiac function failure,” and “patients with aspirin asthma or a history of the disease” are shown in Appendix 2. For diprophylline/acetaminophen, etc. combination drugs, no preparations containing the same active ingredients have been marketed overseas.

### **1.1 Descriptions in the CONTRAINDICATIONS section**

For the overseas product labeling, the above 5 populations have not been specified as contraindications for acetaminophen (single active ingredient drugs).

“Patients with severe renal impairment (creatinine clearance of less than 30 mL/min)” has been specified as a contraindication in the Canadian product monograph of tramadol hydrochloride/acetaminophen combination drugs. However, this was added in January 2017 in accordance with the instruction for preparations containing tramadol by the Canadian regulatory authority in June 2016. (These patients are not specified as a contraindication in the product monograph of acetaminophen (single active ingredient drugs) even in Canada.)

### **1.2 Descriptions in the section other than CONTRAINDICATIONS**

In some of the overseas product labeling of acetaminophen (single active ingredient drugs) and tramadol hydrochloride/acetaminophen combination drugs, the precautionary statements in the section other than CONTRAINDICATIONS have been described only for the necessity of prolonged dosing intervals, dose reduction, etc. in patients with serious renal disorder (the table below). As for dosage and administration of acetaminophen (single active ingredient drugs) in Japan, the usual dosing intervals are specified as 4 to 6 hours or longer, and the upper limit of the total daily dose as 4 000 mg for adults and 60 mg/kg for children (note, however, that the pediatric dosage should not exceed the adult dosage)<sup>2</sup>, and there is no description regarding adjustment of dosage and administration in patients with renal disorder. As for dosage and administration of tramadol hydrochloride/acetaminophen combination drugs, the usual dosing intervals are specified as at least 4 hours, and the administration should not exceed 8 tablets per day (2 600 mg as acetaminophen).

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<sup>2</sup> The upper limit of total daily dose for infants and toddlers less than 2 years old is specified as 30 mg/kg for injections of acetaminophen.

(1) Acetaminophen (single active ingredient drugs)

Dosage form	Country and regions	Descriptions in overseas product labeling (translated and modified as necessary)
Oral dosage form	Germany	In patients with renal disorder, dose reduction is recommended. If creatinine clearance is less than 10 mL/min, the dosing intervals (usually 6 hours) should be prolonged to at least 8 hours. Also, the total daily dose should not exceed 2 g in adults.
	France	If creatinine clearance is less than 10 mL/min, the dosing intervals (usually 6 hours) should be prolonged to at least 8 hours. Also, the total daily dose should not exceed 3 g.
	Canada	Based on available clinical data, acetaminophen can be used in patients with chronic renal disease without dosage adjustment. The habitual consumption of acetaminophen should be discouraged. If indicated medically, the long-term use of acetaminophen should be supervised by a physician.
	Australia	Patients who have been diagnosed with kidney impairment must seek medical advice before taking acetaminophen, and acetaminophen should be used with caution.
Suppository	Germany	If creatinine clearance is less than 10 mL/min, it is necessary to prolong the dosing intervals (usually 6 hours) to at least 8 hours.
	France	If creatinine clearance is less than 10 mL/min, it is recommended that the dosing intervals (usually 6 hours) be prolonged to 8 hours.
Injections	The US	In cases of severe renal impairment (creatinine clearance $\leq$ 30 mL/min), longer dosing intervals and a reduced total daily dose of acetaminophen may be warranted.
	The UK	It is recommended, when giving acetaminophen to patients with severe renal impairment (creatinine clearance $\leq$ 30mL/min), to increase the minimum interval between each administration to 6 hours.
	Germany	If creatinine clearance is less than 10 mL/min, it is recommended that the dosing intervals (usually 4 hours) be prolonged to at least 6 hours.
	France	If creatinine clearance is between 10 and 50 mL/min or less than 10 mL/min, it is necessary to prolong the dosing intervals (usually 4 hours) to 6 hours or 8 hours, respectively.
	Canada	If creatinine clearance is less than or equal to 30 mL/min, longer dosing intervals and/or a reduced total daily dose of acetaminophen may be warranted.
	Australia	If creatinine clearance is less than or equal to 30 mL/min, it is recommended that there be an interval of at least 6 hours between administrations.

(2) Tramadol hydrochloride/acetaminophen combination drugs

Countries and regions	Descriptions in overseas product labeling (translated and modified as necessary)
The US	In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosage of tramadol hydrochloride/acetaminophen not exceed 2 tablets (Note by PMDA: Acetaminophen 650 mg) every 12 hours.
The EU	In patients with renal insufficiency the elimination of tramadol is delayed. In these patients, prolongation of the dosage intervals should be carefully considered according to the patient's requirements. In severe renal insufficiency (creatinine clearance <10ml/min), tramadol hydrochloride/acetaminophen is not recommended.
Australia	In patients with renal insufficiency, prolongation of dosage interval should be carefully considered according to the patient's requirements.

**2. Descriptions of the standard textbooks, guidelines, etc. regarding the use of acetaminophen in each population considered in this investigation**

**2.1 Patients with serious renal disorder**

**(1) Standard textbooks**

**1) Manual for Pharmacy Operation in Patients with Decreased Kidney Function—Points and Actual Cases to Optimize Drug Therapies in CKD Patients (supervised by the Japanese Society of Hospital Pharmacists, 2014)**

The section “3) Administration of Nephrotoxic Drugs to Patients With Decreased Kidney Function With S-Cr Levels of 3.0 mg/dL or Higher” of “Chapter 9: 3. Handling When Nephrotoxic Drugs Are Prescribed” states that acetaminophen should be administered as an alternative drug of NSAIDs. The “4) Administration of Nephrotoxic Drug to Patients on Dialysis” section states that NSAIDs and acetaminophen, both of which are contraindicated for patients with serious renal disorder, are administered to patients on dialysis as the actual practice on a routine basis.

**2) Multidisciplinary Pain Management: Core Curriculum for Education in Pain (edited by the Japanese Association for the Study of Pain, 2016)**

The following points are listed as advantages in “Table 1: Advantages and disadvantages of acetaminophen” under “1. Positioning of Acetaminophen as an Analgesic” in “Chapter 7: Drug Therapy of Pain, C. Acetaminophen.” It is stated that acetaminophen should be considered first in patients with risk factors of adverse reactions (gastric ulcer, renal impairment, bleeding tendency, etc.) of NSAIDs, in the elderly in whom various residual

function is diminished, and in cases which may result in the prolonged prescription.

- Acetaminophen has fewer gastrointestinal adverse reactions.
- Renal impairment is very weak.
- Inhibitory effect on platelet aggregation is low.
- Onset of aspirin asthma is rare.

### **3) Palliative Care Guidebook for Cancer, new edition (supervised by the Japan Medical Association, 2017)**

The “1. Pain (3) Initiation of NSAIDs/Acetaminophen” in the “II Symptom management” section states that, as the key point of treatment, acetaminophen should be selected instead of NSAIDs for patients with gastric ulcer and renal impairment.

## **(2) Guidelines**

### **1) Guidelines for the Use of Anesthetics and Related Drugs 3rd Edition 4th Revision (Japanese Society of Anesthesiologists, 2015)**

The “XI Pain 1. Acetaminophen 4) Precautions (2) Contraindications” section lists the following (1) to (7) as patients to whom the administration of acetaminophen is contraindicated. However, it is described that the inhibitory activity of acetaminophen on prostaglandin synthesis is lower than that of NSAIDs, and that it cannot be considered that administering acetaminophen to these patients falls into absolute contraindications.

- (1) Patients with peptic ulcer
- (2) Patients with a history of serious blood abnormalities
- (3) Patients with serious hepatic impairment
- (4) Patients with serious renal impairment
- (5) Patients with serious cardiac function failure
- (6) Patients with a history of hypersensitivity to acetaminophen
- (7) Patients with aspirin asthma or a history of the disease

### **2) Guidance on Appropriate Medication for Elderly Patients (general) (MHLW, 2018)**

The section “I. Anti-inflammatory Analgesic Drugs” in “Appendix Table 1 Fundamental points to consider regarding drugs frequently used by geriatric patients” states that acetaminophen is not classified into NSAIDs, but it is regarded as an option when using analgesics in the elderly because acetaminophen has a lower risk of adverse drug events



such as digestive bleeding, renal impairment, and cardiovascular disorder compared to NSAIDs.

### **3) Evidence-based Clinical Practice Guidelines for Chronic Kidney Disease 2018 (Japanese Society of Nephrology, 2018)**

In response to “Clinical Question (CQ) 1: Is either an NSAID or acetaminophen recommended for patients with CKD suffering from pain?” in “Chapter 15: Management of drug treatment,” it is stated as follows: Acetaminophen may be safer than NSAIDs for the short-term administration to patients with chronic kidney disease (CKD). In particular, for elderly patients with decreased renal blood flow and glomerular filtration rate (GFR), the use of acetaminophen is proposed. However, even for acetaminophen, the safety of the long-term administration is not certain.

### **4) Clinical Guidelines for Cancer Pain Management Third Edition (Japanese Society for Palliative Medicine)**

The section “5 Non-opioid Analgesics 2. Acetaminophen 1. Pharmacological Characteristics” in “Chapter II Background Knowledge” states as follows: Acetaminophen is a useful drug with analgesic and antipyretic activity equivalent to that of aspirin. Anti-inflammatory action of acetaminophen is very weak, and it is considered that its metabolites mainly act on the central nervous system to cause analgesic activity. The effect of acetaminophen on the gastrointestinal tract, renal function, platelet function, and cardiovascular system is considered to be insignificant, and acetaminophen can be used even when it is difficult to use NSAIDs due to these disorders.

### **(3) Literature**

Published articles concerning the actual prescribing practices and safety of acetaminophen were retrieved using the search conditions shown in Appendix 4 among publications on patients with serious renal impairment published after re-evaluation results in 1994, excluding case reports. As a result of investigating those publications as well as supporting public literature submitted by the Society, no reports showed an apparent risk. In addition, published literature concerning the use of acetaminophen in patients with serious renal impairment shown below was reviewed.



### **1) Acetaminophen: An Old But New Analgesic (Oral Therapeutics and Pharmacology 2009;28: 109-16)**

It is described as follows.

The mechanism of action of acetaminophen is different from that of NSAIDs, and it is considered that antipyretic activity of acetaminophen occurs by acting on the temperature control center and expanding cutaneous blood vessels, and that analgesic activity occurs by acting on the thalamus and cerebral cortex and increasing the pain threshold; acetaminophen has a feature that it rarely causes adverse reactions common to NSAIDs, although anti-inflammatory effect cannot be expected because acetaminophen does not act on peripheral COX-1 or COX-2; also, the package inserts of acetaminophen in Japan state that “acetaminophen is contraindicated to patients with peptic ulcer, those with serious blood abnormalities, those with serious renal disorder, those with serious liver disorder, and those with aspirin asthma,” which is exactly the same as NSAIDs; however, this does not accurately reflect the characteristics of acetaminophen, which may be a possible reason why acetaminophen has been misunderstood to be a kind of NSAIDs in Japan.

### **2) 2008 Report of the 7th Subcommittee of the Academic Panel, Investigations and Research on Appropriate Drug Therapy for Elderly Patients and Patients With CKD—Investigation on Contraindicated Drugs for “Serious Renal Disorder”—2nd Report (Journal of Japanese Society of Hospital Pharmacists 2009;45, 1023-6)**

As a result of conducting awareness survey (questionnaire survey) on analgesics, etc. for 283 specialists in nephrology and dialysis all over Japan (nephrology: 56.3%; urology: 17.6%; internal medicine: 10.4%; surgery: 7.5%; cardiology: 5.0%; others: 3.2%), the prescription rate of acetaminophen in routine pain management was reported to be 39.8% in patients with advanced CKD, 22.0% in dialysis patients, and 31.2% in late-stage elderly patients.

### **3) Pharmacotherapy for Cancer Pain: Nonopioid Analgesics (The Journal of Japan Society for Clinical Anesthesia, 2017;37:355-60)**

The section of “III Comparison of NSAIDs and Acetaminophen (Table 1)” states as follows: NSAIDs are prone to cause gastrointestinal disorder, renal impairment, and impaired platelet function, but acetaminophen rarely causes these adverse reactions; NSAIDs should be avoided, and acetaminophen should be selected in patients for whom occurrence of gastrointestinal disorder, renal impairment, and impaired platelet function will pose a problem.

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It is also stated that the use of NSAIDs should be avoided in case of aspirin asthma (Table 1).

<Table 1 Comparison of acetaminophen and NSAIDs> (excerpt)

	Acetaminophen	NSAIDs
Mechanism of action	Central nervous system effect	Peripheral COX inhibition
Gastrointestinal disorders	The risk of gastrointestinal disorders is low.	The use of NSAIDs in patients with gastrointestinal disorders should be avoided.
Renal impairment	The risk of renal impairment is low. (Note that the dosing intervals should be at least 8 hours if creatinine clearance (Ccr) is 10 mL/min or less.)	The use of NSAIDs in patients with decreased kidney function should be avoided. (If kidney function is totally lost (anuria), it is possible to use NSAIDs because there is no further aggravation.)
Inhibitory effect on platelet aggregation	The impact is small.	The use of NSAIDs should be avoided if the patients have a serious blood disorder.
Aspirin asthma	It is possible to use. (Note that the administration should be initiated at a low dose.)	The use of NSAIDs should be avoided.

The “VIII Metabolism of Acetaminophen in Renal Impairment” section states as follows: Although the use of acetaminophen in patients with renal impairment is considered to be safer than NSAIDs, attention should be paid to the metabolism; caution is required, such as decreasing the dosing frequency, because it is considered that glutathione conjugates and sulfate conjugate are less likely to be eliminated from the body in patients with renal impairment and that enterohepatic circulation (deconjugation, reabsorption) of acetaminophen occurs; the guidelines of the Japanese Society of Nephrology and Pharmacotherapy recommend that acetaminophen be administered every 6 hours in case of Ccr of 10 to 50 mL/min and every 8 hours in case of Ccr of 10 mL/min or less.

#### **4) Influence of acetaminophen on renal function: a longitudinal descriptive study using a real-world database (Int urol nephrol 2021; 53: 129-35)**

The purpose of this study was to investigate the influence of long-term use of acetaminophen on renal function using a database of health data routinely collected from 185 hospitals in Japan. Patients with chronic pain in the field of orthopedics were selected for this retrospective study and 121 142 subjects were included in the analysis (control group:

109 412 subjects; NSAIDs group: 8 950 subjects; acetaminophen group: 2 780 subjects) (median age (range): 78.0 [65-101] years).

(1) Prescription status of acetaminophen in Japan

The prescription rate of acetaminophen increased each year from 2010 (approximately 5 %) to 2016 (approximately 40 %) compared to that of NSAIDs. Also, the baseline eGFR was  $\leq 30$  (mL/min/1.73 m<sup>2</sup>) in 9.6% of patients in the acetaminophen group, 2.8% in the NSAID group, and 4.2% in the control group, indicating that acetaminophen was prescribed significantly more frequently in patients with low renal function.

(2) Long-term use of acetaminophen and influence on renal function in Japan

The chronological changes in renal function, which were measured by using 1/serum creatinine (SCr) for 2 years in patients aged 65 years and above as the outcome, were significantly lower in the acetaminophen group than in the NSAID group.

## 2.2 Patients with serious cardiac function failure

### (1) Standard textbooks

#### 1) Palliative Care Guidebook for Cancer, new edition (supervised by the Japan Medical Association, 2017)

It is described in the section “2 Cardiovascular Diseases (4) Management of Symptoms in End-stage Cardiovascular Diseases” of “IV Palliative Care Approach for Non-cancer Diseases” that the WHO analgesic ladder should be basically followed for pain relief and that the use of NSAIDs, which have the risk of aggravating renal impairment and fluid retention, should be avoided and acetaminophen is recommended.

#### 2) How to Conduct Pharmaceutical Services for Palliative Care of Cardiac Failure (Japan Society of Hospital Pharmacists, 2021)

The section “5-7 Pain” in “5 How to Think About and Use Drugs for the Major Symptoms in Palliative Care for Cardiac Failure” states as follows: In a nationwide survey concerning palliative care for patients with cardiac failure, to which 531 facilities gave answers, acetaminophen was used in 99 out of 403 facilities (25%) where analgesics or sedatives were used; acetaminophen is considered to have high safety profile for pain management in patients with cardiac failure, since acetaminophen, unlike NSAIDs, has little peripheral inhibitory activity of COX resulting in no renal ischaemia effect; it is desirable that acetaminophen should be used as a first-line drug, since those patients are often complicated

with decreased renal function, which is considered to be the most important prognostic factor.

## **(2) Guidelines**

### **1) Same as 2.1 (2) 1), 2), 4) above**

### **2) Guideline on Diagnosis and Treatment of Acute and Chronic Heart Failure (2017 Revision) (Japanese Circulation Society, 2017)**

It is described in the section “4. Symptoms and Treatment of End-Stage Heart Failure (4.2 Pain)” in “XIII. Palliative Care” as follows: Use of NSAIDs should be avoided as much as possible since they have the risk of aggravating renal impairment and fluid retention in patients with end-stage heart failure; acetaminophen is recommended as a non-narcotic analgesic and, in cases where pain management by acetaminophen is difficult, an additional administration of opioids should be considered.

### **3) 2021 Statement on Palliative Care in Cardiovascular Diseases (Joint Guidelines of the Japanese Circulation Society and the Japanese Heart Failure Society, 2021)**

The section “7.2.2 Pain” in “7.2 Dealing With Treatment-Resistant Pain” of “7. Evaluation and Care of Physical Symptoms” states as follows: To deal with pain in palliative care for patients with cardiac failure, first consider oral or intravenous acetaminophen administration, and consider the use of gabapentin or pregabalin, etc. as an analgesic aid; if these drugs are still ineffective, consider using an opioid such as morphine.

## **(3) Literature**

Published articles concerning the actual prescribing practices and safety of acetaminophen were retrieved using the search conditions shown in Appendix 4 among publications on patients with serious cardiac function failure published after re-evaluation results in 1994, excluding case reports. As a result of investigating those publications as well as supporting public literature submitted by the Society, no reports showed an apparent risk. In addition, published literature concerning the use of acetaminophen in patients with cardiac function failure shown below was reviewed.

### **1) Reduced distribution and clearance of acetaminophen in patients with congestive heart failure (J Cardiovasc Pharmacol 1983; 5: 697-9)**

The article reports that a single intravenous dose of acetaminophen 650 mg was administered to 12 patients with congestive heart failure and 12 healthy adults matched with patients for sex and body weight, resulting in a lower acetaminophen clearance in patients with congestive heart failure than in healthy adults (3.56 vs. 4.59 mL/min/kg,  $p < 0.025$ ) and no significantly different elimination half-life values between groups. Of note, there is no description on safety.

## **2.3 Patients with peptic ulcer**

### **(1) Standard textbooks**

**1) Same as 2.1 (1) 2), 3) above**

### **2) The Washington Manual of Medical Therapeutics 36th edition (2019)**

The section “Pain: TREATMENT: Nonopioid Analgesics” in “Chapter1 Inpatient Care in Internal Medicine” describes that the principal advantage of acetaminophen is its lack of gastric toxicity.

### **3) Harrison’s Principles of Internal Medicine 21st Edition (2022)**

The section “Treatment: Acute Pain: Aspirin, Acetaminophen, and Nonsteroidal Antiinflammatory Agents (NSAIDs)” in “Part 2: Cardinal Manifestations and Presentation of Diseases” states that acetaminophen rarely produces gastric irritation and does not interfere with platelet function although toxic to the liver when taken in high doses.

### **(2) Guidelines**

**1) Same as 2.1 (2) 1), 2), 4) above**

### **2) The Practice Guidelines for Primary Care of Acute Abdomen 2015 (the Committee on Publishing: Japanese Society for Abdominal Emergency Medicine, Japan Primary Care Association, Japan Radiological Society, Japan Society of Obstetrics and Gynecology, Japanese Society for Vascular Surgery, 2015)**

CQ 105 in “Chapter X: Initial Treatment of Acute Abdomen” describes the following: As an analgesic for treatment of abdominal pain in acute abdomen, intravenous administration of acetaminophen 1 000 mg is recommended irrespective of pain intensity; acetaminophen can be parenterally administered and is effective with rapid onset of effects.

### **3) Guidelines for Treatment of Peptic Ulcer 2020 (3rd Edition) (The Japanese Society of Gastroenterology, 2020)**

It is described in “Table 1 Risks of Upper Gastrointestinal Haemorrhage<sup>3</sup>” in Background Question (BQ) 5-15 of “(4) Low-Dose Aspirin (LDA)-associated Ulcer <Prevention>” that the adjusted odds ratio of upper gastrointestinal haemorrhage for acetaminophen was 0.8 (95% CI 0.3–1.9) in a case-control study conducted at 14 sites in Japan.

#### **(3) Literature**

Published articles concerning the actual prescribing practices and safety of acetaminophen were retrieved using the search conditions shown in Appendix 4 among publications on patients with peptic ulcer published after re-evaluation results in 1994, excluding case reports. As a result of investigating those publications, no reports showed an apparent risk. In addition, published literature concerning the use of acetaminophen in patients with peptic ulcer shown below was reviewed.

#### **1) Same as 2.1 (3) 1), 3) above**

#### **2) Dose-response relationships between individual nonaspirin nonsteroidal anti-inflammatory drugs (NANSAIDs) and serious upper gastrointestinal bleedings: a meta-analysis based on individual patient data (Br J Clin Pharmacol 2002; 54: 320-6)**

A meta-analysis evaluating the relationships of NSAID and acetaminophen to serious upper gastrointestinal tract haemorrhage concluded that acetaminophen is not associated with upper gastrointestinal haemorrhage at any dose and should be the first-line analgesic.

### **2.4 Patients with serious blood abnormalities**

#### **(1) Standard textbooks**

#### **1) Same as 2.1 (1) 2), 2.3 (1) 3) above**

#### **(2) Guidelines**

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<sup>3</sup> Case-control study on the association of upper gastrointestinal bleeding and nonsteroidal anti-inflammatory drugs in Japan (Eur J Clin Pharmacol 2006; 62: 765-72)

**1) Same as 2.1 (2) 1), 4) above**

**(3) Literature**

Published articles concerning the actual prescribing practices and safety of acetaminophen were retrieved using the search conditions shown in Appendix 4 among publications on patients with serious blood abnormalities published after re-evaluation results in 1994, excluding case reports. As a result of investigating those publications, no reports showed an apparent risk. In addition, published literature concerning the use of acetaminophen in patients with blood abnormalities shown below was reviewed.

**1) Same as 2.1 (3) 1), 3) above**

**2) A randomized controlled feasibility trial of paracetamol during febrile neutropenia in hemato-oncology patients (Leuk Lymphoma 2019; 60: 1540-7)**

It is reported as follows: Thirteen patients with haematological malignancy in the acetaminophen group and 9 in the placebo group developed febrile neutropenia (FN) and were eligible to commence study treatment; acetaminophen was associated with lower peak temperature than placebo during the first 24 hours of FN, with no adverse reactions of acetaminophen referred to as a reason for treatment failure.

**2.5 Patients with aspirin asthma or a history of the disease**

**(1) Standard textbooks**

**1) Same as 2.1 (1) 2) above**

**(2) Guidelines**

**1) Same as 2.1 (2) 1) above**

**2) Asthma Prevention and Management Guidelines 2021 (Committee for Asthma Prevention and Management Guideline, Japan Society of Allergology, 2021)**

In the "Table 7-1 Drugs That Can Be Used for AERD (NSAIDs-induced Asthma, N-ERD, Aspirin Asthma)" in the section "5) Management of Fever and Pain" of the "7-1 AERD (NSAIDs-induced Asthma, N-ERD, Aspirin-induced Asthma)," a dose of acetaminophen 300 mg or less is described as one of the drugs that can be used for aspirin-exacerbated



respiratory disease (AERD) in many cases. Of note, it is stated that 300 mg or less of acetaminophen per dose should be administered to Japanese patients since it has been reported that 34% of patients receiving 1 000 to 1 500 mg of acetaminophen per dose presented with decreased respiratory function while acetaminophen is relatively safe.

### **3) Practical Guidelines for Asthma Management 2022 (Japan Asthma Society, 2022)**

In the “Table 5-8 Selection of NSAIDs in NSAIDs-induced Asthma” in “5-6 NSAIDs-induced Asthma (N-ERD, also known as Aspirin Asthma)” of “5. Complications: Aspects of Asthma,” 500 mg and 300 mg of acetaminophen per dose, respectively, are described as “slightly harmful (drugs with weak COX-1 inhibitory activity)” and “relatively safe (drugs with little COX-1 inhibitory activity).”

### **(3). Literature**

Published articles concerning the actual prescribing practices and safety of acetaminophen were retrieved using the search conditions shown in Appendix 4 among publications on patients with aspirin asthma or a history of the disease published after re-evaluation results in 1994, excluding case reports. As a result of investigating those publications, no reports showed an apparent risk. In addition, published literature concerning the use of acetaminophen in patients with aspirin asthma shown below was reviewed.

#### **1) Same as 2.1 (3) 1), 3) above**

#### **2) Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice (BMJ 2004; 328: 434-7)**

A systematic review evaluating cross-sensitivity of patients with aspirin-induced asthma to commonly used non-prescription analgesics concluded that acetaminophen should be recommended as a first-line drug for patients with aspirin-induced asthma since incidence of cross-sensitivity was 7% for acetaminophen while it was 98% for ibuprofen, 100% for naproxen, and 93% for diclofenac.

#### **3) Aspirin exacerbated respiratory disease: Current topics and trends (Respir Med 2018; 135: 62-75)**

It is reported as follows: Acetaminophen is considered a weak COX-1 inhibitor, since low

doses (generally below 500 mg) are safe for patients with AERD; however, at higher doses (> 1 000 mg), acetaminophen can induce mild asthmatic reactions in 28%–34% of patients with AERD; such percentage may increase in another 6% when the dosage of acetaminophen is  $\geq$  1 500 mg.

### **3. Case reports of adverse drug reactions in Japan after marketing approval**

Among the cases of adverse drug reactions in Japan of the drug products subject to this investigation reported to the PMDA before April 5, 2023, the cases are shown below where descriptions in the column of “primary disease/complications/medical history” in their case forms indicate that they possibly fall into the patient populations under the evaluation for contraindications in this investigation as well as into the reasons for specifying the patient population for contraindications (aggravation/onset of symptoms or serious outcomes<sup>4</sup>). Of note, out of the cases shown below, no cases were found for which a causal relationship between the event and investigated drugs was reasonably possible.

#### **3.1 Acetaminophen (single active ingredient drugs)**

- A total of 70 patients with renal disorder resulting in serious outcomes were reported, comprising 33 cases of death, 10 cases of sequela, and 27 cases of not recovered.
- Aggravation of cardiac disorder was observed in all the 8 patients with cardiac disorder. As a case with a serious outcome, 1 case of death was reported.
- Aggravation of peptic ulcer was observed in all the 8 patients with peptic ulcer. As cases with serious outcomes, 2 cases of death and 1 case of sequelae were reported.
- A total of 31 patients with blood disorder resulting in serious outcomes were reported, comprising 14 cases of death, 3 cases of sequela, and 14 cases of not recovered.
- Aggravation of asthma was observed in all the 7 patients with asthma or a history of the disease. None of them resulted in serious outcomes.

#### **3.2 Tramadol hydrochloride/acetaminophen combination drugs**

- A total of 39 patients with renal disorder resulting in serious outcomes were reported, comprising 25 cases of death, 1 case of sequela, and 13 cases of not recovered.
- Aggravation of cardiac disorder was observed in all the 13 patients with cardiac disorder. As cases with serious outcomes, 2 cases of death were reported.

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<sup>4</sup>The most serious events within a case with outcomes of death, sequelae, or not recovered were tabulated.

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- Aggravation of peptic ulcer was observed in all the 4 patients with peptic ulcer. None of them resulted in serious outcomes.
- A total of 11 patients with blood disorder resulting in serious outcomes were reported, comprising 8 cases of death and 3 cases of not recovered.
- Aggravation of asthma was observed in all the 5 patients with asthma or a history of the disease. None of them resulted in serious outcomes.

### **3.3 Diprophylline/acetaminophen, etc. combination drugs**

- One patient with cardiac disorder leading to a serious outcome was reported, which resulted in death. Of note, this patient was complicated with renal disorder and blood disorder, and no other cases for patients with renal disorder or blood disorder were reported.
- There were no reports for patients with peptic ulcer or those with asthma or a history of the disease.

## **4. Research reports and foreign corrective action reports**

Of the safety measures taken overseas and studies reported to the PMDA before February 21, 2023 from the market authorization holders (MAHs) of the drug products investigated, there was 1 study report related to “patients with peptic ulcer,” “patients with serious blood abnormalities,” “patients with serious renal disorder,” “patients with serious cardiac function failure,” or “patients with asthma or a history of the disease.” The report was as follows.

### **(1) Analgesic use and associated adverse events in patients with chronic kidney disease: a systematic review and meta-analysis (Br J Anaesth 2022; 128: 546-61)**

The aims of the systematic review and meta-analysis were to assess the prevalence of analgesic use and establish the risk of analgesics-related adverse events, in patients with CKD. Medline, Embase, CINAHL, and CENTRAL were searched until January 2021. Sixty-two studies relevant to the prevalence of analgesic use and 33 to analgesic-related adverse events were included, combining data on 2.3 and 3 million individuals, respectively. Pooled analyses found that 41% of the CKD population regularly used analgesia. It was shown that the combination of acetaminophen/hydrocodone was the most commonly prescribed (9.6%) followed by oxycodone (3.6%), tramadol (2.0%), propoxyphene (1.3%), fentanyl (1.0%), etc. (No descriptions were found regarding acetaminophen in the analysis results of adverse drug

reactions related to analgesics.)

## 5. PMDA's judgment based on the investigation results

As a result of investigations shown 1. to 4. above, the PMDA concluded as follows for each patient population considered in this investigation.

### 5.1 Patients with peptic ulcer, patients with serious blood abnormalities, and patients with serious cardiac function failure

The PMDA, based on the following, considered it appropriate to lift contraindications for "patients with peptic ulcer," "patients with serious blood abnormalities," and "patients with serious cardiac function failure" as well as to issue alerts necessary for use:

- The use of acetaminophen is recommended in standard textbooks, guidelines, published literature, etc.
- Contraindications for these patients are not listed in overseas product labeling.

### 5.2 Patients with serious renal disorder

The PMDA, based on the following, considered it appropriate to lift contraindications for "patients with serious renal disorder" and to issue alerts necessary for use:

- The use of acetaminophen is recommended in standard textbooks, guidelines, published literature, etc.
- Although "patients with severe renal impairment (creatinine clearance of less than 30 mL/min)" are listed as contraindications in the Canadian product monograph for tramadol hydrochloride/acetaminophen combination drugs, it is due to tramadol hydrochloride (see Section III. 1. 1). These patients are not listed as contraindications in the product labeling of countries other than Canada.

Of note, although patients with "severe renal disorder" are specified as contraindications for the extended release tablets, which are to be administered once or twice daily, among the preparations containing tramadol hydrochloride marketed in Japan, it is due to difficulty adjusting doses or dosing intervals.<sup>5</sup> These patients are not contraindicated for the OD tablets, whose dosage and administration are similar to those of tramadol hydrochloride/acetaminophen combination drugs which are within the scope of this

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<sup>5</sup> Summaries of product application 1.8.3 for Onetram Tablets 100 mg, review report for Twotram tab. 50 mg, etc. (dated August 6, 2020)

investigation, as well as for the injectable dosage forms.

In addition, consensus is not necessarily reached on the degree of renal disorder which requires adjusting dosage and administration of acetaminophen and the methods of adjusting them, since the language in overseas product labeling about adjustment of them is different and no clear descriptions are included in guidelines, etc. (See Section III. 1. 2 and III. 2. 1). Given that adjustment of dosage and administration of acetaminophen is generally described in the overseas product labeling, a cautionary statement that adjustment of doses and dosing intervals of acetaminophen should be considered in “patients with serious renal disorder” is regarded as necessary, although there is a certain limitation to referring to target patients, etc. specifically.

### **5.3 Patients with aspirin asthma or a history of the disease**

The PMDA, based on the following, considered it appropriate to lift contraindications for “patients with aspirin asthma or a history of the disease” and to issue alerts necessary for use:

- The use of acetaminophen is recommended in standard textbooks, guidelines, published literature, etc.
- Contraindications for these patients are not listed in overseas product labeling.

Based on the current knowledge described in Section III. 2. 5 (2), however, a cautionary statement that 300 mg or less of acetaminophen per dose should be administered to “patients with aspirin asthma or a history of the disease” is regarded as necessary.

In addition, for tramadol hydrochloride/acetaminophen combination drugs among the drug products investigated, which contain 325 mg of acetaminophen per tablet, the PMDA considers as follows:

- These drugs have 2 indications. Of these, for the indication of "pain after tooth extraction," for which the usual dose is 2 tablets per dose (650 mg of acetaminophen), it is appropriate that "patients with aspirin asthma or a history of the disease" should be specified as contraindications as before.
- For the other indication, “non-cancerous chronic pain” (the usual dose of 1 tablet per dose (325 mg of acetaminophen), increasable to 2 tablets per dose (650 mg of acetaminophen)), although cautionary statements as follows are necessary, it is

possible to lift contraindications for patients with aspirin asthma or a history of the disease, since the usual dose does not substantially exceed 300 mg per dose, which is the upper limit of those described as “relatively safe” in the guidelines in Section III. 2. 5 (2), and it is, to a certain degree, lower than the dose of 500 mg or more per dose, which is described as “slightly harmful.”

- The dose should be 1 tablet per dose (325 mg of acetaminophen).
- Adjusting the dose using not the relevant combination drugs but single active ingredient preparations containing acetaminophen should be considered.

#### **IV. Expert discussion**

##### **1. Decision on lifting contraindications for each patient population considered in this investigation**

The PMDA's decision on lifting contraindications for the investigated drugs (Section III.5.1 to III.5.3) was supported by all the expert advisors.

##### **2. Precautions in each patient population after lifting contraindications**

The proposal to provide precautions as proposed in Appendix 3 based on the PMDA's decision (Section III.5.1 to III.5.3) was supported by all the expert advisors. (Appendix 3 is not included in this document. See the detailed information on revisions of PRECAUTIONS.)

#### **V. Overall evaluation**

The PMDA concluded that PRECAUTIONS may be revised according to Appendix 3 based on the above discussions.

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Summary of drug products under investigation

No.	Non-proprietary name	Brand name	Marketing authorization holder	Indications/dosage and administration
(1)	Acetaminophen (oral dosage form) (Therapeutic category: Antipyretics and analgesics)	Calonal powder, Calonal tablets 200, 300, 500, Calonal Fine Gran. 20%, 50%, Calonal Syrup 2%, and the others	AYUMI Pharmaceutical Corporation, and the others	<p>Indications            &lt;Powder, tablets, fine granules&gt;            •Analgesia for various diseases and symptoms            •Antipyresis and analgesia for the following diseases:            Acute upper respiratory inflammation (including acute upper respiratory inflammation associated with acute bronchitis)            •Antipyresis and analgesia in the field of pediatrics            &lt;Syrup&gt;            Antipyresis and analgesia in the field of pediatrics</p> <p>Dosage and administration            &lt;Powder&gt; &lt;Tablets&gt; &lt;Fine granules&gt;            &lt;Analgesia for various diseases and symptoms&gt;            The usual dosage for adults is 300 to 1 000 mg of acetaminophen per dose administered orally. The dosing intervals should be 4 to 6 hours or longer. The dose should be adjusted depending on the age or symptoms of the patients. The maximum total daily dose should be 4 000 mg. It is advisable to have patients avoid taking the drug on an empty stomach.            &lt;Acute upper respiratory inflammation (including acute upper respiratory inflammation associated with acute</p>



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No.	Non-proprietary name	Brand name	Marketing authorization holder	Indications/dosage and administration
				<p>bronchitis)&gt;            The usual dosage for adults is 300 to 500 mg of acetaminophen per dose administered as needed. The dose should be adjusted depending on the age or symptoms of the patients. Note that, in principle, the dosing frequency should be up to twice a day, and the maximum daily dose should be up to 1 500 mg. In addition, it is advisable to have patients avoid taking the drug on an empty stomach.</p> <p>&lt;Antipyresis and analgesia in the field of pediatrics&gt;            The usual dosage for babies, infants, and children is 10 to 15 mg/kg of acetaminophen per dose administered orally. The dosing intervals should be 4 to 6 hours or longer. The dose should be adjusted depending on the age or symptoms of the patients. The maximum total daily dose should be 60 mg/kg. Note that the dose should not exceed the adult dose. In addition, it is advisable to have patients avoid taking the drug on an empty stomach.</p>
(2)	Acetaminophen (suppository) (Therapeutic category: Antipyretics and analgesics)	(a) Alpiny Suppositories 50, 100, 200 (b) Anhiba pediatric suppository 50 mg, 100 mg, 200 mg (c) Calonal Supp. 50	(a) Hisamitsu Pharmaceutical Co., Inc. (b) Mylan EPD G.K. (c) AYUMI Pharmaceutical Corporation	<p>Indications Antipyresis and analgesia in the field of pediatrics</p> <p>Dosage and administration The usual dosage for babies, infants, and children is 10 to 15 mg/kg of acetaminophen per dose inserted into the rectum. The dosing intervals should be 4 to 6 hours or</p>

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No.	Non-proprietary name	Brand name	Marketing authorization holder	Indications/dosage and administration
		for Pediatric, Calonal Supp. 100, 200, 400 and the others	and the others	longer. The maximum total daily dose should be 60 mg/kg. The dose should be adjusted depending on the age or symptoms of the patients. Note that the dose should not exceed the adult dose.
(3)	Acetaminophen (injections) (Therapeutic category: Antipyretics and analgesics)	acelio Bag for Intravenous Injection 1000 mg	Terumo Corporation	<p>Indications Pain and pyrexia when administration of oral preparations and suppositories is difficult</p> <p>Dosage and administration This drug should be administered intravenously over a period of 15 minutes as follows. &lt;Pain in adults&gt; The usual dosage for adults is 300 to 1 000 mg of acetaminophen per dose administered intravenously over a period of 15 minutes. The dosing intervals should be 4 to 6 hours or longer. The dose should be adjusted depending on the age or symptoms of the patients. The maximum total daily dose should be 4 000 mg. Note that the maximum dose for adults weighing less than 50 kg should be 15 mg/kg of acetaminophen administered intravenously, and the dosing intervals should be 4 to 6 hours or longer. The maximum total daily dose should be 60 mg/kg. &lt;Pyrexia in adults&gt; The usual dosage for adults is 300 to 500 mg of acetaminophen per dose administered intravenously</p>

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No.	Non-proprietary name	Brand name	Marketing authorization holder	Indications/dosage and administration
				<p>over a period of 15 minutes. The dosing intervals should be 4 to 6 hours or longer. The dose should be adjusted depending on the age or symptoms of the patients. Note that, in principle, the dosing frequency should be up to twice a day and the maximum daily dose should be 1 500 mg.</p> <p>&lt;Pain and pyrexia in infants aged 2 years or older and children &gt;</p> <p>The usual dosage for infants aged 2 years or older and children is 10 to 15 mg/kg of acetaminophen per dose administered intravenously over a period of 15 minutes. The dosing intervals should be 4 to 6 hours or longer. The dose should be adjusted depending on the age or symptoms of the patients. The maximum total daily dose should be 60 mg/kg. Note that the dose should not exceed the adult dose.</p> <p>&lt;Pain and pyrexia in babies and infants under 2 years of age&gt;</p> <p>The usual dosage for babies and infants under 2 years of age is 7.5 mg/kg of acetaminophen per dose administered intravenously over a period of 15 minutes. The dosing intervals should be 4 to 6 hours or longer. The dose should be adjusted depending on the age or symptoms of the patients. The maximum total daily dose should be 30 mg/kg.</p>
(4)	Tramadol hydrochloride/	Tramcet Combination	Janssen	Indications

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No.	Non-proprietary name	Brand name	Marketing authorization holder	Indications/dosage and administration
	acetaminophen (Therapeutic category: Antipyretics and analgesics)	Tablets, and the others	Pharmaceutical K.K., and the others	<p>Analgesia for the following diseases that cannot be managed by treatment with non-opioid analgesics:</p> <ul style="list-style-type: none"> <li>•Non-cancerous chronic pain</li> <li>•Pain after tooth extraction</li> </ul> <p>Dosage and administration</p> <p>&lt;Non-cancerous chronic pain&gt; The usual dosage for adults is 1 tablet per dose administered orally 4 times a day. The dosing intervals should be at least 4 hours. The dose should be adjusted depending on symptoms of the patients. The dose should be up to 2 tablets with the maximum of 8 tablets per day. In addition, it is advisable to avoid administering the drug on an empty stomach.</p> <p>&lt;Pain after tooth extraction&gt; The usual dosage for adults is 2 tablets per dose administered orally. If the drug is additionally administered, the dosing intervals should be at least 4 hours. The dose should be up to 2 tablets with the maximum of 8 tablets per day. In addition, it is advisable to avoid administering the drug on an empty stomach.</p>
(5)	Diprophylline/dihydrocodeine phosphate/dl-methylephedrine hydrochloride/diphenhydramine salicylate/acetaminophen/	Coughcode-N Combination Tablets	Mylan EPD G.K.	<p>Indications</p> <p>Antitussive, pain relief, and antipyresis in common cold syndrome</p> <p>Antitussive in bronchitis</p>

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No.	Non-proprietary name	Brand name	Marketing authorization holder	Indications/dosage and administration
	bromovalerylurea (Therapeutic category: Antitussives)			<b>Dosage and administration</b> The usual dosage for adults is 2 tablets per dose administered orally 3 times a day. For children aged 12 years or older, the dose should be reduced as appropriate depending on the age of the patients.

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Current descriptions of overseas product labeling

1. Current descriptions of the US product labeling

Oral dosage form	Suppository	Injections
Brand name: ACETAMINOPHEN 325MG-acetaminophen tablet	Brand name: Acetaminophen Suppositories— For Children	Brand name: OFIRMEV (acetaminophen) injection
February, 2021 version	February, 2016 version	March, 2018 version
<p>Do not use</p> <ul style="list-style-type: none"> <li>with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist.</li> <li>if you are allergic to acetaminophen or any of the inactive ingredients in this product.</li> </ul>	<p>Do not use</p> <ul style="list-style-type: none"> <li>with any other drug containing acetaminophen (prescription or nonprescription). If you are not sure whether a drug contains acetaminophen, ask a doctor or pharmacist.</li> </ul>	<p>4 CONTRAINDICATIONS</p> <p>Acetaminophen is contraindicated:</p> <ul style="list-style-type: none"> <li>in patients with known hypersensitivity to acetaminophen or to any of the excipients in the intravenous formulation.</li> <li>in patients with severe hepatic impairment or severe active liver disease [<i>see Warnings and Precautions (5.1)</i>].</li> </ul> <p>8 USE IN SPECIFIC POPULATIONS</p> <p>8.7 Patients with Renal Impairment</p> <p>In cases of severe renal impairment</p>

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		(creatinine clearance $\leq$ 30 mL/min), longer dosing intervals and a reduced total daily dose of acetaminophen may be warranted.
Tramadol hydrochloride/acetaminophen		Diprophylline/dihydrocodeine phosphate/ dl-methylephedrine hydrochloride/ diphenhydramine salicylate/acetaminophen/ bromovalerylurea
Brand name: ULTRACET		Not applicable
February, 2023 version		
<p>2.4 Dosage Modification in Patients with Renal Impairment</p> <ul style="list-style-type: none"> <li>•Severe Renal Impairment: Do not exceed 2 tablets every 12 hours.</li> </ul> <p>4. CONTRAINDICATIONS</p> <p>ULTRACET is contraindicated for:</p> <ul style="list-style-type: none"> <li>•Children younger than 12 years of age [see Warnings and Precautions (5.4)]</li> <li>•Postoperative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy [see Warnings and Precautions (5.4)]</li> </ul>		



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ULTRACET is also contraindicated in patients with:

- Significant respiratory depression [see *Warnings and Precautions (5.3)*].
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment [see *Warnings and Precautions (5.13)*].
- Patients with known or suspected gastrointestinal obstruction, including paralytic ileus [see *Warnings and Precautions (5.17)*].
- Previous hypersensitivity to tramadol hydrochloride, acetaminophen, any other component of this product, or opioids [see *Warnings and Precautions (5.18)*].
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days [see *Drug Interactions (7)*].

#### 8.7 Renal Impairment

The pharmacokinetics and tolerability of ULTRACET in patients with renal impairment has not been studied. Based on studies using tramadol extended-release tablets, the excretion of tramadol and metabolite M1 is reduced in patients with creatinine clearance of less than 30 mL/min.

In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosage of ULTRACET not exceed 2 tablets every 12 hours. [see *Dosage and Administration (2.3)*].

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<p>The total amount of tramadol and M1 removed during a 4 hour dialysis period is less than 7% of the administered dose based on studies using tramadol alone.</p> <p>Monitor closely for signs of respiratory depression, sedation, and hypotension.</p>	
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2. Current descriptions of the summary of product characteristics (SmPC)

<p>Tramadol hydrochloride/acetaminophen</p>	<p>Diprophylline/dihydrocodeine phosphate/ dl-methylephedrine hydrochloride/ diphenhydramine salicylate/acetaminophen/ bromovalerylurea</p>
<p>Brand name: Tramcet 37.5 mg/325 mg film-coated tablets</p>	<p>Not applicable</p>
<p>December 16, 2023 version</p>	
<p>4.2 Posology and method of administration</p> <p>Renal insufficiency/dialysis</p> <p>In patients with renal insufficiency the elimination of tramadol is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements.</p> <p>4.3 Contraindications</p> <p>-Hypersensitivity to the active substance or to any of the excipients listed in section 6.1,</p>	

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<p>-acute intoxication with alcohol, hypnotic drugs, centrally-acting analgesics, opioids or psychotropic drugs,          -Tramadol hydrochloride/Paracetamol should not be administrated to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal (see 4.5. Interactions with other medicinal products and other forms of interaction),          -severe hepatic impairment,          -epilepsy not controlled by treatment (see 4.4. Special Warnings).</p> <p>4.4 Special warnings and precautions for use          Warnings:          -In severe renal insufficiency (creatinine clearance &lt;10 ml/mm), Tramadol hydrochloride/Paracetamol is not recommended.</p>	
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3. Current descriptions of the UK product labeling

Oral dosage form	Suppository	Injections
Brand name: Paracetamol 500 mg Tablets	Brand name: Paraserts 125 mg Suppositories	Brand name: Perfalgan 10 mg/ml Solution for Infusion
January, 2021 version	June 8, 2022 version	May 21, 2021 version
Do not take:	4.3 Contraindications	4.2 Posology and method of administration

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<p>•If you are allergic to any of the ingredients.</p>	<p>Hypersensitivity to the active substance, to any of the excipients listed in section 6.1, soy or peanuts.</p>	<p>The minimum interval between each administration in patients with severe renal insufficiency must be at least 6 hours. It is recommended, when giving paracetamol to patients with severe renal impairment (creatinine clearance <math>\leq</math> 30 mL/min), to increase the minimum interval between each administration to 6 hours (See section 5.2)</p> <p>4.3 Contraindications          PERFALGAN is contraindicated:</p> <ul style="list-style-type: none"> <li>•in patients with hypersensitivity to paracetamol or to propacetamol hydrochloride (prodrug of paracetamol) or to one of the excipients.</li> <li>•in cases of severe hepatocellular insufficiency.</li> </ul> <p>5.2 Pharmacokinetic properties</p>
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		<p>Renal insufficiency</p> <p>In cases of severe renal impairment (creatinine clearance 10-30 mL/min), the elimination of paracetamol is slightly delayed, the elimination half-life ranging from 2 to 5.3 hours.</p> <p>For the glucuronide and sulphate conjugates, the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects. Therefore, it is recommended, when giving paracetamol to patients with severe renal impairment (creatinine clearance <math>\leq</math> 30 mL/min), to increase the minimum interval between each administration to 6 hours (see section 4.2. Posology and method of administration).</p>
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Tramadol hydrochloride/acetaminophen	Diprophylline/dihydrocodeine phosphate/dl-methylephedrine hydrochloride/diphenhydramine salicylate/acetaminophen/
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	bromovalerylurea
Not applicable	Not applicable

#### 4. Current descriptions of the German product labeling

Oral dosage form	Suppository	Injections
Brand name: Paracetamol AbZ 500 mg Tabletten	Brand name: ben-u-ron 75 mg Zäpfchen	Brand name: Paracetamol B. Braun 10 mg/ml Infusionslösung
May, 2019 version	December 23, 2008 version	July, 2022 version
<p>4.2 Dosierung und Art der Anwendung</p> <p>Besondere Patientengruppen</p> <p><u>Niereninsuffizienz</u></p> <p>Bei Patienten mit Niereninsuffizienz wird eine Dosisreduktion empfohlen und ein minimales Dosisintervall von 6 Stunden, siehe Tabelle unten.</p> <p>Bei schwerer Niereninsuffizienz (Kreatinin-Clearance &lt; 10 ml/min) muss ein Dosisintervall von mindestens 8 Stunden eingehalten werden.</p>	<p>4.2 Dosierung und Art der Anwendung</p> <p>Besondere Patientengruppen</p> <p><u>Schwere Niereninsuffizienz</u></p> <p>Bei schwerer Niereninsuffizienz (Kreatinin Clearance &lt; 10 ml/min) muss ein Dosisintervall von mindestens 8 Stunden eingehalten werden.</p> <p>4.3 Gegenanzeigen</p> <p>ben-u-ron darf nicht von Patienten angewendet werden, die überempfindlich</p>	<p>4.2 Dosierung und Art der Anwendung</p> <p>Schwere Niereninsuffizienz</p> <p>Es wird empfohlen, bei der Anwendung von Paracetamol bei Patienten mit schwerer Niereninsuffizienz (Kreatinin-Clearance <math>\leq 30</math> ml/min) die Dosis zu reduzieren und den Mindestabstand zwischen den Verabreichungen auf 6 Stunden zu verlängern (siehe Abschnitt 5.2).</p> <p>4.3 Gegenanzeigen</p>

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<p>Ohne ärztliche Anweisung ist bei Erwachsenen eine tägliche Dosis von 2 g nicht zu überschreiten.</p> <p>Erwachene</p> <table border="1" data-bbox="237 576 808 871"> <thead> <tr> <th>Glomeruläre Filtrationsrate</th> <th>Dosis</th> </tr> </thead> <tbody> <tr> <td>10-50 ml/min</td> <td>500 mg alle 6 Stunden</td> </tr> <tr> <td>&lt; 10 ml/min</td> <td>500 mg alle 8 Stunden</td> </tr> </tbody> </table> <p>4.3 Gegenanzeigen Überempfindlichkeit gegen den Wirkstoff oder einen der in Abschnitt 6.1 genannten sonstigen Bestandteile.</p>	Glomeruläre Filtrationsrate	Dosis	10-50 ml/min	500 mg alle 6 Stunden	< 10 ml/min	500 mg alle 8 Stunden	<p>gegen Paracetamol oder einen der sonstigen Bestandteile sind.</p>	<ul style="list-style-type: none"> <li>• Überempfindlichkeit gegen Paracetamol, Propacetamolhydrochlorid (Prodrug von Paracetamol) oder eine der in Abschnitt 6.1 genannten sonstigen Bestandteile.</li> <li>• Fälle schwerer hepatozellulärer</li> </ul> <p>4.4 Besondere Warnhinweise und Vorsichtsmaßnahmen für die Anwendung Paracetamol sollte in folgenden Fällen mit Vorsicht angewendet werden:</p> <ul style="list-style-type: none"> <li>• Schwerer Niereninsuffizienz (Kreatinin-Clearance <math>\leq 30</math> ml/min) (siehe Abschnitte 4.2 und 5.2)</li> </ul> <p>5.2 Pharmakokinetische Eigenschaften <i>Niereninsuffizienz:</i> Bei Patienten mit Niereninsuffizienz (Kreatinin-Clearance 10-30 ml/min) ist die Elimination von Paracetamol leicht verzögert,</p>
Glomeruläre Filtrationsrate	Dosis							
10-50 ml/min	500 mg alle 6 Stunden							
< 10 ml/min	500 mg alle 8 Stunden							



*This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.*

		<p>wobei die Eliminationshalbwertszeit zwischen 2 und 5.3 Stunden beträgt.</p> <p>Bei Patienten mit schwerer Niereninsuffizienz ist die Eliminationsgeschwindigkeit der Glucuronid und Sulfatkonjugate dreimal langsamer als bei gesunden Personen.</p> <p>Daher wird empfohlen, den Zeitabstand zwischen 6 Stunden zu verlängern, wenn Paracetamol bei Patienten mit schwerer Niereninsuffizienz (Kreatinin-Clearance <math>\leq 30</math> ml/min) angewendet wird (siehe Abschnitt 4.2).</p>
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Tramadol hydrochloride/acetaminophen	Diprophylline/dihydrocodeine phosphate/dl-methylephedrine hydrochloride/diphenhydramine salicylate/acetaminophen/bromovalerylurea
Not applicable	Not applicable

5. Current descriptions of the French product labeling

**Pharmaceuticals and Medical Devices Agency**

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan  
 E-mail: [safety.info@pmda.go.jp](mailto:safety.info@pmda.go.jp)

This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Oral dosage form	Suppository	Injections														
Brand name: PARACETAMOL MYLAN PHARMA 500 mg, comprimé effervescent	Brand name: PANADOL 125 mg, suppositoire	Brand name: PARACETAMOL KABI 10 mg/mL, solution pour perfusion														
June 15, 2020 version	June 7, 2017 version	January 9, 2023 version														
<p>4.2. Posologie et mode d'administration</p> <p>Insuffisance rénale</p> <p>En cas d'insuffisance rénale sévère (clairance de la créatinine inférieure à 10 ml/min), l'intervalle entre deux prises sera au minimum de 8 heures.</p> <p>La dose de paracétamol ne devra pas dépasser 3 g par jour, soit 6 comprimés.</p> <p>4.3. Contre-indications</p> <ul style="list-style-type: none"> <li>- Hypersensibilité à la substance active ou à l'un des excipients mentionnés à la rubrique 6.1.</li> <li>- Insuffisance hépatocellulaire sévère.</li> <li>- Enfant de moins de 6 ans, en raison des</li> </ul>	<p>4.2. Posologie et mode d'administration</p> <p>Insuffisance rénale</p> <p>Les patients qui ont été diagnostiqués comme insuffisants rénaux doivent demander un avis médical avant d'utiliser ce médicament. Chez l'adulte, en cas d'insuffisance rénale et sauf avis médical, il est recommandé de réduire la dose et d'augmenter l'intervalle minimum entre 2 prises selon le tableau suivant :</p> <table border="1"> <thead> <tr> <th>Clairance de la créatinine</th> <th>Intervalle d'administration</th> </tr> </thead> <tbody> <tr> <td>&gt;10 ml/min</td> <td>6 heures</td> </tr> <tr> <td>&lt;10 ml/min</td> <td>8 heures</td> </tr> </tbody> </table>	Clairance de la créatinine	Intervalle d'administration	>10 ml/min	6 heures	<10 ml/min	8 heures	<p>4.2. Posologie et mode d'administration</p> <p><u>Insuffisance rénale</u></p> <p>Chez les patients insuffisants rénaux, l'intervalle minimal entre chaque administration doit être modifié selon le schéma suivant :</p> <table border="1"> <thead> <tr> <th>Clairance de la créatinine</th> <th>Intervalle d'administration</th> </tr> </thead> <tbody> <tr> <td>Clcr ≥ 50 ml/min</td> <td>4 heures</td> </tr> <tr> <td>Clcr 10-50 ml/min</td> <td>6 heures</td> </tr> <tr> <td>Clcr &lt; 10 ml/min</td> <td>8 heures</td> </tr> </tbody> </table> <p>4.3. Contre-indications</p> <p><b>PARACETAMOL KABI est contre-indiqué :</b></p>	Clairance de la créatinine	Intervalle d'administration	Clcr ≥ 50 ml/min	4 heures	Clcr 10-50 ml/min	6 heures	Clcr < 10 ml/min	8 heures
Clairance de la créatinine	Intervalle d'administration															
>10 ml/min	6 heures															
<10 ml/min	8 heures															
Clairance de la créatinine	Intervalle d'administration															
Clcr ≥ 50 ml/min	4 heures															
Clcr 10-50 ml/min	6 heures															
Clcr < 10 ml/min	8 heures															

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risques de fausse route.	<p>4.3 Contre-indications</p> <ul style="list-style-type: none"> <li>· Hypersensibilité à la substance active ou à l'un des excipients mentionnés à la rubrique 6.1.</li> <li>• Insuffisance hépatocellulaire sévère.</li> <li>• Antécédent récent de rectite, d'anites ou de rectorragies.</li> </ul>	<ul style="list-style-type: none"> <li>· en cas d'hypersensibilité au paracétamol ou au chlorhydrate de propacétamol (prologue du paracétamol) ou à l'un des excipients,</li> <li>• en cas d'insuffisance hépato-cellulaire sévère.</li> </ul>
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Tramadol hydrochloride/acetaminophen	Diprophylline/dihydrocodeine phosphate/ dl-methylephedrine hydrochloride/ diphenhydramine salicylate/acetaminophen/ bromovalerylurea
Brand name: TRAMADOL / PARACETAMOL SANDOZ 37,5 mg/325 mg, comprimé pelliculé	Not applicable
October 27, 2022 version	
4.2. Posologie et mode d'administration	

*This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.*

Insuffisance rénale / dialyse

L'élimination du tramadol est retardée chez les insuffisants rénaux. Chez ces patients, une augmentation de l'intervalle entre les prises doit être soigneusement évaluée en fonction des besoins du patient.

4.3. Contre-indications

- Hypersensibilité aux substances actives ou à l'un des excipients listés en rubrique 6.1.
- Intoxication aiguë par l'alcool, les médicaments hypnotiques, les analgésiques centraux, les opioïdes ou les médicaments psychotropes.
- TRAMADOL / PARACETAMOL SANDOZ ne doit pas être administré aux patients qui sont traités simultanément ou qui ont été traités dans les 2 semaines précédentes par les IMAO (voir rubrique 4.5).
- Insuffisance hépatique sévère.
- Epilepsie non contrôlée par un traitement (voir rubrique 4.4).

4.4. Mises en garde spéciales et précautions d'emploi

Mises en garde spéciales

TRAMADOL / PARACETAMOL SANDOZ n'est pas recommandé en cas d'insuffisance rénale sévère (clairance de la créatinine <10 ml/min).

6. Current descriptions of the Canadian product monograph

**Pharmaceuticals and Medical Devices Agency**

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan  
E-mail: [safety.info@pmda.go.jp](mailto:safety.info@pmda.go.jp)

*This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.*

Oral dosage form	Suppository	Injections
Brand name: <b>TYLENOL</b>	Brand name: <b>ACET 120 / ACET 160 / ACET 325 / ACET 650</b>	Brand name: <b>P<sup>r</sup>O FIRMEV</b>
June 15, 2021 version	July 19, 2022 version	January 30, 2018 version
<p><b>Contraindications:</b></p> <p>Hypersensitivity to acetaminophen or to the ingredients of this formulation (see Dosage Forms, Composition and Packaging). Allergic reactions (primarily skin rash) or reports of hypersensitivity secondary to acetaminophen are rare and generally are controlled by discontinuation of the drug and, when necessary, symptomatic treatment. Do not use with any other product containing acetaminophen.</p> <p><b>Warnings and Precautions:</b></p> <p><b>Renal:</b></p> <p>Based on available clinical data,</p>	<p><b>2 CONTRAINDICATIONS</b></p> <ul style="list-style-type: none"> <li>•ACET is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.</li> </ul> <p>For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.</p>	<p><b>CONTRAINDICATIONS</b></p> <ul style="list-style-type: none"> <li>•OFIRMEV is contraindicated in patients who have previously demonstrated hypersensitivity to acetaminophen, to any ingredient in the formulation, or component of the container (see DOSAGE FORMS, COMPOSITION, AND PACKAGING).</li> <li>•OFIRMEV is contraindicated in patients with severe hepatic impairment or severe active liver disease</li> </ul> <p><u>Renal</u></p> <p>Use caution when administering acetaminophen in patients with severe renal impairment (creatinine clearance ≤ 30</p>

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<p>acetaminophen can be used in patients with chronic renal disease without dosage adjustment. Martin found that patients with chronic renal failure had higher plasma concentrations of acetaminophen and the inactive glucuronide and sulfate metabolites than healthy subjects during repeated dosing up to ten days.</p> <p>Several single-dose studies demonstrate accumulation of acetaminophen metabolites in patients with moderate chronic renal failure and in anephric patients 8-10 for whom hemodialysis appeared to be the major route of elimination.</p> <p>The habitual consumption of acetaminophen should be discouraged. If indicated medically, the long-term use of acetaminophen should be supervised by a physician.</p> <p>A National Kidney Foundation position paper</p>		<p>mL/min). Longer dosing intervals and/or a reduced total daily dose of acetaminophen may be warranted in these patients.</p>
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<p>notes that physicians preferentially recommend acetaminophen to patients with renal failure because of the bleeding complications associated with ASA in these individuals. Acetaminophen was recommended as the non-narcotic analgesic of choice for episodic use in patients with underlying renal disease.</p>		
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Tramadol hydrochloride/acetaminophen	Diprophylline/dihydrocodeine phosphate/ dl-methylephedrine hydrochloride/ diphenhydramine salicylate/acetaminophen/ bromovalerylurea
Brand name: TRAMCET	Not applicable
June 7, 2022 version	
CONTRAINDICATIONS	

**Pharmaceuticals and Medical Devices Agency**

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan  
 E-mail: [safety.info@pmda.go.jp](mailto:safety.info@pmda.go.jp)

*This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.*

TRAMACET (tramadol hydrochloride and acetaminophen) tablets is contraindicated in:

- Patients who are hypersensitive to the active substance (tramadol and acetaminophen) or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.
- Patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with severe hepatic or renal impairment (creatinine clearance of less than 30 mL/min and/or Child-Pugh Class C).
- Patients with mild pain that can be managed with other pain medications.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood, and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase inhibitors (MAOIs) (or within 14 days following discontinuation of such therapy).
- Women who are pregnant, nursing or during labour and delivery.
- Any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs.



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<p>TRAMACET may worsen central nervous system and respiratory depression in these patients.</p> <ul style="list-style-type: none"> <li>•Pediatric patients less than 18 years of age who have undergone tonsillectomy and/or adenoidectomy for obstructive sleep apnea syndrome.</li> <li>•Pediatric patients less than 12 years of age.</li> </ul>	
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7. Current descriptions of the Australian product labeling

Oral dosage form	Suppository*	Injections
Brand name: Paracetamol 665 mg/tablet	Brand name: Panadol Children Suppositories	Brand name: PARACETAMOL KABI
September 28, 2021 version	January, 2020 version	October 8, 2020 version
<p>4.3 CONTRAINDICATIONS</p> <p>Contraindicated in patients with a previous history of hypersensitivity to paracetamol or to any of the excipients.</p> <p>4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE</p> <p>Use in renal impairment Paracetamol should be used with caution in patients with impaired kidney function: Administration of</p>	<p>2. What should I know before I use Panadol Children Suppositories?</p> <p>Do not use Panadol Children Suppositories if:</p> <ul style="list-style-type: none"> <li>•you are allergic paracetamol, or any of the ingredients listed at the end of this leaflet.</li> </ul> <p>Always check the ingredients to make sure you can use this medicine.</p> <p>Do not use this medicine if your child is taking any other prescription or non-prescription</p>	<p>4.3 CONTRAINDICATIONS</p> <p>Paracetamol 10 mg/mL solution for infusion is contraindicated:</p> <ul style="list-style-type: none"> <li>•In cases of hypersensitivity to paracetamol or to propacetamol hydrochloride (prodrug of paracetamol) or to any of the excipients</li> <li>•In cases of severe hepatocellular insufficiency</li> <li>•In patients with hepatic failure or decompensated active liver disease.</li> </ul>

**Pharmaceuticals and Medical Devices Agency**

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan  
 E-mail: [safety.info@pmda.go.jp](mailto:safety.info@pmda.go.jp)

*This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.*

<p>paracetamol to patients with moderate to severe renal impairment may result in accumulation of paracetamol conjugates. Patients who have been diagnosed with kidney impairment must seek medical advice before taking this medication.</p>	<p>medicines containing paracetamol to treat pain, fever, symptoms of cold and flu, or to aid sleep.</p>	<p>4.4 Special Warnings and Precautions for Use</p> <p><u>Use in renal impairment</u></p> <p>Paracetamol solution for infusion should be used with caution in cases of severe renal insufficiency (creatinine clearance <math>\leq 30</math> mL/min).</p> <p>5.2 Pharmacokinetic Properties</p> <p><i>Renal impairment</i></p> <p>Paracetamol should be administered with caution to patients with renal impairment. In cases of severe renal impairment (creatinine clearance <math>\leq 30</math> mL/min), the elimination of paracetamol is slightly delayed, the elimination half-life ranging from 2 to 5.3 hours.</p> <p>For the glucuronide and sulphate conjugates,</p>
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		<p>the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects. It is recommended that there be an interval of at least 6 hours between administrations in patients with severe renal impairment (creatinine clearance <math>\leq</math> 30 mL/min) (see section 4.2 Dose and Method of Administration).</p>
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\*Since the product labeling could not be accessed on the Therapeutic Goods Administration (TGA) website, the current description was cited from the Consumer Medicine Information (CMI).

Tramadol hydrochloride/acetaminophen	Diprophylline/dihydrocodeine phosphate/ dl-methylephedrine hydrochloride /diphenhydramine salicylate/acetaminophen/ bromovalerylurea
Brand name: TRAMADOL/PARACETAMOL 37.5/325 (TRAMADOL HYDROCHLORIDE, PARACETAMOL)	Not applicable

**Pharmaceuticals and Medical Devices Agency**

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan  
 E-mail: [safety.info@pmda.go.jp](mailto:safety.info@pmda.go.jp)

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TABLETS	
November 2, 2021 revised version	
<p><b>4.3 CONTRAINDICATIONS</b></p> <ul style="list-style-type: none"> <li>•hypersensitivity to tramadol, paracetamol or to any other components of the tablet,</li> <li>•acute intoxication with alcohol, hypnotic drugs, centrally-acting analgesics, opioids or psychotropic drugs,</li> <li>•tramadol/paracetamol tablets should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal (see section 4.5 - Interactions with other medicines and other forms of interactions),</li> <li>•in cases of severe hepatocellular insufficiency</li> <li>•in patients with severe respiratory disease, acute respiratory disease and respiratory depression</li> <li>•in patients with hepatic failure or decompensated active liver disease,</li> <li>•epilepsy not controlled by treatment (see section 4.4 - Special warnings and precautions for use).</li> </ul> <p><b>4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE</b></p> <p>Use in renal impairment</p> <p>In patients with renal insufficiency the elimination of tramadol is delayed. In these patients prolongation of dosage interval should be carefully considered according to the patient's requirements.</p>	

Search conditions for published literature on “patients with peptic ulcer”

[Japanese literature]

•Ichushi

Search date: March 16, 2022

Search formula:

#1 Acetaminophen/TH or アセトアミノフェン/AL or パラセタモール/AL or Acetaminophen/AL or Acetaminophen/AL or Acetaminofen/AL or "Acetyl Aminophenol"/AL or "Acetyl-Aminophenol"/AL or Paracetamol/AL or APAP/AL

7,985 search results

#2 消化性潰瘍/TH or 消化性潰瘍/AL or 消化潰瘍/AL or 胃十二指腸潰瘍/AL or ストレス潰瘍/AL or "Peptic Ulcer"/AL or "Gastroduodenal Ulcer"/AL

49,122 search results

#3 #1 and #2

114 search results

#4 ((#3 and CK=ヒト) or (#3 not (CK=イヌ,ネコ,ウシ,ウマ,ブタ,ヒツジ,サル,ウサギ,ニワトリ,鶏胚,モルモット,ハムスター,マウス,ラット,カエル,動物)))

113 search results

#5 (#4 not (消化性潰瘍/TH and SH=化学的誘発)) or (#4 and (消化性潰瘍/TH and SH=合併症))

42 search results in total

Pharmaceuticals and Medical Devices Agency

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan  
E-mail: [safety.info@pmda.go.jp](mailto:safety.info@pmda.go.jp)

[Overseas literature]

•MEDLINE

Search date: March 16, 2022

Search formula:

L1 19617 SEA ACETAMINOPHEN+NT/CT

L2 31902 SEA ACETAMINOPHEN?OR ACETOMINOPHEN? OR ACETAMINOFEN?ORPARA(W)ACETYL(W)AMINOPHENOL? OR ACETYL(1W)AMINOPHENOL? OR PARACETAMOL? OR APAP

L3 80095 SEA PEPTIC ULCER+NT/CT

L4 72821 SEA (PEPTIC? OR ?GASTRL? OR ?DUODENAL?)(2A)ULCER?

L5 175 SEA (L1 OR L2) AND (L3 OR L4)

L6 132 SEA L5/HUMAN

L7 89 SEA (L6 NOT L3(L)CI/CT) OR (L6 AND L3(L)CO/CT)

L8 89 SEA L7 NOT (MURINE? OR MICE? OR MOUSE? OR ANIMAL? OR DOG# OR MONKEY? OR CYNOMOLGUS?)/TI

L9 QUE INDUCE? OR PREVENT? OR (ADVERSE? OR SIDE?)(2A)(EVENT? OR EFFECT? OR REACT? OR OUTCOM? OR RESPON?)

L10 76 SEA L8 NOT ((INDUCE?/TI OR PREVENT?/TI OR (ADVERSE?/TI OR SIDE?/TI)(2A)(EVENT?/TI OR EFFECT?/TI OR REACT?/TI OR OUTCOM?/T I OR RESPON?/TI)) OR L9(2A)L4 OR L2(2A)L9 OR (EXCLUD? OR RISK#

OR TOXIC?)(2A)L4 OR L2(4A)(?TOXIC? OR POISON?))

76 search results in total

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E-mail: [safety.info@pmda.go.jp](mailto:safety.info@pmda.go.jp)

Search conditions for published literature on “patients with serious blood abnormalities”

[Japanese literature]

•Ichushi

Search date: August 22, 2022

Search formula:

#1 Acetaminophen/TH or アセトアミノフェン/AL or パラセタモール/AL or Aceta-minophen/AL or Acetaminophen/AL or Acetaminofen/AL or "Acetyl Aminophe-nol"/AL or "Acetyl-Aminophenol"/AL or Paracetamol/AL or APAP/AL

8,202 search results

#2 血液疾患/TH or 血液異常/AL or 血液の異常/AL or 血液が異常/AL or 血液に異常/AL or 血液における異常/AL or 血液での異常/AL or 血液上の異常/AL or 血液学的異常/AL or 血液学的な異常/AL or 血液疾患/AL or 血液の疾患/AL or 血液に疾患/AL or 血液学的疾患/AL or 血液病/AL or 血液障害/AL or 血液の障害/AL or 血液に障害/AL or Dysemia/AL or Hematodyscrasia/AL or hemodyscrasia/AL or hemo-pathy/AL or "Haematological disease"/AL or "Haematological disorder"/AL or "Haematological Dyscrasia"/AL or "Hematological disease"/AL or "Hematological disorder"/AL or "Hematological Dyscrasia"/AL or "Hematologic disease"/AL or "Hematologic disorder"/AL or "Hematologic Dyscrasia"/AL or "blood disease"/AL or "blood disorder"/AL or "blood Dyscrasia"/AL or "Hemic disease"/AL or "Hemic disorder"/AL or "Hemic Dyscrasia"/AL

263,626 search results

#3 #1 and #2

202 search results

#4 ((#3 and CK=ヒト) or (#3 not (CK=イヌ,ネコ,ウシ,ウマ,ブタ,ヒツジ,サル,ウサギ,ニワトリ,鶏胚,モルモット,ハムスター,マウス,ラット,カエ

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ル,動物)))

197 search results

#5 (#4 not (血液疾患/TH and SH=化学的誘発)) or (#4 and (血液疾患/TH and SH=合併症))

122 search results

#6 危篤/TH or 重篤/AL or 重症/AL or 重大/AL or 重度/AL or 重病/AL or 生命の危/AL or 生命を脅/AL or critical/AL or serious/AL or severe/AL or life-threatening/AL or grave/AL

395,105 search results

#7 #5 and #6

20 search results

#8 #5 not #7

102 search results

122 search results in total

[Overseas literature]

•MEDLINE

Search date: August 22, 2022

Search formula:

L1 20008 SEA ACETAMINOPHEN+NT/CT

L2 32624 SEA ACETAMINOPHEN? OR ACETOMINOPHEN? OR ACETA MINOFEN? OR PARA(W)ACETYL(W)AMINOPHENOL? OR ACETYL(1W)AMINOPHENOL? OR PARACETAMOL? OR APAP

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L3 600114 SEA HEMATOLOGIC DISEASES+NT/CT

L4 73004 SEA DYSEMIA? OR HEMATODYSCRASIA? OR HEMODYSCRASIA? OR HEMOPATHY? OR (HAEMATOLOG? OR HEMATOLOG?  
OR BLOOD? OR HEMIC#)(2A)(DISEASE? OR DISORDER? OR DYSCRASIA?)

L5 430 SEA (L1 OR L2) AND (L3 OR L4)

L6 383 SEA L5/HUMAN

L7 201 SEA (L6 NOT (L1(L)(AE OR TO OR PO)/CT OR L3(L)CI/CT)) OR (L6 AND L3(L)CO/CT)

L8 QUE CRITICAL? OR SERIOUS? OR SEVERE? OR LIFE(W)THREATENING? OR GRAVE?

L9 58 SEA L7 AND L8

L10 143 SEA L7 NOT L9

201 search results in total

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### Search conditions for published literature on “patients with serious renal disorder”

[Japanese literature]

•Ichushi

Search date: March 16, 2022

Search formula:

#1 Acetaminophen/TH or アセトアミノフェン /AL or パラセタモール /AL or Acetaminophen/AL or Acetominophen/AL or Acetaminofen/AL or "Acetyl Aminophenol"/AL or "Acetyl-Aminophenol"/AL or Paracetamol/AL or APAP/AL

7,985 search results

#2 腎臓疾患/TH or 腎不全/AL or 腎臓不全/AL or 腎機能低下/AL or 腎臓機能低下/AL or 腎の機能低下/AL or 腎臓の機能低下/AL or 腎障害/AL or 腎臓障害/AL or 腎臓病/AL or 腎疾患/AL or 腎臓疾患/AL or 腎機能異常/AL or 腎臓機能異常/AL or 腎機能不全/AL or 腎臓機能不全 /AL or ネフロパシー /AL or nephropath/AL or "renal dysfunction"/AL or "renal impairment"/AL or "renal damage"/AL or "renal disorder"/AL or "kidney impairment"/AL or "kidney damage"/AL or "kidney disorder"/AL or "renal failure"/AL or "renal insufficiency"/AL or "kidney failure"/AL or "kidney dysfunction"/AL or "impaired renal function"/AL

462,772 search results

#3 #1 and #2

488 search results

#4 ((#3 and CK=ヒト) or (#3 not (CK=イヌ,ネコ,ウシ,ウマ,ブタ,ヒツジ,サル,ウサギ,ニワトリ,鶏胚,モルモット,ハムスター,マウス,ラット,カエル,動物)))

462 search results

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#5 (#4 not (腎臓疾患/TH and SH=化学的誘発)) or (#4 and (腎臓疾患/TH and SH=合併症))

260 search results

#6 危篤/TH or 重篤/AL or 重症/AL or 重大/AL or 重度/AL or 重病/AL or 生命の危/AL or 生命を脅/AL or critical/AL or serious/AL or severe/AL or life-threatening/AL or grave/AL

388,327 search results

#7 #5 and #6

23 search results

#8 #5 not #7

237 search results

260 search results in total

[Overseas literature]

•MEDLINE

Search date: March 16, 2022

Search formula:

L1 19617 SEA ACETAMINOPHEN+NT/CT

L2 31902 SEA ACETAMINOPHEN? OR ACETOMINOPHEN? OR ACETAMINOFEN? OR PARA(W)ACETYL(W)AMINOPHENOL? OR ACETYL(1W)AMINOPHENOL? OR PARACETAMOL? OR APAP

L3 548945 SEA KIDNEY DISEASES+NT/CT

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L4 378531 SEA (RENAL? OR KIDNEY?)(2A)(IMPAIR? OR FAILURE? OR INSUFFICIENC ? OR DYSFUNCT? OR DAMAGE? OR DISORDER? OR INJUR?) OR NEPHROPATH ?

L5 1210 SEA (L1 OR L2) AND (L3 OR L4)

L6 884 SEA L5/HUMAN

L7 502 SEA (L6 NOT L3(L)CI/CT) OR (L6 AND L3(L)CO/CT)

L8 501 SEA L7 NOT (MURINE? OR MICE? OR MOUSE? OR ANIMAL? OR DOG# OR MONKEY? OR CYNOMOLGUS?)/TI

L9 QUE INDUCE? OR PREVENT? OR (ADVERSE? OR SIDE?)(2A)(EVENT? OR EFFECT? OR REACT? OR OUTCOM? OR RESPON?)

L10 335 SEA L8 NOT ((INDUCE?/TI OR PREVENT?/TI OR (ADVERSE?/TI OR SIDE?/TI)(2A)(EVENT?/TI OR EFFECT?/TI OR REACT?/TI OR OUTCOM?/T I OR RESPON?/TI)) OR L9(2A)L4 OR L2(2A)L9 OR (EXCLUD? OR RISK# OR TOXIC?)(2A)L4 OR L2(4A)(?TOXIC? OR POISON?))

L11 QUE CRITICAL? OR SERIOUS? OR SEVERE? OR LIFE(W)THREATENING? OR GRAVE?

L12 19 SEA L10 AND L4(5A)L11

L13 316 SEA L10 NOT L12

335 search results in total

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Search conditions for published literature on “patients with serious cardiac function failure”

[Japanese literature]

•Ichushi

Search date: March 16, 2022

Search formula:

#1 Acetaminophen/TH or アセトアミノフェン /AL or パラセタモール /AL or Acetaminophen/AL or Acetaminophen/AL or Acetaminofen/AL or "Acetyl Aminophenol"/AL or "Acetyl-Aminophenol"/AL or Paracetamol/AL or APAP/A

7,985 search results

#2 心不全/TH or 心不全/AL or 心臓機能不全/AL or 心機能不全/AL or 不全心/AL or 心代償不全/AL or 心臓代償不全/AL or "Heart Failure"/AL or "Cardiac Failure"/AL or "Congestive Failure"/AL

88,816 search results

#3 #1 and #2

43 search results

#4 ((#3 and CK=ヒト) or (#3 not (CK=イヌ,ネコ,ウシ,ウマ,ブタ,ヒツジ,サル,ウサギ,ニワトリ,鶏胚,モルモット,ハムスター,マウス,ラット,カエル,動物)))

42 search results

#5 (#4 not (心不全/TH and SH=化学的誘発)) or (#4 and (心不全/TH and SH=合併症))

41 search results

#6 危篤/TH or 重篤/AL or 重症/AL or 重大/AL or 重度/AL or 重病/AL or 生命の危/AL or 生命を脅/AL or critical/AL or serious/AL or severe/AL or life-threatening/AL or grave/AL

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388,327 search results

#7 #5 and #6

5 search results

#8 #5 not #7

36 search results

41 search results in total

[Overseas literature]

•MEDLINE

Search date: March 16, 2022

Search formula:

L1 19617 SEA ACETAMINOPHEN+NT/CT

L2 31902 SEA ACETAMINOPHEN? OR ACETOMINOPHEN? OR ACETAMINOFEN? OR PARA(W)ACETYL(W)AMINOPHENOL? OR ACETYL(1W)AMINOPHENOL? OR PARACETAMOL? OR APAP

L3 135911 SEA HEART FAILURE+NT/CT

L4 246990 SEA (HEART? OR CARDI? OR CONGESTIV?)(2A)FAILUR?

L5 99 SEA (L1 OR L2) AND (L3 OR L4)

L6 85 SEA L5/HUMAN

L7 79 SEA (L6 NOT L3(L)CI/CT) OR (L6 AND L3(L)CO/CT)

L8 79 SEA L7 NOT (MURINE? OR MICE? OR MOUSE? OR ANIMAL? OR DOG# OR MONKEY? OR CYNOMOLGUS?)/TI

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L9 QUE INDUCE? OR PREVENT? OR (ADVERSE? OR SIDE?)(2A)(EVENT? OR EFFECT? OR REACT? OR OUTCOM? OR RESPON?)

L10 53 SEA L8 NOT ((INDUCE?/TI OR PREVENT?/TI OR (ADVERSE?/TI OR SIDE?/TI)(2A)(EVENT?/TI OR EFFECT?/TI OR REACT?/TI OR OUTCOM?/T I OR RESPON?/TI)) OR L9(2A)L4 OR L2(2A)L9 OR (EXCLUD? OR RISK# OR TOXIC?)(2A)L4 OR L2(4A)(?TOXIC? OR POISON?))

L11 QUE CRITICAL? OR SERIOUS? OR SEVERE? OR LIFE(W)THREATENING? OR GRAVE?

L12 2 SEA L10 AND L4(5A)L11

L13 51 SEA L10 NOT L12

53 search results in total

*This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.*

Search conditions for published literature on “patients with aspirin asthma or a history of the disease”

[Japanese literature]

•Ichushi

Search date: August 22, 2022

Search formula:

#1 Acetaminophen/TH or アセトアミノフェン/AL or パラセタモール/AL or Aceta-minophen/AL or Acetominophen/AL or Acetaminofen/AL or "Acetyl Aminophe-nol"/AL or "Acetyl-Aminophenol"/AL or Paracetamol/AL or APAP/AL

8,202 search results

#2 アスピリン喘息/TH or アスピリン喘息/AL or アスピリン誘導性喘息/AL or アスピリン誘導喘息/AL or アスピリン誘発性喘息/AL or アスピリン誘発喘息/AL or アスピリン感受性喘息/AL or Aspirin 喘息/AL or "Aspirin-Induced Asthma"/AL or "Aspirin Induced Asthma"/AL or "Aspirin-asthma"/AL or "Aspirin asthma"/AL or "Aspirin-sensitive asthma"/AL or "Aspirin sensitive asthma"/AL or "Asthma as-pirin-sensitive"/AL or "Asthma aspirin sensitive"/AL

1,971 search results

#3 非ステロイド性消炎鎮痛剤による喘息/AL or 非ステロイド性消炎鎮痛剤誘発性喘息/AL or 非ステロイド性消炎鎮痛剤誘発喘息/AL or 非ステロイド性消炎鎮痛剤の喘息/AL or 非ステロイド性消炎鎮痛剤を原因とした喘息/AL or NSAID による喘息/AL or NSAID 誘発性喘息/AL or NSAID 誘発喘息/AL or NSAID の喘息/AL or NSAID を原因とした喘息/AL or NSAIDs による喘息/AL or NSAIDs 誘発性喘息/AL or NSAIDs 誘発喘息/AL or NSAIDs の喘息/AL or NSAIDs を原因とした喘息/AL or NSAID 過敏性喘息/AL or NSAID 過敏喘息/AL or NSAID 誘発性喘息/AL or NSAID 誘発喘息/AL or NSAIDs 過敏性喘息/AL or NSAIDs 過敏喘息/AL or NSAIDs 誘発性喘息/AL or NSAIDs 誘発喘息/AL or "NSAID-induced Asthma"/AL or "NSAID induced Asthma"/AL or "Non-Steroidal Anti-Inflammatory Drugs-induced Asthma"/AL or "Non-Steroidal Anti-Inflammatory

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Drugs induced Asthma"/AL or "Non Steroidal Anti-Inflammatory Drugs-induced Asthma"/AL

59 search results

#4 #1 and (#2 or #3)

70 search results

#5 ((#4 and CK=ヒト) or (#4 not (CK=イヌ,ネコ,ウシ,ウマ,ブタ,ヒツジ,サル,ウサギ,ニワトリ,鶏胚,モルモット,ハムスター,マウス,ラット,カエル,動物)))

70 search results

#6 (#5 not (アスピリン喘息/TH and SH=化学的誘発)) or (#5 and (アスピリン喘息/TH and SH=合併症))

67 search results in total

[Overseas literature]

•MEDLINE

Search date: August 22, 2022

Search source: MEDLINE

Search formula:

L1 20008 SEA ACETAMINOPHEN+NT/CT

L2 32624 SEA ACETAMINOPHEN? OR ACETOMINOPHEN? OR ACETA-MINOFEN? OR PARA(W)ACETYL(W)AMINOPHENOL? OR ACETYL(1W)AMINOPHENOL? OR PARACETAMOL? OR APAP

L3 460 SEA ASTHMA, ASPIRIN-INDUCED+NT/CT

L4 1623 SEA ASTHMA?(2A)(ASPIRIN? OR NSAID# OR NON(W)STEROIDAL?(3A)ANTI(W)INFLAMMATOR?(3A)DRUG#)

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L5 31 SEA (L1 OR L2) AND (L3 OR L4)

L6 31 SEA L5/HUMAN

31 search results in total