

Provisional Translation  
from Japanese Original

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## The Standards for Marketing Approval of Antipyretic Analgesics

### 1. Scope of Antipyretic Analgesics

The scope of formulas subject to these standards covers oral medicines intended for the relief of pain or fever (cold remedies, formulations based on Kampo medicine\* formulas and those consisting of crude drugs only are not covered).

\*Kampo medicine is traditional Japanese medicine.

### 2. Approval Standards

The approval standards for antipyretic analgesics are as follows. For remedies deviating from these standards, efficacy and safety data and reasons justifying the combination should be submitted; the preparation in question will be reviewed based on these data.

#### (1) Types of Active Ingredients

- a. The types of active ingredients that may be combined are shown in Table 1.
- b. Either one of the active ingredients from Group 1, Group 2, and Group 3 in Column I of Table 1 must be included.
- c. Active ingredients from different columns of Table 1 may be combined with each other, unless otherwise stipulated.
- d. Up to 3 of the active ingredients from Group 1 or 2 in Column I of Table 1 can be combined.
- e. When the active ingredients from Group 3 in Column I of Table 1 are combined, they should not be combined simultaneously with the active ingredients from the same column. However, this rule does not apply when they are combined simultaneously with either one of acetaminophen from Group 1 of the same column, ethenzamide in Group 2, and the active ingredients from Group 4.
- f. When the active ingredients from Group 3 in Column I of Table 1 are combined or when they are combined simultaneously with either one of acetaminophen in Group 1 and ethenzamide in Group 2 in the same column, the active ingredients from Columns II, III, IV, V, VI, VIII, and IX can be combined. However, when the active ingredients from Group 3 in Column I of Table 1 are combined at the maximum single dose, none of the other ingredients should be combined.
- g. When the active ingredients from Group 4 in Column I of Table 1 are combined, they should be combined simultaneously with either one of acetaminophen from Group 1, ethenzamide from Group 2 and the active ingredients from Group 3 in the same column, and should not be combined simultaneously with other active ingredients from Groups 1 and 2 in the same column.
- h. When the active ingredients from Group 4 in Column I of the Table 1 are combined simultaneously with acetaminophen from Group 1, ethenzamide from Group 2 and the active ingredients from Group 3 in the same column, the active ingredients from Columns II, IV, V, VI, VIII, and IX can be combined.
- i. When the active ingredients from Column II or IV of Table 1 are combined, only one ingredient can be used from the same column.

(2)Quantities of Active Ingredients

- a. The maximum daily dose of each active ingredient should be the dose specified in Table 1, unless otherwise specified.
- b. The lower limit of the single dose for the individual active ingredients in Groups 1 or 2 in Column 1 of Table 1 is half of the maximum single dose. When 2 or more of the active ingredients from Groups 1 and 2 in Column 1 are combined, the lower limit of the daily dose should be 1/5th of the maximum daily dose or half of the maximum single dose, whichever is lower.
- c. The lower limit of the daily dose for the active ingredients from Column II or IV of Table 1 is 1/5th of the maximum daily dose or half of the maximum single dose, whichever is lower.
- d. When used in combinations, the lower limit of the daily amounts of the active ingredients from Column VI of Table 1 is 1/5 of the maximum daily dose. However, if the medicine is taken up to twice a day, the lower limit for the single dose is 1/15th of the maximum daily dose.
- e. When 2 or more of the active ingredients from Groups 1 and 2 in Column I of Table 1 are combined, the sum of the values obtained by dividing the combined amounts of each of the active ingredients by their respective maximum daily doses (the dose within parenthesis for acetaminophen) should not exceed the combination coefficients shown in Table 2, and it must be more than half of the respective coefficient.
- f. In the case where 2 or more active ingredients from Group 1 or 2 in Column I of Table 1 are combined, the sum of the values obtained by dividing the amounts of each of the active ingredients in the combination by their respective maximum daily doses should not exceed 1.
- g. When the active ingredients from Group 1 or 2 in Column I of Table 1 are combined with the active ingredients from column VII, the stipulation in 2 (2) e will apply.
- h. The lower limit of the daily dose for the active ingredients from Columns VII, VIII, or IX of Table 1 should be 1/10th of the maximum daily dose.
- i. When only the active ingredients from Group 3 among the active ingredients from Column I of Table 1 are combined, the maximum single dose is either 200 mg or 150 mg. In the case where a single dose of 200 mg is combined, the maximum daily dose is 400 mg.
- j. When the active ingredients from Group 3 in Column I of Table 1 are combined simultaneously with acetaminophen from Group 1 in the same column or ethenzamide from Group 2 in the same column, combinations of doses should be limited to those shown in Table 3.
- k. When the active ingredients from Group 4 in Column I of Table 1 are combined simultaneously with acetaminophen from Group 1 in the same column, ethenzamide from Group 2 in the same column, or the active ingredients from Group 3 in the same column, combinations of doses should be limited to those shown in Table 4.

(3)Dosage Forms

The dosage forms should be tablets, capsules, pills, granules, and powders.

(4)Dosage and Administration

- A. The following stipulations have been made.
  - a. Once a day administration  
Take the medicine not more than once a day. If possible, avoid taking the medicine on an empty stomach.

- b. Twice a day administration  
Take the medicine not more than twice a day with an interval of at least 6 hours between doses. If possible, avoid taking the medicine on an empty stomach.
- c. Three times a day administration  
Take the medicine not more than 3 times a day with an interval of at least 4 hours between doses. If possible, avoid taking the medicine on an empty stomach.
- B. Dosages for infants under 3 months of age are not approved.
- C. For formulas containing aspirin, aspirin aluminum, sasapyrine, and sodium salicylate from Group 2 in Column I of the Table 1, the active ingredients from Group 3 in Column 1, or the active ingredients from Group 4 in Column I, dosage for children under 15 years of age is not approved.
- D. For formulas containing the active ingredients from Column III of Table 1, dosage for children under 5 years of age is not approved.
- E. For hard capsules, soft capsules larger than 6 mm in diameter, pills, and tablets, dosage for children under 5 years of age is not approved.
- F. For soft capsules smaller than 6 mm in diameter, pills, and tablets, dosage for children under 3 years of age is not approved.
- G. For children under the age of 15 years, the maximum daily doses acceptable are the values obtained by multiplying the amount of the active ingredient given in 2 (2) by the coefficients for each age group in Table 5.
- H. For formulas containing the active ingredients from Column III of Table 1 with dosage for children under 15 years of age, the maximum single dose is 140 mg and the maximum daily dose is 420 mg. The maximum daily dose for children under 15 years of age is the amount obtained by multiplying the maximum daily dose (420 mg) in Table 1 by the coefficient corresponding to the respective age group in Table 5.

(5) Indications

The indications should be within the following scope.

- 1) Relief of headache, toothache, pain after tooth extraction, sore throat (throat pain), earache, joint pain, neuralgia, lumbago, muscular pain, pain due to stiff shoulders, contusion pain, bone fracture pain, pain associated with sprain (sprain pain), painful menses (menstrual pain), and traumatic pain
- 2) Relief of fever at the time of chills (feeling cold due to fever) and fever

Table 1

## Active Ingredients and Maximum Single and Daily Doses

Category		Active ingredient	Maximum single dose (mg)	Maximum daily dose (mg)
Column I	Group 1	Acetaminophen	300	900
		Lactylphenetidine	200	(1500) * 600
	Group 2	Aspirin	750	1500
		Aspirin aluminum	1000	2000
		Ethenzamide	500	1500
		Sasapyrine	500	1500
		Salicylamide Sodium	1000	3000
		salicylate	1000	3000
	Group 3	Ibuprofen	200	450
	Group 4	Isopropylantipyrine	150	450
Column II		Allylisopropylacetylurea	60	180
		Bromvalerylurea	200	600
Column III		Tranexamic acid	250 (93.4)**	750 (280)**
Column IV		Caffeine and sodium benzoate	150	300
		Caffeine hydrate Anhydrous	120	250
		caffeine	120	250
Column V		Vitamin B <sub>1</sub> , its derivatives, and their salts		25 (1)**
		Vitamin B <sub>2</sub> , its derivatives, and their salts		12 (2)**
		Vitamin C, its derivatives, and their salts		500 (50)**
		Hesperidin, its derivatives, and their salts		90 (18)**

Column VI	Glycine Magnesium silicate		900
	Synthetic aluminum silicate		3000
	Synthetic hydrotalcite Magnesium oxide Dihydroxyaluminum and aminoacetate		3000
	Aluminum hydroxide gel (as dried aluminum hydroxide gel)		4000
	Dried aluminum hydroxide gel		500
	Aluminum hydroxide-Sodium hydrogen carbonate coprecipitate		1500
	Aluminum hydroxide-Magnesium carbonate mixed dried gel		1000
	Aluminum hydroxide-Magnesium carbonate-Calcium carbonate coprecipitate		1000
	Magnesium hydroxide-Aluminum potassium sulfate coprecipitation product		900
	Magnesium carbonate		3000
	Magnesium aluminometasilicate		1500
			2000
			1500

\* The figure in parentheses is used when the maximum daily dose of each active ingredient is calculated as specified in 2 (2) e.

\*\* The figures in parentheses are the lower limits of the amounts in a combination. (Crude drugs)

Category	Active ingredient	Maximum daily dose (g)	
		Extract (converted to the crude drug amount)	Powder
Column VII	Earthworm(Lumbricus)	3	2
Column VIII	Japanese Valerian	6	2
	Glycyrrhiza	5	1.5
	Cinnamon Bark	5	1
	Peony Root	5	2
	Mountain Bark	6	2
Column IX	Japanese Zanthoxylum Peel	2	1
	Ginger	3	1
	Citrus Unshiu Peel	5	3

Table 2

Combination Coefficient for Combining 2 or More of Active Ingredients from Group 1 or 2 in Column I

Administration Number of active ingredients combined	Three times daily	Twice daily	Once daily
Two active ingredients	34/30	32/30	18/30
Three active ingredients	38/30	36/30	19/30

Table 3

Combination Patterns for Combining Active Ingredients from Group 3 in Column I and Active Ingredients from Group 1 or 2 in Column I

(daily dose, -: combination not acceptable)

Group 3 in Column I		450mg	432mg	390mg
Group 1 in Column I	Acetaminophen	195mg	-	390mg
Group 2 in Column I	Ethenzamide	-	252mg	-

Table 4

Combination Patterns for Combining Active Ingredients from Group 4 in Column I and Active Ingredients from Group 1, 2 or 3 in Column I

(daily dose, -: combination not acceptable)

Group 4 in Column I		450mg	450mg	300mg
Group 1 in Column I	Acetaminophen	750mg	-	-
Group 2 in Column I	Ethenzamide	-	750mg	-
Group 3 in Column I	Ibuprofen	-	-	100mg

Table 5

Range of Age Coefficients

Age group	Coefficient
15 years of age and over	1
11 to under 15 years of age	2/3
7 to under 11 years of age	1/2
3 to under 7 years of age	1/3
1 to under 3 years of age	1/4
6 months to under 1 year of age	1/5
3 to under 6 months of age	1/6

