Appendix 7

Provisional Translation
from Japanese Original

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The Standards for Marketing Approval of Antivertigo Medicines

1. Scope of Antivertigo Medicines

The scope of preparations subject to these standards covers oral medicines (Kampo medicine* formulas are not covered) intended to prevent or relieve symptoms associated with motion sickness, such as dizziness, nausea, and headaches.

*Kampo medicine is traditional Japanese medicine.

2. Approval Standards

The approval standards for antivertigo medicines intended to prevent or relieve symptoms associated with motion sickness (hereinafter referred to as motion sickness drugs) are as follows.

For motion sickness drugs and antivertigo medicines other than motion sickness drugs not conforming to 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) At least one ingredient from either Column I or Group 1 of Column II of Table 1 must be combined.

(c) Though the active ingredients in Column I, II, III, IV, V, VI, or VII of Table 1 may all be mutually combined, the types of active ingredients that may be combined in oral liquid preparations should be those in Column I, Group 1 of Column II, Column V, and Column VII.

(d) Up to 2 ingredients from each of Column I or V in Table 1 may be included (however, only 1 ingredient from each of Group 1 or 2 of Column V may be combined).
One active ingredient each from Column II, III, IV, VI, or VII may be included.

(e) Other than the active ingredients in Table 1, vitamins listed in the Appendix may be included if there is a sound basis for their combination and the effect is mild.

(2) Quantities of Active Ingredients

(a) Table 1 shows the maximum single and daily doses for each of the active ingredients listed.

(b) When 1 active ingredient listed in either Column I or Group 1 of Column II of Table 1 is used, the lower limit of the single dose of each active ingredient should be half of the maximum single dose.

(c) When 2 of the active ingredients in Column I of Table 1 are used, the lower limit of the single dose of each active ingredient should be 1/5th of the maximum single dose. In addition, the sum of the values obtained by dividing the amounts of each active ingredient by their respective maximum single dose should be not less than 0.5 and not more than 1.

(d) When active ingredients in Column I or Group 1 of Column II of Table are combined mutually, the lower limit of the single dose of each active ingredient should be 1/5th of the maximum single dose. Further, the sum of the values obtained by dividing the amounts of each active ingredient by their respective maximum single dose should be not less than 0.5 and not more than 2.
(e) The lower limit of the single dose of each active ingredient in Group 2 or 3 of Column II, Column III, Column IV, Column V, or Column VI of Table 1 should be 1/5th of the maximum single dose.
(f) When 2 ingredients from Column V of Table 1 are combined, the sum of the values obtained by dividing the amounts of each active ingredient by their respective maximum single dose should not exceed 1.
(g) The lower limit of the single dose of each active ingredient in Column VII of Table 1 should be 1/10th of the maximum single dose.
(h) The maximum daily dose of each active ingredient listed in the Appendix is as specified in the table.

(3) Dosage Form

The dosage forms are capsules, granules, pills, fine granules, powders, tablets (including chewable tablets), and oral liquids.

(4) Dosage and Administration

(a) Dosage is by oral administration from 1 to 3 times a day (with the exception of 1 to 4 times a day for single active ingredient preparations containing dimenhydrinate). The time of administration and intervals between doses should be clearly indicated. For medicines designed to be taken twice a day or more, the interval between doses must be at least 4 hours.
(b) In principle, dosage for children under 3 years of age is not approved. In the case of preparations containing ethyl aminobenzoate, dosage is not approved for children under 6 years of age, and as for preparations containing promethazine hydrochloride or promethazine methylene disalicylate, dosage for those under 15 years of age is not approved.
(c) For capsules, and pills and tablets larger than 6 mm in diameter, dosage for children under 5 years of age is not approved.
(d) The maximum single and daily doses for children under 15 years of age is obtained by multiplying the maximum single and daily doses given in Table 1 by the coefficient for each age group given in Table 2.
(e) The method of administration must be clearly indicated for chewable tablets.

(5) Indications

The indications are “prevention and relief of dizziness, nausea, and headache associated with motion sickness.”

(6) Packaging Units

In principle, the volume of containers for oral liquids should be the amount for a single dose and should not exceed 30 mL.

Table 1

Column		Active ingredient	Maximum single dose (mg)	Maximum daily dose (mg)
Column I		Difenidol hydrochloride	25	75
		Diphenylpyraline hydrochloride	4	12
		Diphenhydramine hydrochloride	50	150
		Promethazine hydrochloride	25	50
		Meclizine hydrochloride	50	75
		Diphenhydramine salicylate	60	180
		Dimenhydrinate	50	200
		Diphenhydramine tannate	150	450
		Fenethazine tannate	30	90
		Diphenylpyraline teoclate	3	9
		Diphenhydramine fumarate	60	180
		Promethazine methylenedisalicylate	30	60
		dl-Chlorpheniramine maleate	4	12
		d-Chlorpheniramine maleate	2	6
		Pheniramine maleate	30	90
Column II	Group I	Scopolamine hydrobromide	0.25	0.50
	Group II	Oxyphencyclimine hydrochloride	2.34	7
		Dicyclomine hydrochloride	10	30
		Methixene hydrochloride	2.92	8.75
		Atropine methylbromide	2	6
		Anisotropine methylbromide	10	30
		Scopolamine methylbromide	1.6	4.8
		Hyoscyamine methylbromide	0.75	2.25
		Metylbenactyzium bromide	10	30
		Belladonna extract	20	60
		Isopropamide iodide	2.5	7.5
		Diphenylpiperidinomethyldioxolan iodide	20	60
		Scopolia extract	20	60
	Group III	Papaverine hydrochloride	30	90
Column III		Ethyl aminobenzoate	100	300
		Cerium oxalate	100	300
		Ethyl p-piperidinoacetylaminobenzoate	200	600
Column IV		Allylisopropylacetylurea	60	180
		Bromovalerylurea	200	600
Column V	Group I	Caffeine	50	150
		Caffeine citrate	100	300
		Anhydrous caffeine	50	150
	Group II	Aminophylline	100	300
		Diprophylline	100	300
		Theophylline	100	300
Column VI		Sodium bicarbonate	1,000	3,000
Column VII		Mentha oil	5	15
		dl-Menthol	30	90
		l-Menthol	30	90

Table 2

Age	Coefficient
15 years old and over	1
11 years old-Under 15	2/3
7 years old-Under 11	1/2
3 years old-Under 7	1/3

Appendix

Ingredients	Maximum daily dose (mg)
Vitamin B_1, its derivatives, and their salts	25
Vitamin B_2, its derivatives, and their salts	12
Vitamin B_6, its derivatives, and their salts	50
Nicotinamide	60
Calcium panthothenate	30