Appendix 13

Provisional Translation
from Japanese Original

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Notification PFSB No.277

The Standards for Marketing Approval of Antihemorrhoids (External Preparations)

1. Scope of Antihemorrhoids (External Preparations)

The scope of preparations subject to these standards covers medicines intended for the relief of hemorrhoidal symptoms in the anus and rectum (Kampo medicine* formulas and non-Kampo crude drug remedies consisting of crude drug only are not covered).

*Kampo medicine is traditional Japanese medicine.

2. Approval Standards

The approval standards for antihemorrhoids (external preparations) are as follows. For preparations deviating from these standards, efficacy and safety data and reasons justifying the combination should be submitted, and 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 listed in Table 1.
b. Active ingredients that must be included are those from Column I in Table 1.
c. Active ingredients in different columns in Table 1 may be mutually combined, unless otherwise specified elsewhere.
d. When active ingredients from Column II, III, V, or VI are to be combined, only 1 ingredient from each column is allowed.
e. When active ingredients from Column VIII or IX are to be combined, only 1 ingredient from the same group is allowed.
f. It is permissible to use 2 of the active ingredients from Group 1 in Column I of Table 1, but the combination of dibucaine hydrochloride with dibucaine and the combination of lidocaine hydrochloride with lidocaine are not permitted.
g. In Column VII of Table 1, the combination of allantoin with aluminum chlorohydroxy allantoinate, that of dried aluminum potassium sulfate with aluminum potassium sulfate, and that of purified yolk lecithin with egg yolk oil is not permitted.

(2) Quantities of Active Ingredients

a. The maximum concentration of each of the active ingredients listed in Table 1 is given in “A” for ointments to be applied by rubbing or external liquids. The maximum single dose of each of the active ingredients is given in “B” for ointments to be applied by an applicator and for suppositories.
b. The minimum concentration or the lowest single dose of each of the active ingredients listed in the individual columns (except for the ingredients of Group 2 in Columns VII and IX) of Table 1 is 1/5th of the corresponding maximum concentration or the maximum single dose. However, if 1 or more of the active

ingredients from Column I is used, the concentration of at least 1 active ingredient must be at least half of the maximum concentration or the maximum single dose.

c. The minimum concentration or the lowest single dose of each of the active ingredients listed in Group 2 of Columns VII and IX is 1/10th of the corresponding maximum concentration or maximum single dose.

d. When 2 active ingredients listed in Group 1 of Column I in Table 1 are combined, the sum of the values obtained by dividing the individual concentrations or doses by their respective maximum concentration or maximum single dose must not exceed 1.

(3) Dosage Form

The dosage forms should be suppositories (including soft capsules), ointments, and external liquids (including aerosols).

(4) Dosage and Administration

a Ointments to be applied by rubbing and external liquids

The preparations should be applied to the anal area up to 3 times a day at maximum. For external liquids, the method of application should be indicated clearly.

b. Ointments to be applied by an applicator and suppositories

[1] The preparations should be applied to the anal area or the rectum 1 dose at a time, up to 3 times a day, at maximum.

[2] For ointments to be applied by an applicator, the method of application should be indicated clearly.

[3] Dosage for children younger than 7 years of age is not approved.

[4] The maximum single dose for those 7 to <15 years of age is half of the maximum single dose given in "B" of Table 1.

(5) Indications

The scope of indications is "Relief of pain, itching, swelling, bleeding, and erosion associated with bleeding piles (ripped piles)/blind piles, and disinfection. The indications of "erosion" and "disinfection" should be limited to ointments to be applied by rubbing and external liquids. The indications given in the upper column of the following table should be limited to cases in which 1 of the active ingredients from a group or column in the lower column of the following table is used at an amount not less than half of the maximum concentration or the maximum single dose as specified in Table 1.

Upper column	Lower column
Itching	Group 1 of Column I, III, VI
Swelling and bleeding	Column II, III, IV
Erosion	Column IV
Disinfection	Group 1 of Column V

Table 1

Classification		Active ingredient	A Maximum concentration (%)	B Maximum single dose (mg)
Column I	Group 1	Ethyl aminobenzoate	10	200
		Dibucaine hydrochloride	0.5	10
		p-Butylaminobenzoyl diethylaminoethyl hydrochloride	0.1	2
		Procaine hydrochloride	2	40
		Meprylcaine hydrochloride	0.5	10
		Lidocaine hydrochloride	3	60
		Oxypolyethoxydodecane	3	60
		Dibucaine	0.5	10
		Mepivacaine	0.75	15
		Lidocaine	3	60
	Group 2	Scopolia Extract	5	100
Column II		Epinephrine solution	0.001 (as epinephrine)	–
		Ephedrine hydrochloride	1	20
		Tetrahydrozoline hydrochloride	0.05	1
		Naphazoline hydrochloride	0.05	1
		Phenylephrine hydrochloride	0.25	5
		dl-Methylephedrine hydrochloride	0.5	10
Column III		Hydrocortisone acetate	0.5	5
		Prednisolone acetate	0.1	1
		Hydrocortisone	0.5	5
		Prednisolone	0.1	1
Column IV		Zinc oxide	20	400
		Tannic acid	5	100
Column V	Group 1	Acrinol	0.2	4
		Alkyl polyaminoethylglycine	0.2	4
		Isopropylmethylphenol	0.1	2
		Cetylpyridinium chloride	0.2	4
		Dequalinium chloride	0.1	2
		Berberine chloride	1.5	30
		Benzalkonium chloride	0.1	2
		Chlorhexidine hydrochloride	0.5	10
		Chlorhexidine gluconate solution	1	–
		Cetrimide	0.125	2.5
		Resorcin	2	40
	Group 2	Sulfadiazine	5	100
		Sulfisomidine	5	100
		Sulfisomidine sodium	5	100
		Homosulfamine	5	100
Column VI	Group 1	Diphenylpyraline hydrochloride	0.1	2
		Diphenhydramine hydrochloride	1	20
		Diphenhydramine	1	20
		Chorpheniramine maleate	0.2	4
	Group 2	Crotamiton	5	100

Column VII	Group 1	Allantoin	1		20	
		Aluminium chlorhydroxy allantoinate	1		20	
		Ichthammol	10		200	
		Lysozyme chloride	1.5 (potency)		30 (potency)	
		Dried aluminum potassium sulfate	1.1		22	
		Glycyrrhetinic acid	1.5		30	
		1,4-Dimethyl-7-isopropylazulene	0.04		0.8	
		Purified yolk lecithin	5		100	
		Egg yolk oil	5		100	
		Aluminum potassium sulfate	2		40	
	Group 2		Extract (converted to crude drug amount)	Powder	Extract (converted to crude drug amount)	Powder
		Lithospermum root	2.5	2.5	50	50
		Horse Chestnut Seed	25	–	500	–
		Witch hazel leaf	25	–	500	–
		Processed Garlic Bulb	1		20	
Column VIII	Group 1	Cod liver oil	120,000 I.U./100 g (as vitamin A)		2,400 I.U. (as vitamin A)	
		Strong cod liver oil	120,000 I.U./100 g (as vitamin A)		2,400 I.U. (as vitamin A)	
		Retinol palmitate	120,000 I.U./100 g (as vitamin A)		2,400 I.U. (as vitamin A)	
		Vitamin A oil	120,000 I.U./100 g (as vitamin A)		2,400 I.U. (as vitamin A)	
	Group 2	Tocopherol acetate	3		60	
		Tocopherol	3		60	
Column IX	Group 1	*d*-Camphor	1		20	
		dl-Camphor	1		20	
	Group 2	Mentha Oil	0.75		15	
		l-Menthol	0.5		10	
		dl-Menthol	0.5		10	
	Group 3	Eucalyptus Oil	0.5		10	