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「小児悪性腫瘍における抗悪性腫瘍薬の臨床評価方法に関するガイダンス」について

小児悪性腫瘍における抗悪性腫瘍薬の臨床評価方法に関する基本的な考え方について、別添のとおりガイダンスを取りまとめましたので、貴管下関係業者に対して周知方お願いします。

なお、本ガイダンスは、現時点における科学的知見に基づく基本的考え方をまとめたものであり、学問上の進歩等を反映した合理的根拠に基づいたものであれば、必ずしもここに示した方法を固守するよう求めるものではないことを申し添えます。

別添

小児悪性腫瘍における抗悪性腫瘍薬の臨床評価方法に関するガイダンス

1　緒言

小児悪性腫瘍における薬剤開発は、原則として「「抗悪性腫瘍薬の臨床評価方法に関するガイドライン」の改訂について」（平成17年11月1日付け薬食審査発第1101001号、以下「抗悪ガイドライン」という。）及び「小児集団における医薬品の臨床試験に関するガイダンスについて」（平成12年12月15日付け医薬審第1334号、以下「小児ガイダンス」という。）にしたがい実施されるべきである。本ガイダンスは、抗悪ガイドライン及び小児ガイダンスを補完する位置付けとして、小児悪性腫瘍に対する抗悪性腫瘍薬の臨床開発のための基本的考え方を示したものである。なお、本ガイダンスで述べる「小児悪性腫瘍」には、抗悪性腫瘍薬治療を必要とする組織学的良性腫瘍を含むすべての小児腫瘍を含めることとする。

小児悪性腫瘍には、小児特有の悪性腫瘍、又は、同じ疾患名であっても小児期に好発する、若しくは病態が小児と成人とで異なる悪性腫瘍があり、また、年間発症症例数が数十例以下の疾患も多く認められる。例えば年間の総患者数が50例未満の疾患群においては、片群100例を超える第III相試験の実施には、対象症例の全例が試験に参加すると仮定しても、症例集積だけで4年以上を要する。この状況を解決する方策として、海外との同時開発、国際共同試験での開発が望まれるが、既に海外開発が終了した薬剤等では国内のみでの開発とならざるを得ない。このような背景のもと、国内における小児悪性腫瘍における臨床開発は喫緊の課題である。

2　背景

（1）　小児悪性腫瘍の疫学

2013年に報告された「がんの統計'13」（公益財団法人　がん研究振興財団編）では、日本国内でのがん（悪性腫瘍）の罹患数は2008年で約75万人であった[1]。このうち20歳未満の小児におけるがんの罹患数は2615人と報告されている。これはがん全体の0.34%にすぎない。同様に、院内がん登録の全国集計データでも、がん全体に占める20歳未満発症のがんの割合は0.55%、3107人であった[2]。

小児悪性腫瘍の内訳は約半数を白血病や悪性リンパ腫をはじめとする造血器腫瘍が占めており、日本小児血液学会（現日本小児血液・がん学会）の疾患登録データによると、2008年～2010年の3年間で白血病は2093人（40.2%）、悪性リンパ腫は452人（8.7%）であった[3]。日本小児がん学会（現日本小児血液・がん学会）の疾患登録データによると、2008年～2010年の3年間で脳・脊髄腫瘍は803人（15.4%）、その他悪性固形腫瘍は1861人（35.7%）であり[4]、1、2、4の資料より計算すると、小児の固形腫瘍と脳腫瘍はすべて合わせても国内に発生するがん全体の0.17－0.3%程度と推計される。しかし、小児固形腫瘍には成人のがんの発生臓器と同様、ほぼ全身の臓器由来の悪性腫瘍が含まれ、胎児性腫瘍や肉腫に大別されるものの、その組織型の種類は多彩である。

個々の疾患の罹患数は、代表的な小児がんで、発生数も最多の固形腫瘍である神経芽腫でも年150例程度、神経芽腫以外の固形腫瘍では全てが年間100例未満であり、多くが年50

例未満である[4]。同様に、脳腫瘍においても多種の組織型が含まれており、個々の組織型で年100例以上の罹患数の組織型はない[5]。

また、小児悪性腫瘍は疾患により小児の中でもその好発年齢が異なる。例えば、急性リンパ性白血病（以下「ALL」という。）は2歳～5歳に発症のピークがあるが、急性骨髄性白血病（以下「AML」という。）は2歳未満に小さな発症ピークがあるものの、その後は年齢とともにゆるやかに増加する。悪性リンパ腫は年齢とともに発症頻度が増加する。神経芽腫、網膜芽腫、腎芽腫、肝芽腫などの胎児性腫瘍は80%以上が4歳以下で発症するのに対し、ユーイング肉腫や骨肉腫の発症ピークは10歳代にある。横紋筋肉腫は全年齢で発症し得るが、5歳以下では多くが胎児型横紋筋肉腫であるのに対し、10歳代では胞巣型横紋筋肉腫が多くを占める。代表的な小児脳腫瘍である髄芽腫の発症ピークは4歳前後であるが、中枢神経胚細胞腫瘍の発症ピークは10歳代前半である。また、両脳腫瘍ともに少数ではあるが、成人年齢においても発症する[3,4,5,6]。

一般に小児悪性腫瘍の予後は良好とされており、代表的疾患である白血病はALLで75%、AMLでも60%が一度も再発することなく治癒し、代表的固形腫瘍である神経芽腫も1歳未満発症のMYCN遺伝子の増幅のない場合は80%以上、また脳腫瘍においても胚細胞腫瘍の予後は良好であり95%以上が治癒可能である[7,8,9,10,11]。一方でALLであっても早期再発例の10年生存率は造血幹細胞移植を行っても20%程度であり、1歳6ヵ月以上での発症で、転移を有する進行期神経芽腫の治癒率は40%未満、再発した神経芽腫の2年生存率は10%以下、脳幹部神経膠腫においても2年生存率は10%以下と極めて予後不良であり、新規治療の開発は急務であり、新薬導入への期待も極めて高い[12,13,14,15]。

（2） 小児悪性腫瘍の病態と小児の特性

小児の悪性腫瘍の病態の一部は成人の悪性腫瘍とは異なることが知られている。成人の悪性固形腫瘍は多くが上皮性の癌であるが、小児の悪性固形腫瘍は薬剤感受性の高い胎児性腫瘍や肉腫が多く、大半は小児特有であるか或いは小児を発症ピークとしている。また同じ組織型が全身の様々な部位に発症するため、小児固形悪性腫瘍の分類は、成人の癌のような原発部位別ではなく、組織形態に基づくべきとされており、国際小児がん分類が用いられる[16]。発症時に遠隔転移を認める症例であっても、薬剤投与により、腫瘍の著明な縮小や消失が得られることも多く、治癒や長期生存が見込める症例も少なくない。また、再発例においても、再発後早期には化学療法の感受性は良好であることが多い。さらに、明らかな腫瘍縮小効果が見られない場合でも、増大・進行なく長期に安定した状態が得られ生存する症例が存在することも小児悪性固形腫瘍の特徴の一つであり、複数回再発症例においても有病ながらも長期に安定した状態が観察されることがある[17]。

一方、小児の造血器腫瘍のうち、フィラデルフィア染色体陽性ALL、AML、一部の悪性リンパ腫などは一般的に成人と共通の病態を持つ。これらの疾患は成人に発症ピークがあり、基本的には成人と同じ薬剤で治療可能な疾患群である。しかし、若年性骨髄単球性白血病やランゲルハンス細胞組織球症のように小児特有の疾患や、ダウン症等の先天性疾患を背景に発症した白血病や悪性リンパ腫などの場合には、その病態に特有の小児に特化した治療が行

われる。また、通常の白血病や悪性リンパ腫であっても、ALLのように小児と成人とでは細胞遺伝学的背景によるサブタイプが異なり小児に発症ピークのある疾患群が含まれるが、このような場合も小児と成人とで異なる治療が行われる。

脳腫瘍とは中枢神経系に発生する腫瘍の総称であり、組織型は多岐にわたり、成人と小児で原発性脳腫瘍の組織型分布は大きく異なる。固形腫瘍と同様に、髄芽腫をはじめとする胎児性腫瘍や胚細胞腫瘍は小児を発症ピークとする組織型である。

一方、成人を発症ピークとする組織型のうち、小児にも発症し、成人と同じ病態を持つものもあり、例えば成人で最も頻度の高い高悪性度神経膠腫も小児では10%程度認められている。正常の脳組織に接する腫瘍の完全摘出が実質的には不可能であること、中枢神経系が自然に獲得した脳血管関門のため、血管内投与した抗腫瘍薬が中枢神経系に到達しにくいこと、抗腫瘍療法が発達途上の正常脳組織に与える悪影響が甚大であることなどが小児脳腫瘍の治療を困難にしている[18]。

薬物療法を行う上での小児の特性として、当該悪性腫瘍以外の合併疾患が少なく、臓器予備能が良好であるため、体表面積や体重換算での投与可能量・MTDは成人とほぼ同等であるものの、造血器腫瘍では、成人と同一疾患に同一治療を行った場合に、小児では予定治療の完遂率や長期の継続投与の忍容性が高いとの報告もある[19,20]。この小児の特性により各レジメンの反復可能回数が多くなり、治療薬総投与量の相対的増量が可能であり、同一疾患に対する同じ治療が小児においてより有効である場合もあることも報告されている[19,20]。

（3） 小児悪性腫瘍に関する薬剤の開発

小児悪性腫瘍は言うまでもなく致死的な疾患であり、新しい薬剤による治療の選択肢が増えることの意義は大きい。医学の進歩に伴い、新規の抗悪性腫瘍剤の開発はより活発になっており、成人悪性腫瘍分野での分子標的薬等の導入に伴い、それら新薬の小児悪性腫瘍への応用が望まれている。

小児悪性腫瘍は、小児ガイダンスの2.3.2.に該当する重篤な疾患であり、早期の開発が望まれている。例えば、殺細胞性の薬剤のように効果の期待が特定のがん種によらない薬剤や、抗体医薬品のように特定の標的を持つ複数の疾患で効果が期待されるような薬剤では、成人に対する開発の早期段階から小児での検討が行われることが望ましく、また、標的となるタンパクの発現や遺伝子変異が小児悪性腫瘍でも存在することが知られている場合は、当該標的分子の修飾を目的とした薬剤も国内の成人と同時開発、あるいは、海外での小児悪性腫瘍を対象とした開発時に国際共同試験として国内小児も対象とした開発を行うことが望ましい。

また、小児ガイダンスの「2.3.1 小児に多い症状又は小児特有の疾患に対する医薬品」の項には、「成人での試験で有益な情報がほとんど得られないか、成人に対して不適当なリスクを生ずるような医薬品については、初期段階から小児集団でのみ臨床試験がなされるのは適切であろう。」と記載されていることから、当該理由から成人悪性腫瘍で開発が行われていないものの、小児悪性腫瘍に対して有効性が期待できる医薬品に該当する場合には初期段階から小児での開発を検討することが望ましい。

（4）まとめ

上記（1）から（3）の内容を踏まえ、抗悪ガイドラインを補完する位置付けとして、小児悪性腫瘍の特性に配慮した臨床評価方法を定めることにより、適正かつ効率的な抗悪性腫瘍剤の開発と導入につながることが期待される。新規薬剤の開発においては、国内開発終了時に欧米では既に新たな薬剤が標準治療に導入されているというような状態を回避することが必要なのは言うまでもないが、欧米と同時期又は先行して、同じ疾患群に対し、欧米と同等の有効性又はより治癒を期待できる治療が国内で可能となることが望まれる。

3　小児悪性腫瘍における開発戦略

（1）　小児に特有の悪性腫瘍（A群）

小児期に発症する造血器腫瘍の多くは、ALL、AML、悪性リンパ腫など、成人と同じ疾患名の腫瘍が多い。一方、疾患名が同じであっても、例えば小児のALLでは成人と比較して、高2倍体（1細胞あたりの染色体が50本を超える）や*ETV6-RUNX1*陽性例の割合が多く、*BCR-ABL1*陽性例が少ない、乳児（1歳未満）においては約80%に*MLL*遺伝子再構成を伴うなど、その細胞遺伝学的背景によるサブタイプが大きく異なり、成人とは病態が異なるため小児に特有の開発が必要になることがある[21]。さらに、小児ALLにおいてはアスパラギナーゼ製剤が重要な薬剤であり治療レジメンにおいて多用されることなど、同じ疾患名であっても標準治療が成人と異なることも多く、小児に特化した開発が必要になる[22,23]。若年性骨髄単球性白血病やランゲルハンス細胞組織球症、ダウン症など先天性疾患に伴う白血病のように、小児に特有の造血器悪性腫瘍に対しては、小児に特化した開発が必要となる[24,25,26,27]。

小児期に発症する固形腫瘍は、非上皮性腫瘍が大半を占める点が大きな特徴であり、胎児性腫瘍、肉腫に大別され、それぞれ種々の組織型を含む。また、小児期に発症する脳腫瘍の組織型の種類は多いが、神経上皮性腫瘍と胎児性腫瘍で大半を占める。これらの腫瘍の多くは成人での発症は稀であり、希少疾患として小児に特化した国内開発が必要となる。

胎児性腫瘍には神経芽腫、網膜芽腫、腎芽腫、肝芽腫、髄芽腫等が含まれ、各器官形成期の未分化細胞（芽球、前駆細胞）を起源として発症する共通性がある。肉腫は成人にも発症するが、小児期に好発する横紋筋肉腫、ユーイング肉腫とも未分化細胞を起源とすることから胎児性腫瘍の性質をも備えている。

これらの胎児性腫瘍や未分化細胞起源の肉腫（いわゆる小円形細胞腫瘍）においては異なる疾患でも類似の抗腫瘍薬感受性を持つ。具体的にはアルキル化剤、植物性アルカロイド、アントラサイクリン系抗生物質、白金製剤が奏効し各々を組み合わせた類似の治療レジメンが第1選択とされてきた[28,29,30,31,32]。

小児期に発症する神経上皮性腫瘍の多くは神経膠腫であるが、遺伝分子細胞学的に成人と小児の神経膠腫では性質が大きく異なり、成人神経膠腫で開発された薬剤やレジメンが、小児の神経膠腫で必ずしも有効ではない。小児の神経上皮性腫瘍の治療成績向上のためには小児に特化した治療開発が求められている[33]。

成人悪性腫瘍においても抗腫瘍薬に対する感受性における共通性から、開発の早期では複数のがん種を一つの臨床試験に組み入れて用量設定を行い、一定の安全性評価と有効性の探

索が行われているように、A群においても用量設定や安全性評価を成人同様に複数の疾患群にて実施することは可能である。

有効性評価においては、個々のがん種ごとに有効性を評価することが原則ではあるが、先に述べた小児悪性腫瘍の特性から、以下に挙げるような条件をすべて満たす場合には、複数のがん種（以下、「開発対象がん種」）の患者を一つの集団と見做して、当該患者に対する有効性及び安全性を評価することができる。

① 開発予定の薬剤を用いた非臨床試験などにおいて、開発予定の複数のがん種に対して有効性が示唆されていること。

② 臨床評価にて共通に有効性が示されている薬剤又は治療が複数ある等、原則として開発対象がん種間で治療体系に明らかな差異がなく、開発対象に対し標準的治療が同一であること又は標準的治療がないこと。

③ 開発対象がん種間で、予測される予後等の病態に明らかな差異がないこと。

（2） 病態が成人悪性腫瘍と同様の小児悪性腫瘍（B群）

小児悪性腫瘍のうち、成人と同じ疾患名を持ち、病態が成人と類似している悪性腫瘍においては、成人での発症率が高い等の理由により、成人を対象とした臨床試験が先行する場合が多い。B群においては、病態が成人と類似していること等を踏まえ、先行又は同時に実施された成人を対象として開発予定薬剤の有効性及び安全性の検討を目的とした臨床試験成績が利用可能であることを前提として、小児に対する用法・用量並びに忍容性及び安全性の検討を目的とした臨床試験を実施した上で、当該試験成績に基づき小児に対する有効性及び安全性を検討することができる。

なお、小児に対する開発という観点からは、成人での開発を検討する段階で、小児も含めた試験を行うことについて検討することが推奨される。ただし、その場合は、成人と小児をまとめて同一試験内で評価することが可能か否か慎重に検討する必要がある。

（3）用法用量の設定

上記A群及びB群のいずれにおいても、海外において、開発対象の小児の薬物動態（以下、「PK」）を検討した臨床試験が実施され、当該患者に対する用法・用量の情報が利用可能、かつ、成人において日本人と外国人との間でPKに明確な差異が認められていない場合、日本人小児患者を対象に臨床試験を実施する際には、海外における小児に対する用法・用量を参考に設定することは可能である。

一方で、海外において、開発対象の小児のPK及び用法・用量に関する情報がいずれも得られていない場合、又は、成人においてPKの国内外差等が想定若しくは不明である場合、日本人小児患者を対象に、用法・用量等の探索を目的とした臨床試験を実施する必要がある。

4 臨床試験

小児悪性腫瘍の各疾患は、患者数が極めて限られていることから、早期開発において、複数種の小児悪性腫瘍（ただし、疾患による毒性の差異に留意する等して、除外すべき特段の理由

を持つ疾患を除く）を対象に開発を行う等、できる限り多くの情報が得られるように臨床試験を計画することも一案である。抗悪ガイドラインで示されているとおり、臨床的有用性を明確に検証するためには第 III 相試験の実施が必要であるが、一方、疾患の希少性などの理由から、内部対照をおいた比較試験の実施が困難な場合には、試験の実施可能性を考慮した上で、疾患レジストリ、先行研究等のヒストリカルデータを参考とした第 II 相試験の実施を検討することは可能である。

ただし、有効性の評価項目と試験デザインは密接に関連していることに留意してデザインを決定すべきである。また、いずれのデザインを用いるにしても、先行試験（例えば、成人における同一治療法の臨床試験、海外における臨床試験など）のデータを最大限活用することや、試験中に蓄積された情報を効果的に用いる適応的デザインを採用することが有益な場合がある。

（1）対象患者の年齢について

小児患者の開発対象年齢については、発達生物学、発達薬理学等を考慮する必要がある。PK が同一とみなせる年齢区分ごとに PK、安全性及び有効性が検討されることが一般的であるが、PK の評価においては広い年齢層でのデータを収集し、年齢の影響を連続した共変量として解析する方がより適切なこともある（小児ガイダンスの「2.5 小児患者の年齢区分」の項参照）。

以上の状況を踏まえると、原則として、臨床試験の対象となる患者の年齢を幅広く設定して臨床試験を実施することが望ましい。なお、上述の臨床試験の結果、特定の年齢層の小児患者が臨床試験に組み入れられなかったことで、当該患者の有効性等の情報が不足した場合には、必要に応じて、製造販売承認後に実施する製造販売後調査等により、当該情報の収集を行う等の対応が求められる。

（2）有効性の評価項目について

有効性の評価項目については、抗悪ガイドラインに準じること。一般に、小児悪性腫瘍は、その患者数を考慮すると、第II相試験における有効性の評価項目として、臨床的意義の説明が可能となるよう適切な項目を設定し、適切な評価が可能となるような試験計画とすることがより重要となる。なお、有効性の評価項目の検討を行う上での候補として、奏効割合、無増悪生存期間（PFS）、全生存期間（OS）等が挙げられる。

ただし、第II相試験における有効性の評価項目として何れを用いたとしても、ICH-E10ガイドライン「臨床試験における対照群の選択とそれに関連する諸問題」において「1.3.5 外部対照（既存対照を含む）」、「1.5 分析感度」等で示された論点を考慮した上で、計画している評価に対して適切な水準の分析感度をもつか否かについて試験開始前に検討する必要がある。

5　PK 試験

PK 試験の実施については、原則として、小児ガイダンスの「2.4.1 薬物動態」の項の記載を踏まえて計画すること。

6　製造販売後調査及び製造販売後臨床試験

複数のがん種の患者又は広い年齢層の患者を対象に臨床試験を実施した場合であって、特定の患者が臨床試験に組み入れられなかったことで、当該患者の有効性等の情報が不足した場合には、必要に応じて、当該情報の収集を行う目的で調査又は新たな臨床試験を実施すること。当該調査又は臨床試験は、各々製造販売後調査又は製造販売後臨床試験として実施される場合もある。

7　その他

希少疾患である小児悪性腫瘍における抗悪性腫瘍薬の臨床評価において利用できる情報を収集するため、アカデミアを中心として、小児悪性腫瘍の疾患レジストリ構築を検討することが望ましい。

また、医薬品の安全性を確保するためには、開発の段階から製造販売後に至るまで常にリスクを適正に管理する方策を検討することが重要であり、小児悪性腫瘍に対する薬剤の開発においても、医薬品リスク管理計画（RMP: Risk Management Plan）を作成し、製造販売後の安全対策の充実・強化を図る必要がある。

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事　務　連　絡
平成27年9月29日

各都道府県衛生主管部（局）薬務主管課　御中

厚生労働省医薬食品局審査管理課

かぜ薬等の製造販売承認基準の英訳について

一般用医薬品のうち、下記のかぜ薬等の製造販売の承認基準（通知）については、別添のとおり、当該基準の英訳を作成したのでお知らせいたします。

記

別添	通知名	発出年月日等
1	かぜ薬の製造販売承認基準について	平成27年3月25日付け薬食発0325第28号
2	解熱鎮痛薬の製造販売承認基準について	平成27年3月25日付け薬食発0325第30号
3	鎮咳去痰薬の製造販売承認基準について	平成27年3月25日付け薬食発0325第26号
4	鼻炎用内服薬の製造販売承認基準について	平成27年3月25日付け薬食発0325第23号
5	胃腸薬製造（輸入）承認基準について	昭和55年4月22日付け薬発第520号
6	瀉下薬製造（輸入）承認基準について	昭和57年5月17日付け薬発第463号
7	鎮暈薬製造（輸入）承認基準について	昭和59年6月1日付け薬発第381号
8	眼科用薬製造（輸入）承認基準について	昭和61年7月29日付け薬発第623号
9	ビタミン主薬製剤製造（輸入）承認基準について	昭和63年2月1日付け薬発第90号
10	浣腸薬製造（輸入）承認基準について	昭和63年2月1日付け薬発第94号
11	駆虫薬製造（輸入）承認基準について	平成元年3月28日付け薬発第300号
12	鼻炎用点鼻薬製造（輸入）承認基準について	平成3年2月1日付け薬発第109号
13	外用痔疾用薬製造（輸入）承認基準等について	平成7年3月22日付け薬発第277号
14	みずむし・たむし用薬製造（輸入）承認基準等について	平成10年5月15日付け薬発第447号
15	鎮痒消炎薬の製造販売承認基準について	平成23年11月1日付け薬発第1号

別添1

Provisional Translation
from Japanese Original

Mar 25, 2015
Notification PB No.28

The Standards for Marketing Approval of Cold Remedies

1. Scope of Cold Remedies

The scope of either medicines subject to these standards covers all oral medicines intended for use in treating cold symptoms (Kampo medicine* formulas are not covered).

*Kampo medicine is traditional Japanese medicine.

2. Approval Standards

The approval standards for cold remedies are as follows. For either medicines 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 1 of the active ingredients from Group 1 or 2 in Column I of Table 1 must be included. However, in the case of formulas consisting of crude drugs only, Earthworm (Lumbricus) from Column XVI of Table 1 should be combined instead of them.
c. Active ingredients from different columns of Table 1 may be combined with each other, unless otherwise stipulated.
d. Active ingredients from Column VIII of Table 1 may be combined only in formulas that contain active ingredients from Column II of the table.
e. Up to 3 of the active ingredients from Group 1 in Column I of Table 1 can be combined.
f. When the active ingredients from Column II, III, IV, V, VI, VIII, IX, or X or the Kampo medicine formulas from Column XVII of Table 1 are combined, one ingredient can be used from each Column. However, the active ingredients from Groups 2 and 3 in Column VI of Table 1 may be combined at the same time.
g. When the active ingredients from Group 2 in Column I of Table 1 are combined, they should not be combined simultaneously with the active ingredients from Group 1 or 3 in the same column.
h. When the active ingredients from Group 2 from Column I of Table 1 are combined, they should not be combined simultaneously with the active ingredients from Group 2 in Column III, Group 3 in Column VI, from Column VII, Column XIII or Column XIV, Earthworm from Column XVII or the Kampo medicine formulas from Column XVII.
i. When the active ingredients from Group 3 in Column I of Table 1 are combined, they should be combined simultaneously with acetaminophen from Group 1 in the same column, and should not be combined simultaneously with other active ingredients from the same column.
j. 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 Group 3 in Column II, Group 2 in Column III, from Column VI, Column XIII or the active ingredients from Column XIV, Earthworm from Column XVI, or the Kampo medicine formulas from Column XVII.

k. When the active ingredients from Group 2 in Column II of Table 1 are combined, they should not be combined simultaneously with the active ingredients from Column XIV or the Kampo medicine formulas from Column XVII.

l. When the active ingredients from Group 3 in Column II of Table 1 are combined, they should not be combined simultaneously with the active ingredients from Group 3 in Column I or from Column XIV or the Kampo medicine formulas from Column XVII.

m. When the active ingredients from Group 2 in Column III of Table 1 are combined, they should not be combined simultaneously with the active ingredients from Group 2 in Column I, Group 3 in Column I, from Column IV, Column VIII, Column IX, Column XIII, Column XIV or Column XV, or Kakkontokakikyo from Column XVII.

n. When the active ingredients from Group 2 in Column VI of Table 1 are combined, they should not be combined simultaneously with the active ingredients from Group 3 in Column I, from Column VIII, Column XIII, Column XIV or the Kampo medicine formulas from Column XVII.

o. When the active ingredients from Group 3 in Column VI of Table 1 are combined, they should not be combined simultaneously with the active ingredients from Group 2 in Column I, Group 3 in Column I, from Column VIII, Column XIII, Column XIV or the Kampo medicine formulas from Column XVII.

p. When the active ingredients from Column VII of Table 1 are combined, they should not be combined simultaneously with the active ingredients from Group 2 in Column I or from Column VIII or the Kampo medicine formulas from Column XVII.

q. When the active ingredients from Column VIII of Table 1 are combined, they should not be combined simultaneously with the active ingredients from Group 2 in Column III, Group 2 and Group 3 in Column VI, from Column VII, Column XIII or Column XIV or the Kampo medicine formulas from Column XVII.

r. When the active ingredients from Column IX of Table 1 are combined, they should not be combined simultaneously with the active ingredients from Group 2 in Column III, from Column XIII or Column XIV or the Kampo medicine formulas from Column XVII.

s. Combinations of glycyrrhizinic acid and its salts from Column IX of Table 1 and Glycyrrhiza from Column XV are not acceptable.

t. Combinations of Ephedra herb or Kampo medicine formulas containing Ephedra herb or their extracts and the active ingredients from Group V of Table 1 are not acceptable.

u. Combinations between the Kampo medicine formulas from Column XVII of Table 1 and the active ingredients from Column XIII, XIV, XV or XVI are not acceptable.

v. Apart from Kososan formula, Kampo medicine or non-Kampo crude drug medicines must be in the extract form when used in combinations.

w. The crude drugs used in the Kampo medicine formulas from Column XVII of Table 1 and their combination ratios must be as specified in Table 2.

(2)Quantities of Active Ingredients

a. The maximum daily dose of each of the active ingredients is that specified in Table 1, unless otherwise specified. However, when the active ingredients from Column V or XIII in Table 1 are combined with the ingredients in Column X, the

sum of the values obtained by dividing the amounts of each of the active ingredients by their respective maximum daily doses should not exceed 2/3rd.

b. When 2 or more of the active ingredients from Group 1 in Column I of Table 1 are combined or when 2 or more of the active ingredients from Column XIII, XIV, or XV are combined, the sum of the values obtained by dividing the amounts of each of the active ingredients by their respective maximum daily doses should not exceed 1.

c. When the active ingredients from Group 1 in Column I of Table 1 are combined with Earthworm, Kakkonto formula, Maoto formula, or Kakkontokakikyo, the sum of the values obtained by dividing the amounts of the active ingredients or the formulations combined by their respective maximum daily doses should not exceed 1.

d. When used in combinations, the amounts of the Kampo medicine formulas from Column XVII of Table 1 must not be less than 1/5th and not more than half of the maximum daily dose.

e. The lower limit of the amounts of each of the active ingredients should be half of the maximum daily dose, unless otherwise specified.

f. When 2 or more of the active ingredients from Group 1 in Column I of Table 1 are combined, the lower limit of the amounts should be 1/5th of the maximum daily dose for each active ingredient, and the sum of the values obtained by dividing the amounts of each of the active ingredients by their respective maximum daily doses should be not less than half.

g. When used in combinations, the lower limit of the amounts of the active ingredients from Columns X and XII of Table 1 is 1/5th of the maximum daily dose.

h. When used in combinations, the lower limit of the amounts of glycyrrhizinic acid and its salts from columns IX of Table 1 and the active ingredients from Columns XIII, XIV, XV, and XVI is 1/10th of the respective maximum daily doses. However, in the case of combination with Earthworm as described in (1) b, the maximum daily dose from Column XVI should be combined.

i. In cases where indications for treatment of coughing and sputum are based only on the active ingredients from Columns XIII, XIV, or XV of Table 1, when used in combinations, the lower limits of the active ingredients from Columns XIII, XIV, or XV should be half of the respective maximum daily doses.
However, in cases where 2 or more of the crude drugs from Column XV are combined, the lower limit should be 1/5th of the respective maximum daily doses, and the sum of the values obtained by dividing the amounts of each of the active ingredients by their respective maximum daily dose should be not less than half.

j. The daily dose of the active ingredients from Group 2 in Column I of Table 1 should be limited to 450 mg.

k. The daily dose of the active ingredients from Group 3 in Column I of Table 1 should be limited to 300 mg, and the amount of acetaminophen from Column 1 in the same column, which is combined simultaneously, should be limited to 450 mg.

l. The daily dose of the active ingredients from Group 2 in Column II of Table 1 should be limited to 1 mg as clemastine.

m. The daily dose of the active ingredients from Group 3 in Column II of Table 1 should be limited to 4 mg.

n. The daily dose of the active ingredients from Group 2 in Column III of Table 1 should be limited to 30 mg.

o. The daily dose of the active ingredients from Group 3 in Column VI of Table 1 should be limited to 750 mg.

(3)Dosage Forms

The dosage forms are tablets, capsules, pills, granules, powders, and syrups.

(4)Dosage and Administration

a. Except for syrups, cold remedies are to be taken by oral administration 3 times a day within 30 minute after a meal. Syrups are to be taken, in principle, after every meal. However, if required, they can also be taken before going to bed. If it is absolutely necessary, they can be taken approximately every 4 hours up to a maximum of 6 times a day.
b. 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. Even for capsules smaller than 6 mm in diameter, dosage for children under 3 years of age is not approved.
c. For tablets 6 mm in diameter or less, dosage for children under 3 years of age is not approved.
d. For other dosage forms, dosage for infants under 3 months of age is not approved.
e. 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 3, unless otherwise specified. The maximum single dose of syrups is calculated by using the range of coefficients, and dissolving or suspending 1/6th of the calculated value in water to make less than 10 mL in each case.
f. For formulas containing aspirin, aspirin aluminum, and sasapyrine from Group 1 in Column I, the active ingredients from Group 2 in Column 1, promethazine methylenedisalicylate from Group 1 in Column II, or the active ingredients from Group 3 in Column II, dosage for children under 15 years of age is not approved.
g. For formulas containing the active ingredients from Group 3 in Column VI, dosage for children under 8 years of age is not approved.
h. For formulas containing the active ingredients from Group 3 in Column I or Group 2 in Column II or tranexamic acid from Column IX, dosage for children under 5 years of age is not approved.
i. For formulas containing the active ingredients from Group 2 in Column III, dosage for children under 3 years of age is not approved.
j. For formulas containing tranexamic acid from Column IX of Table 1 with dosage for children under 15 years of age, 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 3.

(5)Indications

Relief of various symptoms of a common cold: running nose, stuffy nose, sneezing, sore throat, cough, phlegm (sputum), chills (feeling cold due to fever), fever, headache, joint pain, and muscle pain.

However, when any single type of the active ingredients listed in the right column of the following table is not included, the indications in the left column of the table cannot be claimed.

Left column	Right column
Runny nose, stuffy nose, sneezing	Ingredients from Column II of Table 1
Cough	Ingredients from Columns III, IV, V, XIII, or XIV of Table 1
Phlegm (sputum)	Tipepidine citrate or tipepidine hibenzate from Column III of Table 1 or the ingredients from Columns V, VI, VII, XIII, or XV

(6)Packaging Units

For syrups, the maximum volume of the containers is a 2-day supply at the maximum daily dosage for children aged 6 years.

Table 1

Active ingredients and Maximum Daily Doses

Category		Name of active ingredient	Maximum daily dose (mg)
Column I	Group 1	Aspirin	1500
		Aspirin aluminum	2000
		Acetaminophen	900
		Ethenzamide	1500
		Sasapyrine	1500
		Salicylamide	3000
		Lactylphenetidine	600
	Group 2	Ibuprofen	450
	Group 3	Isopropylantipyrine	300
Column II	Group 1	Isothipendyl hydrochloride	7
		Difeterol hydrochloride	90
		Tripelenamine hydrochloride	100
		Thonzylamine hydrochloride	50
		Fenethazine hydrochloride	50
		Methodilazine hydrochloride	8
		Chlorpheniramine maleate	7.5
		d-Chlorpheniramine maleate	3.5
		Carbinoxamine diphenyldisulfonate	7.5
		Diphenylpyraline hydrochloride	4
		Diphenylpyraline teoclate	4.5
		Diphenhydramine hydrochloride	75
		Diphenhydramine salicylate	75
		Alimemazine tartrate	5
		Diphenhydramine tannate	75
		Triprolidine hydrochloride	4
		Mebhydrolin napadisilate	150
		Promethazine methylenedisalicylate	40
		Carbinoxamine maleate	7.5
		Difeterol phosphate	90
	Group 2	Clemastine fumarate	1 [as clemastine]
	Group 3	Mequitazine	4
Column III	Group 1	Alloclamide hydrochloride	75
		Tipepidine citrate	60
		Cloperastine hydrochloride	48
		Chloperastine phendizoate	84
		Codeine phosphate	48
		Dihydrocodeine phosphate	24
		Dibunate sodium	90
		Tipepidine hibenzate	75
		Dextromethorphan hydrobromide	48
		Dextromethorphan phenolphthalinate	72
		Carbetapentane citrate	48
	Group 2	Dimemorfan phosphate	30
Column IV		Noscapine	48
		Noscapine hydrochloride	48

Column V		dl-Methylephedrine hydrochloride dl-Methylephedrine saccharinate	60 60
Column VI	Group 1	Guaifenesin Potassium guaiacolsulfonate Potassium cresolsulphonate	250 250 250 (135)
	Group 2	Bromhexine hydrochloride	12 (8)
	Group 3	L-carbocysteine	750
Column VII		Ethyl L-cysteine hydrochloride	300
Column VIII		Belladonna total alkaloid Isopropamide iodide extract	0.3 (0.12) 6 (1.5)
Column IX		Glycyrrhizinic acid and its salts Tranexamic acid	39 [as glycyrrhizinic acid] 750 (280)
Column X		Caffeine and sodium benzoate Caffeine hydrate Anhydrous caffeine	300 150 150
Column XI		Vitamin B_1, its derivatives, and their salts Vitamin B_2, its derivatives, and their salts Vitamin C, its derivatives, and their salts Hesperidin, its derivatives, and their salts	25 (1) 12 (2) 500 (50) 90 (18)

Column XII	Glycine	900
	Magnesium silicate	3000
	Synthetic aluminum silicate	3000
	Synthetic hydrotalcite	4000
	Magnesium oxide	500
	Dihyrdoxyaluminum and aminoacetate (aluminum glycinate)	1500
	Aluminum hydroxide gel (as dried aluminum hydroxide gel)	1000
	Dried aluminum hydroxide gel	1000
	Aluminum hydroxide-Sodium hydrogen carbonate coprecipitate	900
	Aluminum hydroxide-Magnesium carbonate mixed dried gel	3000
	Aluminum hydroxide-Magnesium carbonate-Calcium carbonate coprecipitate	1500
	Magnesium hydroxide-Aluminum potassium sulfate coprecipitation product	1800
	Magnesium carbonate	2000
	Magnesium aluminometasilicate	1500

(Note) A numerical value within parentheses is the lower limit of amounts for combination.

Crude drugs and Kampo medicine formulas

Classification	Name of crude drug or Kampo medicine formula	Maximum daily dose (g)	
		Extract (converted to the amount of crude drug or preparation)	Powder
Column XIII	Ephedra Herb	4	–
Column XIV	Nandina Fruit	10	–
Column XV	Cherry Bark	4	–
	Polygala Root	5	–
	Glycyrrhiza	5	1.5
	Platycodon Root	4	2
	Plantago Seed	5	–
	Plantago Herb	10	–
	Lycoris Radiata Bulb	0.8	–
	Senega	4	1.5
	Fritillaria Bulb	2.5	1.5

Classification	Name of crude drug or Kampo medicine formula	Maximum daily dose (g)	
		Extract (converted to the amount of crude drug or preparation)	Powder
Column XVI	Fennel	3	–
	Phellodendron Bark	3	3
	Coptis Rhizome	3	1.5
	Zedoary	3	3
	German Chamomile Flower	10	–
	Cinnamon Bark	5	1
	Gentian	0.5	0.5
	Oriental Bezoar	–	0.02
	Animal gall (including Bear Bile)	0.5	0.5
	Adenophora Root	5	2.5
	Ginger	3	1
	Atractylodes Lancea Rhizome	5	2
	Clove	2	0.5
	Citrus Unshiu Peel	5	3
	Atractylodes Rhizome	5	2
	Earthworm (Lumbricus)	3	2
	Panax Japonicus Rhizome	6	3
	Ginseng	6	3
Column XVII	Kakkonto	25	–
	Kakkontokakikyo	29	–
	Keishito	15	–
	Kososan	11	6
	Saikokeishito	24	–
	Shosaikoto	24	–
	Shoseiryuto	24	–
	Bakumondoto	30	–
	Hangekovokuto	16	–
	Maoto	13	–

(Note) Powder combinations will not be accepted where no maximum daily dose is given in the powder column.

Table 2

Name of Kampo medicine formula		Kakkonto	Kakkontokakikyo	Keishito	Kososan	Saikokeishito	Shosaikoto	Shoseiryuto	Bakumondoto	Hangekovokuto	Maoto
Component crude drugs and combination ratios	Scutellaria Root					2	3				
	Pueraria Root	8	8								
	Glycyrrhiza	2	2	2	1	2	2	2	2		2
	Platycodon root		4								
	Apricot Kernel										4
	Cinnamon Bark	3	3	4		3		3			3
	Cyperus Rhizome				4						
	Brown Rice								10		
	Magnolia Bark									3	
	Schisandra Fruit							3			
	Bupleurum Root					5	7				
	Asiasarum Root							3			
	Peony Root	3	3	4		3		3			
	Ginger	1	1	1	1	1	1	2		1	
	Perilla Herb				2					2	
	Jujube	4	4	4		2	3		3		
	Citrus Unshiu Peel				3						
	Ginseng					2	3		2		
	Ophiopogon Tuber								8		
	Pinellia Tuber					4	5	5	5	5	
	Poria Sclerotium									5	
	Ephedra Herb	4	4					3			4

Table 3

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 months to under 6 months of age	1/6

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Provisional Translation
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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, Group2, and Group3 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 1 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 (1500)*
		Lactylphenetidine	200	600
	Group 2	Aspirin	750	1500
		Aspirin aluminum	1000	2000
		Ethenzamide	500	1500
		Sasapyrine	500	1500
		Salicylamide	1000	3000
		Sodium 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	120	250
		Anhydrous caffeine	120	250
Column V		Vitamin B_1, its derivatives, and their salts		25 (1)**
		Vitamin B_2, 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		900
	Magnesium silicate		3000
	Synthetic aluminum silicate		3000
	Synthetic hydrotalcite		4000
	Magnesium oxide		500
	Dihyrdoxyaluminum and aminoacetate		1500
	Aluminum hydroxide gel (as dried aluminum hydroxide gel)		1000
	Dried aluminum hydroxide gel		1000
	Aluminum hydroxide-Sodium hydrogen carbonate coprecipitate		900
	Aluminum hydroxide-Magnesium carbonate mixed dried gel		3000
	Aluminum hydroxide-Magnesium carbonate-Calcium carbonate coprecipitate		1500
	Magnesium hydroxide-Aluminum potassium sulfate coprecipitation product		1800
	Magnesium carbonate		2000
	Magnesium aluminometasilicate		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
	Mountan 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

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Provisional Translation
from Japanese Original

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Notification PB No.26

The Standards for Marketing Approval of Antitussives and Expectorants

1. Scope of Antitussives and Expectorants

The scope of remedies subject to these standards covers oral remedies (including troches and drops) intended for use as antitussives and expectorants.
However, remedies based on 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 antitussives and expectorants are as follows.
For remedies 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. Table 1 lists the active ingredients that may be used.
The types of active ingredients that may be used in troches and drops are limited to those marked by △ in Table 1. The active ingredients from Column X should only be combined for troches and drops.
b. One ingredient from Columns I, II, III, XII, or XIII of Table 1 must be included.
However, cases where only the active ingredients from Groups 2 and 3 in Column VI of the same table are combined simultaneously are excluded.
c. Active ingredients from different columns of Table 1 may be combined with each other, unless otherwise stipulated.
d. Active ingredients from Group IX of Table 1 may be combined only in remedies that contain active ingredients from Column I or VIII in this table.
e. In Columns I to III and Columns V to X of Table 1, only 1 ingredient from each group may be used.
However, cases where only the active ingredients from Groups 2 and 3 in Column VI of the same table are combined simultaneously are excluded.
f. Active ingredients from Column XII of Table 1 should not be combined simultaneously with the active ingredients from Column II or V of the same table.
g. Active ingredients from Group 2 in Column I of Table 1 should not be combined simultaneously with the active ingredients from Columns III, IV, V, XII, XIII, or XIV.
h. Active ingredients from Column IV of Table 1 should not be combined simultaneously with the active ingredients from Group 2 in Column I, or from Columns V, XII, or XIII.
i. Active ingredients from Group 2 in Column VI of Table 1 should not be combined simultaneously with the active ingredients from Column V, XII, or XIII of the same table.
j. Active ingredients from Group 3 in Column VI of Table 1 should not be

combined simultaneously with the active ingredients from Column V, XII, or XIII of the same table.

k. Active ingredients from Group 2 in Column VIII of Table 1 should not be combined simultaneously with the active ingredients from Column V or XIII of the same table.

(2)Quantities of Active Ingredients

a. The maximum single dose and maximum daily dose of each active ingredient in Table 1 should be the doses specified in the same table, unless otherwise specified.

b. When the active ingredients from Column IX are combined with those from Column II, V, or XII of Table 1 are combined, the maximum single and daily doses of the ingredients in Column IX should be half of the amounts specified in Table 1.

c. When 2 or more of the active ingredients from Columns II and V of Table 1 are combined or when 2 or more of the active ingredients from Column XII, XIII, or XIV are combined, the sum of the values obtained by dividing the amounts of each of the active ingredients by their respective maximum daily doses should not exceed 1.

d. The lower limit of the combined amounts of each active ingredient in Table 1 should be half of the maximum single or daily dose, unless otherwise specified. However, for the active ingredients from Column IX, the limit should be 1/5th.

e. When the active ingredients from Group 2, Column VI of Table 1 are combined simultaneously with only the active ingredients from Group 3 in the same column, the single dose should be 4 mg and the daily dose should be limited to 12 mg.

f. The single dose of the active ingredients from Group 3 in Column VI of Table 1 should be limited to 250 mg and the daily dose should be limited to 750 mg.

g. The single dose of the active ingredients from Group 2 in Column VIII of Table 1 should be 0.334 mg as clemastine and the daily dose should be limited to 1 mg as clemastine.

h. In the case of troches and drops containing Group I ingredients from Column X of Table 1 and having a dosage regimen for children, the coefficients given in Table 2 should not be used to calculate the combined amount of the ingredients from Column X.

i. In the case of troches and drops to be taken 5 to 6 times per day, the lower limits of the combined amounts of each active ingredient should be half of the maximum daily dose.

j. When the active ingredients from Column II of Table 1 are combined simultaneously with the active ingredients from Column V, the lower limits of the combined amounts should be as follows.

- When the active ingredients from Column II of Table 1 are indicated for "cough," "cough associated with wheezing (wheezy, whistling)," or "sputum," the lower limit of the amounts of the ingredients in Column V should be 1/5th of the maximum single and daily doses.
- When other ingredients with an indication of "coughing" are combined, the lower limits of the amounts of ingredients from both Column II and V should be 1/5th of the respective maximum single and daily doses.
  However, in the case of proportional combinations, lower limits should be such that the sum of the values obtained by dividing the amount of each active ingredient by its maximum daily dose equals half.
- When the active ingredients from Column V of Table 1 are indicated for "cough associated with wheezing (wheezy, whistling)" or "sputum," the lower limit of the amounts of the ingredients in Column II should be 1/5th of the maximum single and daily doses.

k. When used in combinations, the lower limit of the daily amounts of the active ingredients from Column XI of Table 1 is 1/5 of the maximum daily dose.
l. The lower limits of the amounts of crude drugs should be 1/10th of the maximum daily dose. However, when the indications approved for a particular crude drug are claimed, the lower limit should be half of the maximum daily dose.

(3)Dosage Forms

The dosage forms are tablets, capsules, pills, granules, powders, troches, drops, and oral solutions (with the exception of elixirs; hereinafter the same should apply), and syrups.

(4)Dosage and Administration

a. The dosage is "3 to 4 times a day," and the timing of doses or intervals between doses must also be indicated.
However, as for troches, drops, and oral solutions, and syrups, the dosage may be up to 6 doses per day. For dosages of 5 to 6 doses a day, troches and drops should be taken at intervals of at least 2 hours and oral solutions and syrups at intervals of about 4 hours, in principle.
b. The dosage for troches and drops should be allowed to dissolve slowly in the mouth without chewing.
c. For hard capsules, troches, syrups, and soft capsules larger than 6 mm in diameter, pills, and tablets, dosage for children under 5 years of age is not approved. Even for capsules smaller than 6 mm in diameter, dosage for children under 3 years of age is not approved.
d. Dosages for infants under 3 months of age are not approved.
e. For remedies containing promethazine hydrochloride or promethazine methylene disalycilate from Group 1 in Column VIII of Table 1, dosage for children under 15 years of age is not approved.
f. For remedies containing the active ingredients from Group 3 in Column VI of Table 1, dosage for children under 8 years of age is not approved.
g. For remedies containing the active ingredients from Column IV of Table 1 or the active ingredients from Group 2 in Column VIII, dosage for children under 5 years of age is not approved.
h. For remedies containing the active ingredients from Group 2 in Column I of Table 1, dosage for children under 3 years of age is not approved.
i. The maximum daily dose for children under 15 years of age is the amount obtained by multiplying the maximum daily dose in Table 1 by the coefficient corresponding to the respective age group in Table 2, unless otherwise specified.
j. The maximum single dose of the active ingredients in oral solutions and syrups is 1/6th of the maximum daily dose (for children under 15 years of age, the maximum daily dose according to i. above), and the maximum single dose is 10 mL, unless otherwise specified.
k. For remedies containing the active ingredients from Group 2, Column I of Table 1 with dosage for children under 15 years of age, the maximum single dose is 10 mg and the maximum daily dose is 30 mg. The maximum daily dose for children under 15 years of age is the amount obtained by multiplying the maximum daily dose (30 mg) by the coefficient corresponding to the respective age group in Table 2.
l. For remedies containing the active ingredients from Column IV 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) by the coefficient corresponding to the respective age group in Table 2.

(5)Indications

a. The indications include "cough, cough associated with wheezing (wheezy, whistling), and sputum."
However, for indications in the left column of the following table to be claimed, at least 1 of the ingredients from the corresponding right column must be included.

b. When the active ingredients from Column IV of Table 1 are combined, the indications are "cough or sputum associated with sore throat." However, they should be combined concomitantly with any ingredient with indications of "cough" and "sputum" from the left column of the next table.

c. When only the active ingredients from Group 2 and Group 3 in Column VI of Table 1 are combined concomitantly, the indications are "sputum and cough with sputum".

d. For troches and drops, in addition to the above indications, the following may also be given: hoarse voice due to throat inflammation, rough throat, throat discomfort, sore throat, and swollen throat.

Left column	Right column
Cough	Ingredients from Columns I, II, III, XII, or XIII of Table 1
Cough associated with wheezing (wheezy, whistling)	Ingredients from Column II, V, or XII in Table 1, except for cases in which an ingredient from Column I of Table 1 is also combined.
Phlegm (sputum)	Tipepidine citrate or tipepidine hibenzate from Group 1 in Column I of Table 1 or the ingredients from Columns II, V, VI, VII, XII, or XIV
Cough associated with sore throat and sputum	Ingredients from Column IV of Table 1, only when combined concomitantly with any ingredient with indications of "cough" and "sputum."
Sputum and cough with sputum	Only when combined concomitantly with only the ingredients from Group 2 and Group 3 in Column VI of Table 1.

(6)Packaging Units

The maximum volume of containers for oral solutions and syrups is a 4-day supply at the maximum daily dose for adults (15 years of age and older).

Table 1

Active Ingredients and Maximum Single and Daily Doses

Category		Name of active ingredient	Maximum single dose (mg)	Maximum daily dose (mg)
Column I	Group1	Alloclamide hydrochloride	25	75
		Tipepidine citrate	20	60
		Cloperastine hydrochloride	20	60
		Chloperastine phendizoate	35	105
		Codeine phosphate	20	60
		Dihydrocodeine phosphate	10	30
		Dibunate sodium	30	90
		Tipepidine hibenzate	25	75
		Dextromethorphan hydrobromide	20	60
		△Dextromethorphan phenolphthalinate	30	90
		Carbetapentane citrate	20	60
	Group2	Dimemorfan phosphate	15 (10)	60 (30)
Column II		Trimethoquinol hydrochloride	2	6
		△*dl*-Methylephedrine hydrochloride	25	75
		l-Methylephedrine hydrochloride	25	75
		Methoxyphenamine hydrochloride	50	150
Column III		△Noscapine	20	60
		Noscapine hydrochloride	20	60
Column IV		Tranexamic acid	250 (70)	750 (280)
Column V		Aminophylline	100	300
		Diprophylline	100	300
		Theophylline	200	600
		Proxyphylline	70	210
Column VI	Group 1	Foeniculated ammonia spirit (as 1 ingredient)	2mL	-
		Ammonium chloride	300	900
		△Guaifenesin	100	300
		△Potassium guaiacolsulfonate	90	270
		△Potassium cresolsulphonate	90	270
		l-Menthol	-	90
	Group 2	Bromhexine hydrochloride	4 (2)	12 (8)
	Group 3	L-carbocysteine	250	750
Column VII		Ethyl L-cysteine hydrochloride	100	300
		Methyl L-cysteine hydrochloride	100	300
		Lysozyme chloride	20	60

Column VIII	Group1	Alimemazine tartrate	2.5	7.5
		Isothipendyl hydrochloride	4	12
		Iproheptine hydrochloride	50	150
		Difeterol hydrochloride	30	90
		Tripelenamine hydrochloride	25	75
		Thonzylamine hydrochloride	20	60
		Fenethazine hydrochloride	30	90
		Chlorpheniramine maleate	4	12
		d-Chlorpheniramine maleate	2	6
		Carbinoxamine diphenyldisulfonate	4	12
		Diphenylpyraline hydrochloride	2	6
		Diphenylpyraline teoclate	3	9
		Diphenhydramine hydrochloride	30	90
		Diphenhydramine salicylate	40	120
		Diphenhydramine tannate	50	150
		Fenethazine tannate	45	135
		Triprolidine hydrochloride	2	6
		Promethazine hydrochloride	5	15
		Promethazine methylene disalycilate	6	18
		Carbinoxamine maleate	4	12
		Difeterol phosphate	30	90
	Group2	Clemastine fumarate	0.334 [as clemastine]	1 [as clemastine]
Column IX		Caffeine and sodium benzoate	100	300
		Caffeine hydrate	100	300
		Anhydrous caffeine	100	300
Column X		△Chlorhexidine hydrochloride	5	-
		△Cetylpyridinium chloride	1	-
		△Dequalinium chloride	0.25	-
Column XI		Glycine		900
		Magnesium silicate		3000
		Synthetic aluminum silicate		3000
		Synthetic hydrotalcite		4000
		Magnesium oxide		500
		Dihyrdoxyaluminum and aminoacetate		1500
		Aluminum hydroxide gel (as dried aluminium hydroxide gel)		1000
		Dried aluminum hydroxide gel		1000
		Aluminum hydroxide-Sodium hydrogen carbonate coprecipitate		900
		Aluminum hydroxide-Magnesium carbonate mixed dried gel		3000
		Aluminum hydroxide-Magnesium carbonate-Calcium carbonate coprecipitate		1500
		Magnesium hydroxide-Aluminum potassium sulfate coprecipitation product		1800
		Magnesium carbonate		2000
		Magnesium aluminometasilicate		1500

(Crude drugs)

Category	Name of crude drug or Kampo medicine formula	Maximum daily dose (g)	
		Extract (converted to the crude drug amount)	Powder
Column XII	Ephedra Herb	4	-
Column XIII	Nandina Fruit	10	-
Column XIV	Cherry Bark	4	-
	Polygala Root	5	-
	Glycyrrhiza	5	1.5
	Platycodon Root	4	2
	Apricot Kernel	4	-
	Plantago Seed	5	-
	Plantago Herb	10	-
	Lycoris Radiata Bulb	0.8	-
	Senega	4	1.5
	Ipecac	0.05	0.05
	Fritillaria Bulb	2.5	1.5
Column XV	Gambir	-	2
	Fennel	3	-
	Scutellaria Root	6	3
	Trichosanthes Seed	2	-
	Cinnamon Bark	5	1
	Oriental Bezoar	-	0.02
	Schisandra Fruit	5	-
	Asiasarum Root	3	-
	Aster Root	5	-
	Musk	-	0.01
	Adenophora Root	5	2.5
	Ginger	3	1
	Mulberry Bark	5	-
	Perilla Herb	2	-
	Panax Japonicus Rhizome	6	3
	Citrus Unshiu Peel	5	3
	Ginseng	6	3
	Ophiopogon Tuber	10	-
	Pinellia Tuber	5	-

(Note) A numerical value within parentheses is the lower limit of amounts for combination.

Table 2

Range of Age Coefficients

Age	Coefficient
15 years of age and older	1
11 to under 15 years of age	2/3
8 to under 11 years of age	1/2
5 to under 8 years of age	1/3
3 to under 5 years of age	1/4
1 to under 3 years of age	1/5
3 months to under 1 year of age	1/10

別添4

Provisional Translation
from Japanese Original

Mar 25, 2015
Notification PB No.23

The Standards for Marketing Approval of Oral Remedies for Rhinitis

1. Scope of Oral Remedies for Rhinitis

The scope of remedies subject to these standards covers oral medicines (with the exception of cold remedies, anti-allergic agents, remedies based on Kampo medicine* formulas) formulated with the intent of relieving symptoms of rhinitis.

*Kampo medicine is traditional Japanese medicine.

2. Approval Standards

The approval standards for oral remedies for rhinitis are as follows.

For remedies not conforming to these standards, data concerning the efficacy and safety 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. Table 1 shows the types of active ingredients that may be used.
b. The active ingredients that must be used are those listed in Column I of Table 1.
c. Active ingredients from different columns of Table 1 may be combined with each other, unless otherwise stipulated..
d. When active ingredients from Column I, Column III, Column IV, or Column V are to be combined, only 1 ingredient from each column may be used.
e. When active ingredients from Column II of Table 1 are combined, up to 2 active ingredients from Group 1 may be used, but only 1 from Group 2 may be used. However, the combination of dl-methylephedrine hydrochloride and l-methylephedrine hydrochloride or that of pseudoephedrine hydrochloride and pseudoephedrine sulfate is not permitted.
f. When the active ingredients from Group 2 in Column I of Table 1 are combined, only formulas other than oral solutions and syrups can be used. They should not be combined concomitantly with the active ingredients from Column VI.

(2)Quantities of Active Ingredients

a. The maximum daily doses of individual active ingredients should be those given in Table 1, unless otherwise indicated. The maximum single dose is 1/3rd of the maximum daily dose.
However, the maximum single dose of oral solutions and syrups is 1/6th of the maximum daily dose.
b. When active ingredients from Column V of Table 1 are combined with those of Group 1 in Column II, the maximum daily dose of ingredients from Column V should be half of those specified in Table 1.
c. When 2 or more active ingredients from Column II of Table 1 are combined, the sum of the values obtained by dividing the amount of each active ingredient by the respective maximum daily dose should not exceed 2.

d. The lower limit of the daily dose for each active ingredient from Column I of Table 1 is half of its maximum daily dose.
e. The lower limit of the daily dose for each active ingredient from Columns II, III, and V of Table 1 is 1/5th of its maximum daily dose.
f. The lower limit of the daily dose for each active ingredient from Columns IV and VI of Table 1 is 1/10th of its maximum daily dose.
g. The daily dose of the active ingredients from Group 2 in Column I of Table 1 should be limited to 4 mg.

(3)Dosage Forms

The dosage forms are capsules, granules, pills, powders, tablets, oral solutions (with the exception of elixirs; hereinafter the same should apply), and syrups.

(4)Dosage and Administration

a. Dosage and administration are to be 3 times a day, in principle. The times of administration and intervals between them should be clearly indicated, but intervals between doses should be 4 or more hours. For oral solutions and syrups, taking them up to 6 times a day is acceptable, but when dosing is 6 times a day, each dose is to be taken at approximately 4-hour intervals, in principle.
b. Dosage for infants less than 3 months of age is not approved.
c. For formulas containing promethazine hydrochloride or promethazine methylenedisalicylate from Group 1 in Column I of Table 1 and the active ingredients from Group 2 in Column I, dosage for children under 15 years of age is not approved.
d. For formulas containing pseudoephedrine hydrochloride or pseudoephedrine sulfate from Group 1 in Column II of Table 1, dosage for children under 3 years of age is not approved.
e. For hard capsules, and soft capsules, pills, and tablets larger than 6 mm in diameter, dosage for children under 5 years of age is not approved.
f. For soft capsules, pills, and tablets of a diameter of 6 mm or less, dosage for children under 3 years of age is not approved.
g. The maximum daily dose for children under 15 years of age is that obtained by multiplying the maximum daily doses listed in Table 1 by the coefficient for the respective age groups in Table 2.
h. The maximum single dose for oral solutions and syrups is 10 mL.

(5)Indications

The indications are to be within the following scope:

Relief of the following symptoms due to acute rhinitis, allergic rhinitis or sinusitis; sneezing, runny nose (excessive nasal discharge), stuffy nose, watery eyes, sore throat, dull headache (heaviness in the head).

(6)Packaging Units

The maximum volume of containers for oral solutions and syrups is a 4-day supply at the maximum daily dose.

Table 1 Active Ingredients and Maximum Daily Doses

Category		Active ingredient		Maximum daily dose
Column I	Group1	Alimemazine tartrate		5mg
		Isothipendyl hydrochloride		12mg
		Iproheptine hydrochloride		150mg
		Difeterol hydrochloride		90mg
		Tripelenamine hydrochloride		100mg
		Thonzylamine hydrochloride		50mg
		Methodilazine hydrochloride		8mg
		Chlorpheniramine maleate		12mg
		d-Chlorpheniramine maleate		6mg
		Carbinoxamine diphenyldisulfonate		7.5mg
		Diphenylpyraline hydrochloride		12mg
		Diphenylpyraline teoclate		4.5mg
		Diphenhydramine hydrochloride		75mg
		Diphenhydramine salicylate		75mg
		Diphenhydramine tannate		75mg
		Triprolidine hydrochloride		6mg
		Promethazine hydrochloride		15mg
		Promethazine methylenedisalicylate		40mg
		Carbinoxamine maleate		16mg
	Group2	Mequitazine		4mg
Column II	Group 1	Phenylephrine hydrochloride		30mg
		Pseudoephedrine hydrochloride		180mg
		Pseudoephedrine sulfate		180mg
		dl-Methylephedrine hydrochloride		110mg
		l-Methylephedrine hydrochloride		110mg
		Methoxyphenamine hydrochloride		150mg
	Group 2			as total alkaloids
		Datura Extract		0.6mg
		Belladonna (Total) Alkaloids		0.6mg
		Belladonna Extract		60mg
		Isopropamide iodide extract		7.5mg
		Scopolia Extract		60mg
Column III		Bromelain		120,000 Units
		Lysozyme chloride		90 mg (potency)
Column IV	Group 1	Glycyrrhizinic acid and its salts		as glycyrrhizinic acid 200mg
	Group 2	Glycyrrhiza	Extract (converted to the crude drug amount)	Powder
			5g	1.5g
Column V		Caffeine and sodium benzoate		300mg
		Caffeine hydrate		300mg
		Anhydrous caffeine		300mg

		Extract (converted to the crude drug amount)	Powder
Column VI	Schizonepeta Spike	3g	-
	Asiasarum Root	3g	-
	Ginger	3g	1g
	Magnolia Flower	3g	-
	Peucedanum Root	3g	-
	Angelica Dahurica Root	3g	1g

Table 2

Range of ages and coefficients

Age	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 months to under 6 months of age	1/6

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Provisional Translation
from Japanese Original

Apr 22, 1980
Notification PFSB No.520
Final revision Mar 28, 1986

The Standards for Marketing Approval of Gastrointestinal Medicines

1. Scope of Gastrointestinal Medicines

The scope of preparations subject to these standards covers all medicines for oral use formulated with the intent of relieving symptoms of gastrointestinal diseases (evacuants and Kampo medicine* formulas are not covered).

*Kampo medicine is traditional Japanese medicine.

2. Approval Standards

The approval standards for gastrointestinal medicines are as follows. For preparations 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 used are shown in Table 1.

(b) Preparations mainly containing active ingredients from Column I, II, III, or IV can be mutually combined with other active ingredients from Columns I, II, III, and IV as well as the active ingredients from Columns V (limited to those with a "△" mark in Groups 3, 4, and 5), VII, and VIII.
However, notwithstanding the above rules, preparations having their main active ingredients only from Column I cannot include the following active ingredients: those in Group 2 of Column IV or those with a "△" mark in Group 5 of Column V. Preparations mainly containing active ingredients only from Column IV cannot include the active ingredients from Column VII.

(c) Preparations mainly containing active ingredients from Column V of Table 1 can include the active ingredients from Column I, II, III, IV, or VI (limited to Scopolia Extract in Group 1 and ingredients in Group 4).

(d) Preparations mainly containing active ingredients from Column VI of Table 1 can include the active ingredients from Column I (except Group 3), II, III, or V (limited to Groups 3 and 4).
However, preparations mainly containing active ingredients from Group 1 of Column VI cannot include the active ingredients from Column II (limited to Nux Vomica Extract in Group 1 or ingredients in Group 3). When the active ingredients from Column VI (except for Group 4) are used in combination, they should be limited to 1 type from each group.

(e) When the active ingredients from Column VII (except for Group 9) of Table 1 are used in combination, they should be limited to 1 type from each group.

(f) The active ingredients from Column I (excluding Group 3) and Group 2 of Column II cannot be combined in the same preparation.

(g) When the same active ingredient appears in at least 2 columns of Table 1, it

should not be duplicated in the formula.

(h) Berberine chloride and berberine tannate in Group 1 of Column V must not be combined with Coptis Rhizome or Phellodendron Bark in Group 1 of Column II or Group 5 of Column V of Table 1. Glycyrrhizinic acid, its salts, and glycyrrhiza extracts in Group 3 of Column VII cannot be combined with Glycyrrhiza in Group 9 of Column VII.

(i) The vitamins given in the Appendix may be combined with the active ingredients listed in Table 1 as long as there is good reason for their combination and the effect is mild.

(2)Quantities of Active Ingredients

(a) The maximum daily doses of the active ingredients listed in Table 1 (except for those in Group 1 of Column III and Group 1 of Column IV) should correspond to data in Table 1. The maximum single dose should be 1/3rd of the maximum daily dose.

(b) When not less than 2 active ingredients in Group 1 or Group 2 of Column I listed in Table 1 are combined, the sum of the values obtained by dividing the amount of each active ingredient by its respective maximum daily dose should not exceed 2.

(c) When at least 2 active ingredients in Group 2 or Group 3 of Column II are combined, or when at least 2 active ingredients in Group 2 of Column III or at least 2 active ingredients in Group 1, 2, 3, or 4 of Column V of Table 1 are included, the sum of the values obtained by dividing the amount of each active ingredient by its respective maximum daily dose should not exceed 1 for any group.

(d) When the crude drugs marked with "*" in Group 1 of Column II in Table 1 are combined in preparations for which the main active ingredient comes from Column I, the daily dose of the crude drug concerned should not be more than 1/10th of the maximum daily dose shown in Table 1.

(e) When preparations whose main active ingredients are from Groups 1 and 2 of Column I and which are tested for acid-neutralizing capacity or pH by the methods specified elsewhere, the acid-neutralizing capacity of the daily dose of the preparation should not be less than 150 mL when expressed as the amount of 0.1N hydrochloric acid consumed, and the pH of the preparation should not be less than 3.5.
The acid-neutralizing capacity of a single dose of the preparation should be not less than 50 mL.

(f) In preparations mainly containing active ingredients from Group 1 of Column III of Table 1, the digestive activity of the digestive enzymes included in a single dose of the preparation should not be less than the minimum daily unit for at least 1 of the following: starch saccharifying activity, starch dextrinizing activity, starch liquefying activity, protein digesting activity, fat digesting activity, fibrin saccharifying activity, or fibrin disintegrating activity specified in Group 1 of Column III.
The minimum unit for a single dose shall be 1/3rd of the minimum daily unit.

(g) For preparations mainly containing active ingredients from Group 1 of Column IV in Table 1, the minimum daily dose of the active ingredient concerned should be the amount shown in Table 1, and the minimum single dose should be 1/3rd of the minimum daily dose.

(3)Dosage Form

The dosage forms should be capsules, granules, pills, fine granules, powders, electuaries, tablets, infusions, decoctions, or liquids for oral use (limited to mildly

acting preparations mainly containing ingredients from Column I or II).

(4)Dosage and Administration

(a) In principle, dosage and administration should be 3 times a day.
Oral liquids mainly containing ingredients from Column I or II, or preparations mainly containing ingredients from Column V or VI listed in Table 1 can be taken 1 to 3 times a day, and if they are taken not less than 2 times a day, the interval between doses must not be less than 4 hours.

(b) For infusions and decoctions, the method of preparation at the time of use should be indicated.

(c) The time of administration (such as before or after meals, between meals) and the administration interval should be indicated.

(d) Dosage in infants less than 3 months of age is not approved.

(e) For capsules, pills, or tablets larger than 6 mm in diameter, dosage in children less than 5 years of age is not approved.

(f) For pills or tablets smaller than 6 mm in diameter, dosage in children less than 3 years of age is not approved.

(g) The maximum daily dose for children less than 15 years of age should be obtained by multiplying the maximum daily doses listed in Table 1 by the values given in the coefficient column for the corresponding age ranges stated in Table 2.

(h) The minimum daily doses specified in (2) (e) and (2) (f) should be multiplied by the values given in the coefficient column for the corresponding age ranges in Table 2 to obtain the minimum daily dose for children less than 15 years of age. However, the minimum daily doses specified in (2) (g) should be applied irrespective of age.

(5)Indications

(a) The range of indications for preparations mainly containing active ingredients from the columns of Table 1 (except Columns VII and VIII) is shown in Table 3. When active ingredients from at least 2 of Columns I, II, III, and IV are used as the main ingredients, the indications should cover all of those in the columns concerned.
The indications in Column III of Table 3 can be claimed for preparations whose main active ingredients are from Group 1 in Column III, only if the minimum daily units of at least 1 of the following are achieved: starch saccharifying activity, starch dextrinizing activity, starch liquefying activity, protein digestive activity, and fat digestive activity.

(b) For preparations claiming the indications mentioned in Column V or VI of Table 3, the indications listed in the other columns of the same table should not be claimed.

(c) Notwithstanding the above standards, the indications in Column I of Table 3 cannot be claimed in cases where Nux Vomica Extract in Group 1 of Column II is included in preparations containing active ingredients from Column I in Table 1.
In addition, the indications in Column I of Table 3 cannot be claimed for preparations containing active ingredients only from Group 3 of Column I in Table 1.

(Table 1)

Classification		Active ingredient	Maximum daily dose
Column I	Group 1	Dried aluminum hydroxide gel	3 g
		Magnesium aluminosilicate	4 g
		Magnesium silicate	6 g
		Synthetic aluminum silicate	10 g
		Synthetic hydrotalcite	4 g
		Magnesium oxide	1 g
		Magnesium hydroxide-aluminum hydroxide co-precipitate	4 g
		Aluminum hydroxide gel	30 mL (1.2 g as aluminum oxide)
		Aluminum hydroxide-sodium bicarbonate co-precipitate	2 g
		Dried mixed aluminum hydroxide and magnesium carbonate gel	3 g
		Aluminum hydroxide-magnesium carbonate-calcium carbonate co-precipitate	4 g
		Magnesium hydroxide	2.4 g
		Sodium bicarbonate	5 g
		Magnesium carbonate	2 g
		Precipitated calcium carbonate	3 g
		Magnesium aluminometasilicate	4 g
		Anhydrous dibasic calcium phosphate	2.4 g
		Dibasic calcium phosphate	3 g
		Cuttlefish Bone	3 g
		Abalone Shell	3 g
		Oyster Shell	3 g
	Group 2	Aminoacetic acid	0.9 g
		Dihydroxyaluminum aminoacetate	3 g
	Group 3	Scopolia Extract	30 mg

Classification		Active ingredient	Maximum daily dose (g)	
			Extract (converted to crude drug amount)	Powder
Column II	Group 1	Aniseed	3	1
		Aloe	–	0.15
		Fennel	3	1
		Turmeric	6	2
		Lindera Root	5	1
		Isodon Herb	10	3
		Scutellaria Root	6	3
		Phellodendron Bark	3	3
		Coptis Rhizome	3	1.5
		Processed Garlic Bulb	–	0.2
		Zedoary	3	3
		Pogostemon Herb	8	3
		Calamus Root	6	2
		Processed Ginger	3	1
		Orange Fruit	5	2
		Immature Orange	5	2
		Cinnamon Bark	5	1
		Gentian	1.5	0.5
		Red Ginseng	6	3
		Magnolia Bark	5	1.5
		Euodia Fruit	3	1
		*Pepper	5	1.5
		Calumba	5	1.5
		Condurango	9	3
		*Japanese Zanthoxylum Peel	3	1
		Resurrection Lily Rhizome	6	2
		Perilla Fruit	6	3
		Amomum Seed	3	1
		Ginger	3	1

Classification		Active ingredient	Maximum daily dose (g)	
			Extract (converted to crude drug amount)	Powder
Column II	Group 1	Citrus Unshiu Peel	5	3
		*Capsicum	–	0.1
		Bitter Orange Peel	5	3
		Animal bile (including Bear Bile)	–	0.5
		Picrasma Wood	5	0.5
		Nutmeg	3	1
		Ginseng	6	3
		Mentha Herb (including peppermint)	3	1
		Long pepper	2	0.5
		Atractylodes Rhizome	5	2
		Hop Strobile	3	1
		Nux Vomica Extract	–	0.03
		Menyanthes trifolia herb	4	1.3
		Saussurea Root	3	1
		Bitter Cardamon	3	1
		Japanese Gentian	15	0.5
		Alpinia Officinarum Rhizome	3	1
		Fennel Oil	0.08	
		Cinnamon Oil	0.03	
		Ginger Oil	0.03	
		Cardamon Oil	0.03	
		Clove Oil	0.02	
		Bitter Orange Peel Oil	0.03	
		Mentha Oil	0.03	
		Lemon Oil	0.03	
		l-Menthol	0.18	
		dl-Menthol	0.18	

		Cardamon	3	1	Group 2	Betaine hydrochloride	0.6
		Immature Citrus Unshiu Peel	5	3		L-Glutamic acid hydrochloride	1.8
		Acorus Gramineus Rhizome	6	2			
		Centaury Herb	2	0.7			
		Swertia Herb	1.5	0.05			
		Atractylodes Lancea Rhizome	5	2	Group 3	Carnitine chloride	0.6
		Perilla Herb	2	1		Bethanechol chloride	0.045
		Star Anise	3	1			
		Rhubarb	0.2	0.1			
		Panax Japonicus Rhizome	6	3	Group 4	Dried yeast	10
		Clove	2	0.5			

Classification		Active ingredient	Minimum daily unit[Note 1)]
Column III	Group 1	Starch digestive enzymes	Starch saccharifying activity: 250 units Starch dextrinizing activity: 210 units Starch liquefying activity: 360 units
		Protein digestive enzymes	Proteolytic activity: 1,500 units
		Fat digestive enzymes	Fat digestive activity: 100 units
		Fibrin digestive enzymes	Fibrin saccharifying activity: 13 units Fibrin disintegrating activity: 25 units

		Active ingredient	Maximum daily dose (g)
Column III	Group 2	Ursodesoxycholic acid	0.06
		Oxycholanates	0.15
		Cholic acid	0.9
		Gall powder	1.5
		Gall extract (powder)	0.5
		Dehydrocholic acid	0.5
		Animal bile (including Bear Bile)	0.5

Note 1) Methods for measuring the digestive activity of each digestive enzyme are specified separately.

		Active ingredient	Minimum daily dose	
Column IV	Group 1	Live bacteria for intestinal regulation	1×10^6	
	Group 2		Maximum daily dose (g)	
			Extract (converted to crude drug amount)	Powder
		Mallotus Bark	5	1.5
		Gambir	–	2
		Processed Mume	10	3
		Cassia Seed	10	3
		Geranium Herb	10	3

Classification		Active ingredient	Maximum daily dose (g)	
Column V	Group 1	Acrinol	0.3	
		Berberine chloride	0.3	
		Guaiacol	0.6	
		Creosote	0.5	
		Phenyl salicylate	1	
		Guaiacol carbonate	1.2	
		Berberine tannate	0.3	
	Group 2	Bismuth subsalicylate	3	
		Bismuth subnitrate	2	
		Bismuth subcarbonate	3	
		Bismuth subgallate	2	
		Tannic acid	1.2	
		Albumin tannate	4	
		Methylene thymol tannin	2	
	Group 3	Kaolin	10	
		Natural aluminum silicate	10	
		Aluminum hydroxynaphthoate	0.9	
		Pectin	0.6	
		Medicinal carbon	5	
	Group 4	Precipitated calcium carbonate	3	
		Calcium lactate	5	
		Dibasic calcium phosphate	3	
			Extract (g) (converted to crude drug amount)	Powder (g)
	Group 5	△ Gambir	-	2
		△ Processed Mume	10	3
		Phellodendron Bark	9	3
		Coptis Rhizome	3	1.5
		Sophora Root	3	1.5
		△ Geranium Herb	10	3
		Rhus Javanica Nutgall	-	3
		△ Crataegus Fruit	8	3
		Swertia Herb	-	0.9
		Myrica Rubra Bark	5	2

Classification		Active ingredient	Maximum daily dose	
Column VI	Group 1	Oxyphencyclimine hydrochloride	7 mg	
		Dicyclomine hydrochloride	30 mg	
		Methixene hydrochloride	8.75 mg	
		Scopolamine hydrobromide	0.3 mg	
		Atropine methylbromide	6 mg	
		Anisotropine methylbromide	30 mg	
		Scopolamine methylbromide	4.8 mg	
		l-Hyoscyamine methylbromide	2.25 mg	
		Methylbenactyzium bromide	30 mg	
		Belladonna extract	60 mg	
		Isopropamide iodide	7.5 mg	
		Diphenylpiperidinomethyldioxolane iodide	60 mg	
		Scopolia Extract	60 mg	
		Scopolia Rhizome (Total) Alkaloid citrates	1 mg	
	Group 2	Papaverine hydrochloride	90 mg	
	Group 3	Ethyl aminobenzoate	0.6 mg	
			Extract (g) (converted to crude drug amount)	Powder (g)
	Group 4	Corydalis Tuber	5	1.5
		Glycyrrhiza	5	1.5
		Magnolia Bark	5	1.5
		Peony Root	5	2

Classification		Active ingredient	Maximum daily dose (g)	
Column VII	Group 1	Sodium azulene sulfonate	0.006	
	Group 2	Aldioxa	0.3	
	Group 3	Glycyrrhizinic acid, its salts, and glycyrrhiza extracts	(as glycyrrhizinic acid) 0.2	
	Group 4	L-Glutamine	2	
	Group 5	Potassium copper chlorophyllin Sodium copper chlorophyllin	0.2 0.2	
	Group 6	Histidine monohydrochloride	0.18	
	Group 7	Pepsin decomposition products of pig stomach wall Acid hydrolysis products of pig stomach wall	0.3 0.3	
	Group 8	Methylmethioninesulfonium chloride	0.15	
	Group 9		Extract (g) (converted to crude drug amount)	Powder (g)
		Mallotus Bark	5	1.5
		Corydalis Tuber	5	1.5
		Glycyrrhiza	5	1.5
Column VIII		Dimethylpolysiloxane	0.18 g	

(Table 2) Age coefficients

Age	Coefficients
15 years of age or over	1
11 to under 15 years of age	2/3
8 to under 11 years of age	1/2
5 to under 8 years of age	1/3
3 to under 5 years of age	1/4
1 to under 3 years of age	1/5
3 months to under 1 year of age	1/10

(Table 3)

Main ingredient	Indications
Column I	Hyperacidity, heartburn, feeling of discomfort in the stomach, feeling of fullness in the stomach, constricted feeling in the stomach (stomach heaviness), heaviness in the stomach, heaviness in the chest, belching (burping), nausea (retching, stomach retching, retching due to hangovers and overdrinking, sick feeling, and feeling of sickness), vomiting, excessive drinking (overdrinking), and stomachache
Column II	Loss of appetite (anorexia), feeling of fullness in the stomach and abdomen, indigestion, weak stomach, excessive eating (overeating), excessive drinking (overdrinking), heartburn, constricted feeling in the stomach (stomach heaviness), heaviness in the chest, nausea (retching, stomach retching, retching due to hangovers and overdrinking, sick feeling, and feeling of sickness), and vomiting
Column III	For promoting digestion, indigestion, loss of appetite (anorexia), excessive eating (overeating), constricted feeling in the stomach (stomach heaviness), heaviness in the chest, and feeling of fullness in the stomach and abdomen due to indigestion
Column IV	Intestinal regulation (regulation of stool), feeling of fullness in the abdomen, soft stool, and constipation
Column V	Diarrhea, diarrhea due to indigestion, food poisoning, vomiting and purging, water poisoning, loose bowels, soft stool, and diarrhea accompanied by abdominal pain[Note 1)]
Column VI	Stomachache, abdominal pain, gripping pain (colic, spasms), hyperacidity, and heartburn

Note 1) Only when scopolia extract in Group 1 of Column VI is included.

(Appendix)

1. Vitamins that can be included in preparations mainly containing active ingredients from Column II or III are indicated below, together with their maximum daily doses.

Ingredient	Maximum daily dose
Vitamin B_1, its derivatives, and their salts	25 mg

2. Vitamins that can be included in preparations mainly containing active ingredients from Column IV are listed below, together with their maximum daily doses.

Ingredient	Maximum daily dose
Nicotinamide	5 mg
Calcium panthothenate	30 mg
Biotin	25 μg
Vitamin B_1, its derivatives, and their salts	25 mg
Vitamin B_2, its derivatives, and their salts	12 mg
Vitamin B_6, its derivatives, and their salts	50 mg
Vitamin C, its derivatives, and their salts	500 mg

However, the combination of biotin and nicotinamide is permitted only when including live lactic acid bacteria or lactic acid producing bacteria for intestinal regulation.

3. Vitamins that can be included in preparations mainly containing active ingredients from Column V are listed below, together with their maximum daily doses.

Ingredient	Maximum daily dose
Vitamin B_1, its derivatives, and their salts	25 mg
Vitamin B_2, its derivatives, and their salts	12 mg

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Provisional Translation
from Japanese Original

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Notification PB No.463
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The Standards for Marketing Approval of Laxatives

1. Scope of Laxatives

The scope of preparations subject to these standards covers oral medicines intended for the relief of the symptoms of constipation or the elimination of intestinal contents (except for preparations covered by the Standards for Marketing Approval of gastrointestinal medicines and Kampo medicine* formulas.

* Kampo medicine is traditional Japanese medicine.

2. Approval Standards

The approval standards for laxatives are as follows.

For preparations not conforming to these standards, concerning the 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 used in laxatives are shown in Tables 1 and 2.

(b) At least 1 of the active ingredients in Table 1 must be used.

(c) Preparations mainly containing the active ingredients from Group I, II, III, or IV in Column A of Table 1 may be made by mutual combination of the active ingredients in these 4 groups, and may also include the active ingredients in Table 2.

(d) When active ingredients from Group I, Group II, or Group III in Column A of Table 1 are combined, only 1 ingredient from each group should be used. When active ingredients from Group IV are used, up to 4 active ingredients from this group may be included.
However, when active ingredients from 2 or more groups, among Groups I, II, III, and IV, are combined, up to 4 active ingredients from Column A of Table 1 (except Group V) may be combined.

(e) The following combinations are not permitted among the active ingredients of Group IV in Column A of Table 1: Aloes with aloin, Cascara sagrada bark with casanthranol, Pharbitis seeds with Pharbitis seed resin, Senna or Senna fruit with sennoside or sennosides A and B, and Jalap tuber with Jalap resin.

(f) For preparations mainly containing the active ingredients from Group V of Column A in Table 1, combinations with the other active ingredients in these standards are not permitted.

(g) When the active ingredients from Column B of Table 1 are used as a main ingredient, only 1 active ingredient can be used in a preparation and none of the other active ingredients covered by these standards should be combined.

(h) When the active ingredients from Column I or II of Table 2 are combined, up to 4 active ingredients in the same column may be used.
When active ingredients in both Columns I and II of Table 2 are combined, up

to 5 of the active ingredients from the whole table may be used.

(i) Other than the active ingredients in Tables 1 and 2, vitamins 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) The maximum single and daily doses of the active ingredients from Column A of Table 1 are as indicated in the table.

(b) The maximum single doses of the active ingredients from Column B of Table 1 are as indicated in the table.

(c) The maximum daily dose of each of the active ingredients from Column I (except live bacteria for intestinal regulation) and Column II of Table 2 are as given in the table. The maximum single dose should be 1/3rd of the maximum daily dose.

(d) When 2 or more of the active ingredients from Column A of Table 1 are combined, the sum of the values obtained by dividing the amounts of each of the active ingredients by their respective maximum daily doses should not exceed 2.

(e) When 2 or more of the active ingredients from either Column I or Column II of Table 2 are combined, the sum of the values obtained by dividing the amounts of each of the active ingredients by their respective maximum daily doses should not exceed 2 in each column.

(f) The minimum daily dose of live bacteria for intestinal regulation from Column I of Table 2 is as given in the same group, and the minimum single dose should be 1/3rd of the minimum daily dose.

(3) Dosage Forms

The dosage forms are capsules, granules, pills, fine granules, powders, lingual tablets (limited to preparations mainly containing the active ingredients from Group V of Column A of Table 1), tablets, infusions, decoctions, chocolate preparations and liquids for oral use (limited to syrups and preparations mainly containing the active ingredients from Group I of Column A or those from Column B of Table 1).

(4) Dosage and Administration

(a) Preparations should, in principle, be taken by oral administration 1 to 3 times daily, and the administration times and intervals must be clearly indicated. When the preparation is taken twice a day or more, the interval between doses must be not less than 4 hours.
However, preparations mainly containing the active ingredients from Column B of Table 1 should be taken not more than once a day, to be taken when required.

(b) For preparations mainly containing the active ingredients from Column A of Table 1, the dosage range for different degrees of constipation must be indicated.
Since there are individual differences with respect to the degree of constipation, it must be stated that the minimum dose should be taken initially and then the dose should be gradually increased (or decreased) depending on the condition of relief.

(c) In principle, dosage for children under 3 years of age is not permitted.

(d) Regardless of the rules described in (a), (b), or (c), preparations mainly containing the active ingredients from Group V of Column A in Table 1 will be approved only for small children and infants. Entries for dosage and

administration should be made in accordance with Table 5.

(e) In the case of infusions and decoctions, the method of preparation at the time of use should be clearly indicated.

(f) For capsules, and pills and tablets larger than 6 mm in diameter, dosage for children under 5 years of age is not approved.

(g) The maximum single and daily doses for those under 15 years of age are the values obtained by multiplying the coefficients corresponding to the respective age groups in Table 3 by the maximum single and daily doses shown in Tables 1 and 2.
However, the minimum daily dose of live bacteria for intestinal regulation from Column I of Table 2 should be applied irrespective of age.

(5) Indications

(a) The indications for preparations mainly containing the active ingredients from Column A of Table 1 are shown from Column I of Table 4. However, the indications for preparations mainly containing the active ingredients from Group V of Column A in Table 1 are as specified in Table 5.

(b) The indications for preparations mainly containing the active ingredients from Column B of Table 1 are as specified from Column II of Table 4.

(6) Packaging Units

The maximum volume of syrup containers is a 2-day supply at the maximum daily dose for adults (15 years of age and over).

Table 1

Classification		Active ingredients	Maximum single dose (g)		Maximum daily dose (g)	
Column A	Group I	Magnesium oxide	0.7 (2)		2	
		Magnesium hydroxide	0.7 (2.1)		2.1	
		Magnesium carbonate	2.7		8	
		Sodium sulfate	5		15	
		Magnesium sulfate	5		15	
	Group II	Carboxymethylcellulose calcium	2		6	
		Carboxymethylcellulose sodium	2		6	
		Plantago ovata coating (Ispaghula husk)	3.5		10.5	
	Group III	Sodium dioctyl·sulfosuccinate	0.067 (0.12)		0.2	
	Group IV	Aloin	0.02		0.06	
		Sulfur	0.5		1.5	
		Casanthranol	0.067 (0.1)		0.2	
		Sennoside (as sennosides A and B)	0.016 (0.024)		0.048	
		Sennosides A and B	0.016 (0.024)		0.048	
		Bisacodyl	0.007 (0.015)		0.02	
			Powder (g)	Extract (g) (converted to crude drug amount)	Powder (g)	Extract (g) (converted to crude drug amount)
		Aloes	0.25 (0.38)	0.25 (0.38)	0.75	0.75
		Rose fruit	0.67	1.7	2	5
		Cascara sagrada bark	–	1 (1.5)	–	3
		Pharbitis seed	0.1	–	0.3	–
		Pharbitis seed resin	0.05	–	0.15	–
		Senna	0.5 (0.75)	2 (3)	1.5	6
		Senna fruit	0.5 (0.75)	–	1.5	–
		Rhubarb	1 (1.5)	1.4 (2)	3	4
		Frangula bark	–	1 (1.5)	–	3
		Jalap root	0.1	–	0.3	–
		Jalap resin	0.05	–	0.15	–
	Group V	Malt extract	As per Table 5			
Column B		Aromatic castor oil	20 mL		–	
		Castor oil	20 mL		–	

(Note) Figures in parentheses are the maximum single dose applicable when the dosage is once or twice a day.

Table 2

Classification	Active ingredient	Maximum daily dose (g)	
	Ursodeoxycholic acid		0.06
	Oxycolanate		0.15
	Dried yeast		10
	Cholic acid		0.9
	Dimethylpolysiloxane		0.18
	Live bacteria for intestinal regulation		1×10^9 (*)
	Sodium bicarbonate		3
	Dehydrocholic acid		0.5
		Powder (g)	Extract (g) (converted to crude drug amount)
Column I	Linseed	2	–
	Japanese valerian	2	–
	Glycyrrhiza	1.5	5
	Cassia seed	3	10
	Smilax rhizome	1.5	5
	Gardenia fruit	1	3
	Rehmannia root	1.5	5
	Peony root	2	6
	Houttuynia herb	5	15
	Cimicifuga rhizome	1	3
	Cnidium rhizome	1.5	5
	Jujube	1.5	5
	Bile extract (powder)	0.5	
	Japanese angelica root	1.5	5
	Animal bile	0.5	–
	Moutan bark	1.3	4
	Hemp fruit	5	–
	Coix seed	6	20

(*) Minimum daily dose

Classification	Active ingredient	Maximum daily dose (g)	
		Powder (g)	Extract (g) (converted to crude drug amount)
Column II	Fennel	0.5	1.5
	Plectranthus herb	1.5	5
	Scutellaria root	1.5	3
	Phellodendron Bark	1.5	1.5
	Coptis Rhizome	0.75	1.5
	Zeodary	1.5	1.5
	Calamus Root	1	3
	Immature orange	1	2.5
	Cinnamon Bark	0.5	2.5
	Gentian	0.25	0.75
	Magnolia bark	0.75	2.5
	Condurango	1.5	4.5
	Resurrection Lily Rhizome	1	3
	Ginger	0.5	1.5
	Swertia herb	0.025	0.75
	Atractylodes Lancea Rhizome	1	2.5
	Perilla Herb	0.5	1
	Citrus Unshiu Peel	1.5	2.5
	Bitter orange peel	1.5	2.5
	Ginseng	1.5	3
	Mentha herb	0.5	1.5
	Mentha oil	0.015	
	Atractylodes rhizome	1	2.5
	Nux vomica extract	0.015	
	dl-Menthol	0.09	
	l-Menthol	0.09	
	Saussurea root	0.5	1.5
	Japanese gentian	0.25	0.75

Table 3 Age coefficient

Age	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

Table 4

	Indications
Column I	○ Constipation ○ Relief of the following symptoms due to constipation: dull headache, hot flush, skin roughness, eruption, loss of appetite (anorexia), fullness in the abdomen, abnormal fermentation in the intestines, and hemorrhoids
Column II	○ Rapid excretion of intestinal contents (food poisoning, etc.)

Table 5

Dosage and administration (maximum single dose)	Indications
1 to under 3 years of age: 15 g/dose 6 months to under 1 year of age: 9 g/dose Under 6 months of age: 9 g/dose Take orally up to 3 times a day in each case	Constipation in infants and small children

Appendix

Ingredients	Maximum daily dose
Vitamin B_1, its derivatives, and their salts	25 mg
Vitamin B_6	50 mg
Nicotinamide	5 mg
Calcium panthothenate	30 mg

(Note) Nicotinamide is to be combined only when lactic acid bacteria or lactic acid producing bacteria are used as live bacteria for intestinal regulation.

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Provisional Translation
from Japanese Original

Jun 1, 1984
Notification PB No.381

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

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Provisional Translation
from Japanese Original

Jul 29, 1986
Notification PB No.623

The Standards for Marketing Approval of Ophthalmic Medicines

1. Scope of Ophthalmic Medicines

The scope of preparations subject to these standards covers medicines to be applied to the mucous membrane of the eyes to treat symptoms of eye diseases and those to be used when inserting contact lenses.

2. Approval Standards

The approval standards for ophthalmic medicines are as follows.

For preparations 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) Active ingredients that may be used in ophthalmic medicines are listed in Table I.

(b) At least 1 active ingredient from Column A, B, C, or D; Group 1, 2, or 3 of Column E; Column F, G, or H; Group 1 of Column I; or Column J in Table I must be used.

(c) Preparations mainly containing the active ingredients in Column A, B, C, or D; Group 1, 2, or 3 of Column E; or Group 1 of Column F (hereinafter referred to as "ordinary eye drops") in Table I may be formulated through the mutual combination of any of the active ingredients in these columns and groups, and may also include the active ingredients in Group 4, 5, or 6 of Column E or those in Group 2 or 3 of Column F in Table I.

(d) Preparations mainly containing active ingredients in Column G (hereinafter referred to as "antibacterial eye drops") in Table I may include up to 3 active ingredients from Column A, B, C, D, E, or F.

(e) Preparations mainly containing active ingredients in Groups 2 or 3 of Column F or those in Column H of Table I (hereinafter referred to as "artificial tears") may be formulated through the mutual combination of any of the active ingredients in Group 2 or 3 of Column F or those in Column H, and may also include the active ingredients in Group 1 of Column F or those in Column I.

(f) Preparations mainly containing active ingredients in Group 1 of Column I (hereinafter referred to as "contact lens insertion preparations") of Table I may also include active ingredients in Column F or H or those in Group 2 of Column I.

(g) Preparations mainly containing active ingredients in Column C, D, H, or J, listed in Table I, are used for washing the eyes and are referred to as "eyewashes." Those mainly containing active ingredients from Column C or D may be formulated by combining any of the active ingredients from Column C or D, and may also include active ingredients from Column E or F. Preparations mainly containing active ingredients from Column H or J of

Table I can include only 1 active ingredient from Column H or J, and no other active ingredients mentioned in these standards should be used.

(h) When the active ingredients from Column A, D, or G of Table I are combined, only 1 ingredient from each column may be used.

(i) When the active ingredients from Column C, E, or F of Table I are combined, up to 3 ingredients from each column may be used, but only 1 from each group is permitted.

(2) Quantities of Active Ingredients

(a) The maximum concentrations of the active ingredients from Column A, B, C, D, E, F, or G; Group 1 of Column I; or Column J should be those given in mentioned in Table I.
However, in the case of eyewashes, the maximum concentrations of the active ingredients in Columns C, D, E, and F should be 1/10th of the maximum concentrations mentioned in Table I.

(b) When 2 or more of the active ingredients from any 1 of Column C, E, or F of Table I are combined, the sum of the values obtained by dividing the concentration of each active ingredient by its respective maximum concentration should not exceed 2.
However, in the case of eyewashes, the maximum concentration stipulated in (2) (a) shall apply.

(c) In the case of ordinary eye drops, when only 1 active ingredient from Column A, B, C, or D; Group 1, 2, or 3 of Column E; or Group 1 of Column F of Table I is included, the minimum concentration of the ingredients should be half of the maximum concentration. When 2 or more of these active ingredients are combined, the minimum concentration of each shall be 1/5 of the maximum concentration.

(d) In the case of antibacterial eye drops, when active ingredients in Column G of Table I are included, the minimum concentration of these active ingredients should be half of the maximum concentration. When active ingredients from Column A, B, C, or D; Group 1, 2, or 3 of Column E; or Group 1 of Column F are included, their minimum concentrations should be 1/5 of the maximum concentration.

(e) In the case of artificial tears, when active ingredients listed in Column F or Group 1 of Column I in Table I are used, their minimum concentrations should be 1/10th the maximum concentration. pH values must be in the range of 5.5 to 8.0, and specific osmotic pressures (specific osmotic pressures with respect to physiological saline) must be in the range of 0.85 to 1.55 when pH and osmotic pressures are measured by the methods specified elsewhere.

(f) For contact lens insertion preparations, when 1 active ingredient from Group 1 of Column I in Table I is used, the minimum concentration should be half of the maximum concentration. When 2 active ingredients are included, their minimum concentrations should be 1/5th of the maximum concentration. When active ingredients in Column F are combined, their minimum concentrations should be 1/10th of the maximum concentration.

(g) In the case of eyewashes, when active ingredients from Column C, D, or J of Table I are combined, the minimum concentration should be 1/5th of the maximum concentration specified in (2) (a). When active ingredients in Column E or F are used, the minimum concentration should be 1/10th of the maximum concentration specified in (2) (a). pH values must be in the range of 5.5 to 8.0, and specific osmotic pressures (specific osmotic pressure with respect to physiological saline) must be in the range of 0.60 to 1.55 when pH and osmotic pressures are measured by the methods specified elsewhere.

(h) Unless otherwise specified, when active ingredients in Groups 4, 5, and 6 of Column E, or Groups 2 and 3 of Column F in Table I are combined, the minimum concentration should be 1/10th of the maximum concentration.

(3) Dosage Form

The dosage form shall be ophthalmic solutions (eye drops and eyewashes).

(4) Dosage and Administration

(a) Ordinary eye drops, antibacterial eye drops, and artificial tears are to be administered 3 to 6 times a day.

(b) For contact lens insertion preparations, the detailed method of use should be stated.

(c) Eyewashes are to be used 3 to 6 times a day to wash the eyes.

(5) Indications

(a) The range of indications for ordinary eye drops is shown in Table II-1. However, for indications in the upper column of the following table to be claimed, at least 1 of the ingredients from the columns listed in the corresponding lower column must be included.

Upper column	Lower column
Conjunctival congestion	Columns A, C, and D
Inflammation of eyes (snow blindness), blepharitis (inflammation of the eyelids), and itchy eyes due to ultraviolet light and other rays	Columns C and D and Group 1 of Column E

(b) The range of indications for antibacterial eye drops is shown in Table II-2.

(c) The range of indications for artificial tears is shown in Table II-3. However, "treatment of feeling of discomfort when inserting soft contact lenses" cannot be claimed when the effect is brought about due to the effect of ingredients on the lenses, such as adsorption on the lenses.

(d) The range of indications for contact lens insertion preparations is shown in Table II-4. However, "ease of insertion of soft contact lenses" cannot be claimed when the effect is brought about due to the effect of ingredients on the lenses, such as adsorption on the lenses.

(e) The range of indications for eyewashes is shown in Table II-5.

(6) Packaging Units

(a) The maximum volume of containers for ordinary eye drops, antibacterial eye drops, and artificial tears is 20 mL.

(b) The maximum volume of containers for contact lens insertion preparations is 100 mL.

(c) The maximum volume of containers for eyewashes is 500 mL.

Table I

Column	Group	Active ingredient	Maximum concentration (%)
A		Epinephrine	0.003
		Epinephrine hydrochloride	0.003 (as epinephrine)
		Ephedrine hydrochloride	0.1
		Terahydrozoline hydrochloride	0.05
		Naphazoline hydrochloride	0.003
		Naphazoline nitrate	0.003
		Phenylephrine hydrochloride	0.1
		dl-Methylephedrine hydrochloride	0.1
B		Neostigimine methylsulfate	0.005
C	1	ε-Aminocaproic acid	5
	2	Allantoin	0.3
	3	Berberine chloride	0.025
		Berberine sulfate	0.025
	4	Sodium azulene sulfonate	0.02
	5	Dipotassium glycyrrhizinate	0.25
	6	Zinc sulfate	0.25
		Zinc lactate	0.25
	7	Lysozyme chloride	0.5 (potency)
D		Diphenhydramine hydrochloride	0.05
		Chlorpheniramine maleate	0.03
E	1	Sodium flavine adenine dinucleotide	0.05
	2	Cyanocobalamin	0.02
	3	Retinol acetate	50,000 units/100 mL
		Retinol palmitate	50,000 units/100 mL
	4	Pyridoxine hydrochloride	0.1
	5	Panthenol	0.1
		Calcium pantothenate	0.1
		Sodium pantothenate	0.1
	6	Tocopherol acetate	0.05
F	1	Potassium L-aspartate	1
		Magnesium L-aspartate	1
		Mixture of magnesium L-aspartate and potassium L-aspartate (equal mixture)	2
	2	Aminoethyl sulfonic acid	1
	3	Sodium chondroitin sulfate	0.5

G		Sulfamethoxazole	4
		Sodium sulfamethoxazole	4
		Sulfisoxazole	4
		Sodium sulfisomidine	5
H		Potassium chloride	–
		Calcium chloride	–
		Sodium chloride	–
		Sodium bicarbonate	–
		Sodium carbonate	–
		Dried sodium carbonate	–
		Magnesium sulfate	–
		Sodium hydrogen phosphate	–
		Monobasic sodium phosphate	–
		Monobasic potassium phosphate	–
I	1	Polyvinyl alcohol	2
		Polyvinylpyrrolidone	2.5
	2	Hydroxyethl cellulose	–
		Hydroxypropylmethyl cellulose	–
		Glucose	–
		Methylcellulose	–
J		Alkylpolyaminoethylglycine	0.1
		Boric acid	2

Table II

1 (general ophthalmic drops)	Eyestrain, redness of the conjunctiva, prevention of eye troubles (after swimming, or to wash out sweat or dust etc.) , ophthalmia by ultraviolet rays etc. (snow blindness etc.), blepharitis (running eye), foreign-body feeling by contact lenses, itchy eyes, blurred vision (eye mucus)
2 (antibiotic ophthalmic drops)	Conjunctivitis (pink-eye), chalazia, blepharitis (running eye), itchy eyes
3 (Artificial tears)	Eyestrain, prevention of dry-eyes, foreign-body feeling by contact lenses, blurred vision (eye mucus)
4 (eye-lotions for contact lenses)	Help to wear hard contact lenses or soft contact lenses
5 (eye washes)	Irrigation of eyes, prevention of eye troubles (after swimming, or to wash out sweat or dust etc.)

別添9

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The Standards for Marketing Approval of Vitamin Preparations

1. Scope of Vitamin Preparations

Vitamin Preparations, as defined here, are oral vitamin preparations which contain one or more vitamins for the purpose of alleviating symptoms against which such a vitamin should be effective or for vitamin supplementation.

2. Standards

The following standards shall be applied to Vitamin Preparations.

For vitamin preparations which do not conform to these standards, the submission of documents regarding the efficacy, safety, and the basis for combination shall be required for review.

(1) Types of Active Ingredients

A) The types of active ingredients which may be combined in vitamin preparations are listed in the attached Table 1.

B) For preparations mainly consisting of the active ingredients listed in Column I of the attached Table 1 (hereinafter referred to as Vitamin A preparations), those mainly consisting of the active ingredients in Group 1 may include the active ingredients listed in Column II or IV of the same Table and those mainly consisting of the active ingredients in Group 2 may include the active ingredients in Group 1 of Column I, Column III, IV, or VIII.

C) Preparations mainly consisting of the active ingredients listed in Column II of the attached Table 1 (hereinafter referred to as Vitamin D preparations) may include the active ingredients listed in Group 1 of Column I, Column III, VIII, or Group 7 of Column X of the same Table.

D) Preparations mainly consisting of the active ingredients listed in Column III of the attached Table 1 (hereinafter referred to as Vitamin E preparations) may include the active ingredients listed in Column IV, Group 2 of Column V, Column VI, VII, VIII, Group 1 or 2 of Column IX, Group 2, 3, 6, or 9 of Column X, or Group 1 or 2 of Column XI of the same Table.

E) Preparations mainly consisting of the active ingredients listed in Column IV of the attached Table 1 (hereinafter referred to as Vitamin B_1 preparations) may include the active ingredients listed in Column III, V, VI, VII, Group 1 or 2 of Column IX, Group 1, 6, or 9 of Column X, or Group 1 of Column XI of the same Table.

F) Preparations mainly consisting of the active ingredients listed in Column V of the attached Table 1 (hereinafter referred to as Vitamin B_2 preparations) may include the active ingredients listed in Column IV, VI, VIII, IX, Group 4, 5, 6, or 8 of Column X, or Group 3 of Column XI of the same Table.

G) Preparations mainly consisting of the active ingredients listed in Column VI of the attached Table 1 (hereinafter referred to as Vitamin B_6 preparations) may include the active ingredients listed in Column III, IV, V, VII, VIII, IX, Group 4, 5, 6, or 8 of Column X, or Group 3 of Column XI of the same Table.

H) Preparations mainly consisting of the active ingredients listed in Column VIII of the attached Table 1 (hereinafter referred to as Vitamin C preparations) may include the active ingredients listed in Column III, V, VI, IX, or Group 4, 5, or 8 of Column X of the same Table.

I) Preparations mainly consisting of the active ingredients in Group 1 of Column I and Column II of the attached Table 1 (hereinafter referred to as Vitamin A and D preparations) may include the active ingredients listed in Column III, IV, VIII, or Group 7 of Column X of the same Table.

J) Preparations mainly consisting of the active ingredients listed in Columns V and VI of the attached Table 1 (hereinafter referred to as Vitamin B_2 and B_6 preparations) may include the

active ingredients listed in Column VIII, IX, Group 4, 5, or 8 of Column X, or Group 3 of Column XI of the same Table.

K) Preparations mainly consisting of the active ingredients listed in Columns III and VIII of the attached Table 1 (hereinafter referred to as Vitamin E and C preparations) may include the active ingredients listed in Group 2 of Column V, Column VI, Group 1 or 2 of Column IX, or Group 3 of Column X of the same Table.

L) Preparations mainly consisting of the active ingredients listed in Columns IV, VI, and VII of the attached Table 1 (hereinafter referred to as Vitamin B_1, B_6 and B_{12} preparations) may include the active ingredients listed in Column III, Group 1 or 2 of Column IX, or Group 6 of Column X of the same Table.

M) If active ingredients from Column II, III, IV, V, VI, or VII of the attached Table 1 are combined, only one active ingredient from each column may be used.

N) If active ingredients from Column VIII of the attached Table 1 are combined, no more than 2 active ingredients from the column may be used.

O) If active ingredients from Column I, IX, or Group 4 or 8 of Column X of the attached Table 1 are combined, only one active ingredient from each column or group may be used.

(2)Quantities of active ingredients

A) When the active ingredients in the attached Table 1 are used as the main ingredients of vitamin preparations, the maximum daily dose, minimum daily dose, maximum single dose, and minimum single dose shall be those given in Section A of the Table.

B) When the active ingredients in the attached Table 1 in vitamin preparations are used as active ingredients other than the main vitamins, the maximum daily dose, minimum daily dose, and maximum single dose shall be those given in Section B of the Table.

C) When 2 of the active ingredients in Column I or VIII of the attached Table 1 are combined or when 2 or more of the active ingredients in Group 7 of Column X are combined, the sum of the values obtained by dividing the amounts of each active ingredient used by their respective maximum daily dose shall not exceed one, or the sum of the values obtained by dividing the amounts of each active ingredient used by their respective minimum daily dose should be at least one.

(3)Dosage forms

The dosage forms of vitamin preparations shall be capsules, granules, pills, powders, electuaries, tablets, jelly type drops, or oral liquids.

(4)Dosage and administration

A) In principle, the dosage of vitamin preparations shall not exceed 3 doses a day.

B) Dosage and administration suggesting that the preparations may be given to infants less than 3 months of age are not permitted.

C) Hard capsules and soft capsules, pills or tablets over 6 mm in diameter intended to be taken by children less than 5 years old are not permitted.

D) Soft capsules, pills or tablets not more than 6 mm in diameter intended to be taken by children less than 3 years old are not permitted.

E) The maximum and minimum daily and single doses for people under 15 years of age shall be calculated by multiplying the maximum and minimum daily and single doses shown in the attached Table 1 by the values specified in the Coefficient column for the corresponding age ranges in the attached Table 2.

(5) Indications

The indications of vitamin preparations should be within the scope of the attached Table 3.

Attached Table 1

Classification		Active ingredient	A		B		Remarks
			Maximum daily dose	Minimum daily dose	Maximum daily dose	Minimum daily dose	
Column I	Group 1	Retinol acetate	4,000I.U.	2,000I.U.	2,000I.U.	500I.U.	as vitamin A
		Retinol palmitate	4,000I.U.	2,000I.U.	2,000I.U.	500I.U.	as vitamin A
		Vitamin A oil	4,000I.U.	2,000I.U.	2,000I.U.	500I.U.	as vitamin A
	Group 2	Cod liver oil	4,000I.U.	2,000I.U.	2,000I.U.	500I.U.	as vitamin A
		Strong cod liver oil	4,000I.U.	2,000I.U.	2,000I.U.	500I.U.	as vitamin A
Column II		Ergocalciferol	400I.U.	200I.U.	200I.U.	50I.U.	as vitamin D
		Cholecalciferol	400I.U.	200I.U.	200I.U.	50I.U.	as vitamin D
Column III		*d*-α-Tocopherol succinate	300mg (100mg)	100mg (50mg)	100mg	10mg	as *dl*-α-tocopherol succinate
		dl-α-Tocopherol succinate	300mg (100mg)	100mg (50mg)	100mg	10mg	
		dl-α-Tocopherol calcium succinate	300mg (100mg)	100mg (50mg)	100mg	10mg	
		d-α-Tocopherol acetate	300mg (100mg)	100mg (50mg)	100mg	10mg	
		dl-α-Tocopherol acetate	300mg (100mg)	100mg (50mg)	100mg	10mg	
		d-α-Tocopherol	300mg (100mg)	100mg (50mg)	100mg	10mg	
		dl-α-Tocopherol	300mg (100mg)	100mg (50mg)	100mg	10mg	
Column IV	Group 1	Thiamine hydrochloride	30mg (10mg)	1mg (1mg)	25mg (10mg)	1mg	
		Thiamine nitrate	30mg (10mg)	1mg (1mg)	25mg (10mg)	1mg	
		Bisthiamine nitrate	30mg (10mg)	1mg (1mg)	25mg (10mg)	1mg	as thiamine disulfide
		Thiamine disulfide	30mg (10mg)	1mg (1mg)	25mg (10mg)	1mg	
		Thiamine dicetylsulfate	30mg (10mg)	1mg (1mg)	25mg (10mg)	1mg	as thiamine nitrate or thiamine hydrochloride
	Group 2	Dicethiamine hydrochloride	100mg	5mg	25mg	1mg	as thiamine hydrochloride
		Fursultiamine hydrochloride	100mg	5mg	25mg	1mg	as fursultiamine
		Octotiamine	100mg	5mg	25mg	1mg	
		Cycothiamine	100mg	5mg	25mg	1mg	
		Bisibuthiamine	100mg	5mg	25mg	1mg	
		Bisbentiamine	100mg	5mg	25mg	1mg	as thiamine hydrochloride
		Fursultiamine	100mg	5mg	25mg	1mg	
		Prosultiamine	100mg	5mg	25mg	1mg	
		Benfotiamine	100mg	5mg	25mg	1mg	as thiamine hydrochloride
Column V	Group 1	Flavin adenine dinucleotide sodium	45mg	5mg	12mg	2mg	as flavin adenine dinucleotide
		Riboflavin	30mg	2mg	12mg	2mg	
		Riboflavin sodium phosphate	30mg	2mg	12mg	2mg	as riboflavin
	Group 2	Riboflavin butyrate	20mg	5mg	12mg	2mg	

Column VI		Pyridoxine hydrochloride	100mg	10mg	50mg	5mg	
		Pyridoxal phosphate	60mg	10mg	50mg	5mg	
Column VII		Hydroxocobalamin hydrochloride	1,500μg	60μg	60μg	1μg	as hydroxocobalamin
		Hydroxocobalamin acetate	1,500μg	60μg	60μg	1μg	as hydroxocobalamin
		Cyanocobalamin	1,500μg	60μg	60μg	1μg	
		Hydroxocobalamin	1,500μg	60μg	60μg	1μg	
Column VIII		Ascorbic acid	2,000mg	50mg	500mg	50mg	
		Calcium ascorbate	2,000mg	50mg	500mg	50mg	as ascorbic acid
		Sodium ascorbate	2,000mg	50mg	500mg	50mg	as ascorbic acid
Column IX	Group 1	Nicotinic acid			60mg	12mg	
		Nicotinamide			60mg	12mg	
	Group 2	Panthenol			30mg	5mg	
		Calcium pantothenate			30mg	5mg	
		Sodium pantothenate			30mg	5mg	
	Group 3	Biotin			500μg	10μg	
Column X	Group 1	Mixture of potassium aspartate and magnesium aspartate (equal mixture)			400mg	200mg	
	Group 2	Inositol hexanicotinate			400mg	80mg	
	Group 3	Ursodeoxycholic acid			60mg	10mg	
	Group 4	*L*-Cysteine hydrochloride			160mg	30mg	
		L-Cysteine			160mg	30mg	
	Group 5	Orotic acid			200mg	60mg	
	Group 6	γ-Oryzanol			10mg	5mg	
	Group 7	Calcium glycerophosphate			300mg	30mg	as calcium
		Calcium gluconate			300mg	30mg	as calcium
		Precipitated calcium carbonate			300mg	30mg	as calcium
		Calcium lactate			300mg	30mg	as calcium
		Anhydrous dibasic calcium phosphate			300mg	30mg	as calcium
		Dibasic calcium phosphate			300mg	30mg	as calcium
	Group 8	Glucuronolactone			1,000mg	200mg	
		Glucuronamide			1,000mg	200mg	
	Group 9	Sodium chondroitin sulfate			900mg	180mg	

Column XI	Group 1	Processed Garlic Bulb			200mg	20mg	
	Group 2	Ginseng	Extract (Crude drug conversion value)		3g	0.6g	
			Powder		1.5g	0.3g	
	Group 3	Coix seeds	Extract (Crude drug conversion value)		10g	1g	
			Powder		3g	0.3g	

(Note) The figures in parentheses in the maximum daily dose or minimum daily dose columns indicate the maximum or minimum single dose, respectively.

Attached Table 2

Age	Coefficient	
15 years old and over	1	(1)
11 years old·Under 15	2/3	(2/3)
7 years old·Under 11	1/2	(2/3)
3 years old·Under 7	1/3	(1/2)
1 year old·Under 3	1/4	(1/2)
6 months·Under 1	1/5	(1/2)
3 months·Under 6 months	1/6	(1/2)

(Note) The coefficients in parentheses are used for the active ingredients in Columns I and II for vitamins A, D, and A and D preparations.

Attached Table 3

Preparations		Indications
Vitamin A preparations	Preparations with Group 1 ingredients	Relief of the following symptoms: dryness of the eyes Night blindness (nyctalopia) Supplementation of Vitamin A in the following cases: during pregnancy and lactation, decreased strength during and after illness, and for growing children
	Preparations with Group 2 ingredients	Relief of the following symptoms: dryness of the eyes Night blindness (nyctalopia) Supplementation of Vitamin A and D in the following cases: during pregnancy and lactation, decreased strength during and after illness, and for growing children and the elderly
Vitamin D preparations		To treat bone and teeth developmental defects Prevention of rickets Supplementation of Vitamin D in the following cases: during pregnancy and lactation, and for growing children and the elderly

Preparations	Indications
Vitamin E preparations	Relief of the following symptoms due to peripheral circulatory disturbances: stiffness in the shoulder and neck, numbness/chills in the limbs and chilblains Relief of the following symptoms in the climacterium: stiffness in the shoulder and neck, chills, numbness in the limbs and hot flashes, irregular menstruation (A physician or pharmacist should be consulted if there is no improvement after about one month of administration) Supplementation of Vitamin E in the following case: for the elderly
Vitamin B_1 preparations	Relief of the following symptoms: neuralgia, muscle and joint pain (lumbago, stiff shoulder, frozen shoulder), numbness in the limbs, constipation, and eye strain Beriberi (A physician or pharmacist should be consulted if there is no improvement after about one month of administration) Supplementation of Vitamin B_1 in the following cases: physical fatigue, during pregnancy and lactation, decreased strength during and after illness
Vitamin B_2 preparations	Relief of the following symptoms: angular stomatitis, canker sores, stomatitis, glossitis, eczema, dermatitis, rash, sores, acne, skin roughness, rosacea, congestion of the eye, and itchy eyes (A physician or pharmacist should be consulted if there is no improvement after about one month of administration) Supplementation of Vitamin B_2 in the following cases: physical fatigue, during pregnancy and lactation, and decreased strength during and after illness
Vitamin B_6 preparations	Relief of the following symptoms: angular stomatitis, canker sores, stomatitis, glossitis, eczema, dermatitis, rash, sores, acne, skin roughness, and numbness in the limbs (A physician or pharmacist should be consulted if there is no improvement after about one month of administration) Supplementation of Vitamin B_6 in the following cases: during pregnancy and lactation, and decreased strength during and after illness
Vitamin C preparations	Relief of the following symptoms: spots, freckles, and pigmentation due to sunlight/rash Prevention of bleeding in the following cases: bleeding of the gums and nose bleeds (A physician, pharmacist, or dentist should be consulted if there is no improvement after about one month of administration) Supplementation of Vitamin C in the following cases: physical fatigue, during pregnancy and lactation, decreased strength during and after illness, and for the elderly
Vitamin A and D preparations	Relief of the following symptoms: dryness of the eyes Bone and teeth developmental defects Night blindness (nyctalopia) Prevention of rickets Supplementation of Vitamin A and D in the following cases: during pregnancy and lactation, decreased strength during and after illness, and for growing children and the elderly
Vitamin B_2 and B_6 preparations	Relief of the following symptoms: angular stomatitis, canker sores, stomatitis, glossitis, eczema, dermatitis, rash, sores, acne, and skin roughness (A physician or pharmacist should be consulted if there is no improvement after about one month of administration) Supplementation of Vitamin B_2 and B_6 in the following cases: physical fatigue, during pregnancy and lactation, and decreased strength during and after illness

Preparations	Indications
Vitamin E and C preparations	Relief of the following symptoms due to peripheral circulatory disturbances: stiffness in the shoulder and neck, numbness/chills in the limbs and chilblains Relief of the following symptoms: spots, freckles, and pigmentation due to sunlight/rash Prevention of bleeding in the following cases: bleeding of the gums and nose bleeds (A physician, pharmacist, or dentist should be consulted if there is no improvement after about one month of administration) Supplementation of Vitamin E and C in the following cases: physical fatigue, decreased strength during and after illness, and for the elderly
Vitamin B_1, B_6, and B_{12} preparations	Relief of the following symptoms: neuralgia, muscle and joint pain (lumbago, stiff shoulder, frozen shoulder), numbness in the limbs, and eye strain (A physician or pharmacist should be consulted if there is no improvement after about one month of administration) Supplementation of Vitamin B_1, B_6, and B_{12} in the following cases: physical fatigue, during pregnancy and lactation, and decreased strength during and after illness

別添 10

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The Standards for Marketing Approval of Enemas

1. Scope of Enemas

The scope of preparations subject to these standards covers medicines for rectal application formulated with the intent of treating constipation.

2. Approval Standards

The approval standards for enemas are as follows.

For preparations 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 the may be used are those listed in Table 1 for liquid preparations and those listed in Table 2 for suppositories.

(b) The active ingredients that must be included are those from Column I of Table 1 and Column I or II of Table 2.

(c) The active ingredients from Column II of Table 1 can be combined with the active ingredients from Column I.

(d) The active ingredients from Columns I and II of Table 2 may not be used in the same preparation.

(2) Quantities of Active Ingredients

(a) The maximum and minimum single doses of the active ingredients in Tables 1 and 2 are those specified in the respective tables.

(b) The concentration of glycerin in Column I of Table 1 for liquid preparations is 42% to 50%.

(3) Dosage Form

The dosage forms are liquids and suppositories.

(4) Dosage and Administration

(a) Liquid preparations

[1] When dilution is required, water should be added so that the concentration of glycerin reaches 42% to 50%.

[2] When no effect is obtained by intra-rectal administration of a single dose of the preparation, administer the same amount again.

(b) Suppositories

If no effect is obtained by the insertion of a single suppository, insert 1 more. In the case of suppositories containing ingredients from Column II of Table 2, the daily dose is limited to 0.02 g.

(c) Dosages for children under 3 years of age is not approved.

(d) For children under 12 years of age, the single dose of the active ingredients in Table 1 is that obtained by multiplying the single doses listed in the table by the coefficient for the corresponding age range in Table 3. The single dose of the active ingredients from Column I of Table 2 is that obtained by multiplying the single doses listed in the table by the coefficient in Table 4. The single dose of the active ingredients from Column II of Table 2 is that obtained by multiplying the single doses listed in the table by the coefficient in Table 5.

(5) Indications

The indication is limited to constipation.

Table 1

Liquids

Column	Active ingredient	Single dose (g)	
		Minimum	Maximum
I	Glycerin	12	18
II	D-Sorbitol	–	10

Table 2

Suppositories

Column	Active ingredient	Single dose (g)	
		Minimum	Maximum
I	Glycerin	1.5	2.5
II	Bisacodyl	0.005	0.01

Table 3

Age	Coefficient
12 years of age or over	1
6 to under 12 years of age	2/3
1 to under 6 years of age	1/3
Under 1 year of age	1/6

Table 4

Age	Coefficient
12 years of age or over	1
3 to under 12 years of age	2/3

Table 5

Age	Coefficient
12 years of age or over	1
6 to under 12 years of age	1/2
3 to under 6 years of age	1/5

別添 11

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Final revision May 15, 1998

The Standards for Marketing Approval of Anthelmintics

1. Scope of Anthelmintics

The scope of preparations subject to these standards covers all oral preparations intended to eradicate parasites (Kampo medicine* formulas are not covered).

* Kampo medicine is traditional Japanese medicine.

2. Approval Standards

The approval standards for anthelmintics are as follows.

For preparations 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 used are shown in Table 1.

(b) One or more of the active ingredients from Column A of Table 1 must be included.

(c) Preparations mainly containing active ingredients from Group 1 of Column A in Table 1 may include active ingredients from Column B or C.

(d) Preparations mainly containing active ingredients from Group 2a of Column A in Table 1 may include active ingredients from Column B.

(e) Preparations mainly containing active ingredients from Group 2b of Column A in Table 1 may include active ingredients from Group 2 of Column B, or Column D. However, the active ingredient from Group 2 of Column D may be included only when an active ingredient from Group 2 of Column B is also included.

(f) Preparations mainly containing active ingredients from Group 3 of Column A or Group 4 of Column A in Table 1 may not include any other active ingredient.

(g) Preparations mainly containing active ingredients from Groups 1 and 2 of Column A, those mainly containing active ingredients from Groups 1 and 3 of Column A, and those mainly containing active ingredients from Groups 1, 2, and 3 of Column A in Table 1 may also include active ingredients from Column B or C.

(h) In the case of Columns B and C in Table 1, only 1 active ingredient from each column may be used in the preparation.

(i) Only 1 active ingredient from Group 2 of Column A in Table 1 may be included from this group.

(2) Quantities of Active Ingredients

(a) The maximum daily dose of each of the active ingredients in Table 1 is the amount shown in this table.

(b) When an active ingredient from Group 1 of Column A in Table 1 is combined

with another active ingredient from Column A, or when active ingredients from Group 1 of Column B in Table 1 are combined, the lower limit of the daily dose is half of the maximum daily dose.

(c) When an active ingredient from Group 2 of Column A in Table 1 is combined with another active ingredient from Column A, the lower limit of the daily dose is 1/4th of the maximum daily dose.

(d) When an active ingredient from Group 3 of Column A in Table 1 is combined with another active ingredient from Column A, the lower limit of the daily dose is 3/4 of the maximum daily dose.

(e) The lower limit of the daily dose of the active ingredients from Group 4 of Column A in Table 1 is 2/5th of the maximum daily dose.

(f) The lower limit of the daily dose of the active ingredients from Group 2 of Column B, and Column D of Table 1 is 1/10th of the maximum daily dose.

(g) The lower limit of the daily dose of the active ingredients from Column C of Table 1 is 1/5th of the maximum daily dose.

(h) When 2 or more of the active ingredients from Column A of Table 1 are combined, the lower limit of the daily dose of each active ingredient is 1/5th of the maximum daily dose, and the sum of the values obtained by dividing the amount of each active ingredient combined by its maximum daily dose must be at least half, and should not exceed 2/3.

However, when 2 or more of the active ingredients only from Group 3 of Column A are combined, the sum of the values obtained by dividing the amount of each active ingredient combined by its maximum daily dose should be at least 3/4 and not exceed 1.

(i) When 2 or more of the active ingredients from Group 1 of Column D in Table 1 are combined, the sum of the values obtained by dividing the amount of each active ingredient combined by its maximum daily dose should not exceed 1.

(3) Dosage Form

The dosage forms are capsules, granules, pills, powders, tablets, decoctions (only preparations mainly containing the active ingredients from Group 2b of Column A in Table 1), chocolate tablets, and oral liquids.

(4) Dosage and Administration

(a) Dose regimen

(i) Preparations mainly containing the active ingredients from Group 1 of Column A in Table 1

Take twice a day on an empty stomach, or take once before bed after a light evening meal and once on the following morning.
Do not take more than twice in succession.

(ii) Preparations mainly containing the active ingredients from Group 2a of Column A in Table 1

Take once or twice a day on an empty stomach.
Do not take more than twice in succession.

(iii) Preparations mainly containing the active ingredients from Group 2b of Column A in Table 1

Take once or twice a day on an empty stomach.

(iv) Preparations mainly containing the active ingredients from Group 3 of Column A in Table 1

[1] For eradication of ascarids

Take once or twice a day on an empty stomach for 1 to 2 days.
Do not take for more than 2 successive days.

[2] For eradication of oxyurids

Take once or twice a day on an empty stomach for 1 week.
Do not take for more than 7 successive days.

(v) Preparations mainly containing the active ingredients from Group 4 of Column A in Table 1
Take once a day.
Do not take more than twice in succession.

(vi) Preparations mainly containing the active ingredients from Groups 1 and 2 of Column A, those mainly containing the active ingredients from Groups 1 and 3 of Column A, and those mainly containing the active ingredients from Groups 1, 2, and 3 of Column A in Table 1
Take once or twice a day on an empty stomach, or take once before bed after a light evening meal and once on the following morning.
Do not take more than twice in succession.

(b) For decoctions, the method of preparation at the time of use should be clearly described.

(c) Dosage for infants younger than 3 months of age is not approved.

(d) For capsules, and pills and tablets larger than 6 mm in diameter, dosage for children under 5 years of age is not approved.

(e) For pills and tablets, dosage for infants younger than 3 years of age is not approved, even if the diameter is less than 6 mm.

(f) The maximum daily doses for children under 15 years of age are the amounts obtained by multiplying the maximum daily dose in Table 1 by the coefficients for the respective age groups shown in Table 2.

(5) Indications

(i) Preparations mainly containing the active ingredients from Group 3 of Column A in Table 1
Eradication of ascarids and oxyurids

(ii) Preparations mainly containing the active ingredients from Group 4 of Column A in Table 1
Eradication of oxyurids

(iii) Other preparations
Eradication of ascarids

Table 1

Classification			Active ingredient	Maximum daily dose		Remarks
Column A	Group 1		Santonin	200 mg		
	Group 2	a	Kainic acid	20 mg		
		b	Digenea	Powder	Extract (converted to the crude drug amount)	
				–	10 g	
	Group 3			For ascarids	For oxyurids	
			Piperazine adipate	4000 mg	2000 mg	As piperazine hexahydrate
			Piperazine citrate	4000 mg	2000 mg	As piperazine hexahydrate
			Piperazine hexahydrate	4000 mg	2000 mg	
			Piperazine malate	4000 mg	2000 mg	As piperazine hexahydrate
			Piperazine phosphate	4000 mg	2000 mg	As piperazine hexahydrate
	Group 4		Pyrvinium pamoate	250 mg		As pyrvinium base
Column B	Group 1		Sulfur	1000 mg		
			Magnesium oxide	2000 mg		
			Dioctyl sodium sulfosuccinate	200 mg		
			Bisacodyl	20 mg		
	Group 2			Powder	Extract (converted to the crude drug amount)	
			Aloes	0.75 g	0.75 g	
			Senna Leaf	1.5 g	6 g	
			Rhubarb	3 g	4 g	
Column C			Aminoethylsulfonic acid	2000 mg		
			Bile extract (powder)	500 mg		
			Bile powder	1500 mg		
			Dehydrocholic acid	500 mg		
Column D	Group 1			Powder	Extract (converted to the crude drug amount)	
			Melia Bark	–	10 g	
			Japanese Zanthoxylum Peel	–	3 g	
			Rangoon Creeper Fruit	–	3 g	
	Group 2		Glycyrrhiza	–	3.3 g	

Table 2

Age group	Coefficient
15 years of age and over	1
11 to under 15 years of age	2/3
8 to under 11 years of age	1/2
5 to under 8 years of age	1/3
3 to under 5 years of age	1/4
1 to under 3 years of age	1/5
3 months to under 1 year of age	1/7

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Provisional Translation
from Japanese Original

Feb 1, 1991
Notification PB No.109
Final revision Jan 19, 2012

The Standards for Marketing Approval of Nasal Drops for Rhinitis

1. Scope of Nasal Drops for Rhinitis

The scope of preparations subject to these standards covers intranasal medicines intended for the relief of symptoms of rhinitis.

2. Approval Standards

The approval standards for nasal drops for rhinitis are as follows.

For preparations 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 used are shown in Table 1.
b. The active ingredients that must be included are those from Column I of Table1.
c. Active ingredients from different columns of Table 1 may be combined with each other.
d. When the active ingredients from Column I, II, III, or IV of Table 1 are combined, only 1 ingredient per column is permitted.

(2) Quantities of Active Ingredients

a. The maximum concentration of each of the active ingredients is shown in Table1.
b. The minimum concentration of each of the active ingredients from Column I of Table 1 is half of the respective maximum concentrations, and that of the active ingredients from the other columns is 1/5th of the respective maximum concentrations.

(3) Dosage Form

The dosage forms are intranasally-applied liquid preparations.

(4) Dosage and Administration

a. Preparations are to be applied intranasally not more than 6 times a day. The application method and intervals must be clearly indicated. The application interval is to be at least 3 hours.
b. Dosages for infants under 2 years of age are not approved.
c. The maximum concentrations for children under 7 years of age are half of the maximum concentration shown in Table 1.

(5) Indications

The indications are to be within the following scope: relief of the following

symptoms due to acute rhinitis, allergic rhinitis or sinusitis; stuffy nose, runny nose (excessive nasal discharge), sneezing, dull headache (heaviness in head).

(6) Packaging Units

The maximum volume of containers for liquids is limited to 30 mL.

Table 1

Classification	Active ingredient	Maximum concentration (%)
Column I	Epinephrine	0.01
	Ephedrine hydrochloride	0.5
	Tetrahydrozoline hydrochloride	0.1
	Naphazoline hydrochloride	0.05
	Phenylephrine hydrochloride	0.5
	dl-Methylephedrine hydrochloride	0.5
	Tetrahydrozoline nitrate	0.1
	Naphazoline nitrate	0.05
Column II	Iproheptine hydrochloride	0.5
	Diphenhydramine hydrochloride	0.2
	Diphenhydramine	0.2
	Chlorpheniramine maleate	0.5
Column III	Acrinol	0.05
	Cetylpyridinium chloride	0.05
	Benzalkonium chloride	0.02
	Benzethonium chloride	0.02
Column IV	Lidocaine hydrochloride	0.5
	Lidocaine	0.5
Column V	Dipotassium glycyrrhizinate	0.3
	Methyl salicylate	0.05

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Provisional Translation
from Japanese Original

Mar 22, 1995
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	

別添 14

Provisional Translation
from Japanese Original

May 15, 1998
Notification PSB No.447

The Standards Marketing Approval of Athlete's Foot and Ringworm Remedies

1 Scope of Athlete's Foot and Ringworm Remedies

The scope of preparations subject to these standards covers external medicines intended for the relief of symptoms associated with athlete's foot and ringworm 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 athlete's foot and ringworm remedies are as follows. For preparations 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 listed in Table 1.
b. At least 1 of the active ingredients from either Column I (apart from the ingredients in Groups 12 and 13) or Column II of Table 1 must be combined.
c. Active ingredients in different columns listed in Table 1 may be mutually combined.
d. When active ingredients from Column V of Table 1 are to be combined with other ingredients in the same Column, the use of only 1 ingredient is allowed.
e. Up to 3 active ingredients from Column I of Table 1 may be used. However, with the exception of undecylenic acid and zinc undecylenate in Group 1, the use of only 1 ingredient from each group is allowed. Active ingredients marked with "△" must not be combined with the other ingredients in this column.
f. When active ingredients from Group 1 of Column III or Group 1 of Column IV listed in Table 1 are to be combined, the use of only 1 ingredient from the same group is allowed.
g. Up to 3 active ingredients from Group 2 of Column III listed in Table 1 may be used. However, acetic acid should not be combined with the other ingredients in this group.
h. In Column VI, the combination of allantoin with aldioxa and the combination of glycyrrhizinic acid or its salts with glycyrrhetinic acid are not permitted. In Column VII, the combination of *d*-camphor with *dl*-camphor and the combination of mentha oil with *dl*-menthol and *l*-menthol are not permitted.

(2) Quantities of Active Ingredients

a. The maximum concentration of each of the active ingredients is shown in Table 1.
b. The minimum concentration of individual active ingredients listed in Column I (except for Groups 12 and 13) and Column II of Table 1 is 1/5th of the maximum

concentration (for ingredients with a concentration in parentheses, the minimum concentration is 1/5th of the one in the parentheses). In this case, the concentration of 1 or more ingredients must be at least half of the specified maximum concentration (for ingredients with concentrations in parentheses, the minimum concentration must be the one provided in parentheses).

c. The minimum concentration of individual active ingredients listed in Groups 12 and 13 of Column I and those listed in Columns III, IV, V, VI, VII, VIII, and IX of Table 1 is 1/10th of the maximum concentration. However, in the case of benzalkonium chloride in Group 1 of Column III, the concentration must be as listed in the maximum concentration column.

(3) Dosage Form

The dosage forms are aerosols, ointments, external liquids, and external powders.

(4) Dosage and Administration

Preparations should be applied to the skin surface several times a day. The method of application should be clearly indicated.

(5) Indications

The indications are to be within the scope of "athlete's foot, jock itch, and ringworm."

Table 1

Classification		Active ingredient	Maximum concentration (%)
Column I	Group 1	Undecylenic acid	10
		Zinc undecylenate	20
		△ Phenyl-11-iode-10-undecynoate	0.5
	Group 2	△ Exalamide	5
	Group 3	△ Clotrimazole	1
		△ Econazole nitrate	1
		△ Miconazole nitrate	1
		△ Tioconazole	1
	Group 4	△ Zinc diethyldithiocarbamate	25
	Group 5	△ Ciclopirox olamine	1
	Group 6	△ Siccanin	1 (potency)
		△ Trichomycin	15,000,000 units/100 g
		△ Pyrrolnitrin	0.5 (potency)
	Group 7	Thianthol	30
	Group 8	2,3,6-Tribromphenol caproate	2
	Group 9	Trimethylcetylammonium pentachlorophenate	2
	Group 10	△ Tolciclate	1
		Tolnaftate	2
	Group 11	△ Haloprogin	1
	Group 12	Sulfur	10
	Group 13	Hibiscus syriacus bark (converted to the crude drug amount)	10
Column II	Group 1	Salicylic acid	10 (2)
	Group 2	Zinc oxide	60 (2)
Column III	Group 1	Acrinol	0.2
		Alkylpolyaminoethyl glycine	1
		Berberine benzoate	0.5
		Isopropylmethylphenol	3
		Dequalinium chloride	0.5
		Benzalkonium chloride	0.05
		Benzethonium chloride	0.5
		Chlorhexidine hydrochloride	1
		Chlorhexidine gluconate solution	2.5
		Dequalinium acetate	1
		Hinokitiol	0.1
		Resorcin	5
	Group 2	Benzoic acid	12
		Chlorobutanol	1
		Acetic acid	2
		Phenol	2
		Iodine tincture	20

Column IV	Group 1	Diphenylpyraline hydrochloride	0.2
		Diphenhydramine hydrochloride	2
		Chlorpheniramine	0.5
		Diphenhydramine salicylate	2
		Diphenylimidazole	0.2
		Diphenhydramine	1
		Chlorpheniramine maleate	0.5
	Group 2	Crotamiton	10
Column V		Ethyl aminobenzoate	6
		Dibucaine hydrochloride	0.5
		Procaine hydrochloride	2
		Lidocaine hydrochloride	2.5
		Oxypolyethoxydodecane	3
		Dibucaine	0.5
		Lidocaine	2.5
Column VII	Group 1	Allantoin	1
		Aldioxa	0.2
		Ichthammol	6
		Glycyrrhizinic acid and its salts	1
		Glycyrrhetinic acid	1
		Methyl salicylate	2.5
		Dimethyl isopropylazulene	0.04
	Group 2	Lithospermum root (converted to the crude drug amount)	6
		Japanese angelica root (converted to the crude drug amount)	6
Column VII		*d*-Camphor	4
		dl-Camphor	4
		Thymol	2.5
		Mentha oil	0.5
		dl-Menthol	3
		dl-Menthol	3
		d-Borneol	5
Column VIII		Urea	10
		Diethyl phthalate	25
Column IX		Aluminum hydroxychloride	10

別添 15

Provisional Translation
from Japanese Original

Nov 1, 2011
Notification PFSB No.1101-1

The Standards for Marketing Approval of Antipruritic and Anti-inflammatory Drugs

1. Scope of Antipruritic and Anti-inflammatory Drugs

The scope of preparations subject to these standards covers medicines mainly containing adrenocortical hormones or antihistamines for dermal application formulated with the intent of using as antipruritic and anti-inflammatory drugs.

2. Approval Standards

The approval standards for antipruritic and anti-inflammatory drugs are as follows: For antipruritic and anti-inflammatory drugs mainly containing adrenocortical hormones or antihistamines that do not conform 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 active ingredients that may be combined in the preparations are shown in the Table.

b) At least 1 ingredient from either Column I or Column II of the Table must be combined.

c) Preparations mainly containing the active ingredients from Column I of the Table may include the active ingredients from Column II, III, IV, V, VI, VII, VIII, IX, X, or XII.

d) Preparations mainly containing the active ingredients from Column II of the Table may include the active ingredients from Column III, IV, V, VI, VII, VIII, IX, X, XI, or XII.

e) In the case of Column I, II, IV, V, VII, VIII, or IX in the Table, only 1 active ingredient from each column may be used in a preparation. When the active ingredient from Group 1 or 2 of Column X, or Group 1 or 3 of Column XII is combined, only 1 active ingredient from each group may be used in a preparation.

(2) Quantities of Active Ingredients

a) The maximum concentration of each of the active ingredients in the Table is that shown in the table.

b) The minimum concentration of each of the active ingredients listed in Columns II, III, V, VI, VIII, Groups 2 and 3 of Column X, Column XI, and Group 2 of Column XII is 1/5th of the maximum concentration (for ingredients with a concentration in parentheses, the minimum concentration must be the amount shown in the parentheses). However, in the case of preparations mainly containing the active ingredients from Group 1 of Column I or Group 2 of Column II, the minimum concentration of each active ingredient must be at

least half of the maximum concentration, and in the case of preparations mainly containing the active ingredients from Group 2 of Column I or Group 1 of Column II, the concentration is fixed to the maximum concentration.

c) The minimum concentration of each of the active ingredients listed in Column IV, VII, or IX, Group 1 of Column X, or Groups 1 and 3 of Column XII of the Table is 1/10th of the maximum concentration (for ingredients with a concentration in parentheses, the minimum concentration must be the amount shown in the parentheses).

(3) Dosage Form

The dosage forms are liquids for external use, sprays, ointments, creams, and gels. However, for sprays, preparations mainly containing the active ingredients listed in Column I of the Table are excluded.

(4) Dosage and Administration

The preparation should be applied to the skin surface several times a day. The method of application must be clearly indicated.

(5) Indications

The indications are shown by main ingredient in the following table.

Main ingredients	Indications
Group 1 of Column I	Eczema, dermatitis, miliaria, irritated skin, itching, chilblain, insect bites, urticaria
Group 2 of Column I	Eczema, dermatitis, miliaria, irritated skin, itching, insect bites, urticaria
Column II	Eczema, dermatitis, skin sore, miliaria, irritated skin, itching, chilblain, insect bites, urticaria

Table

Classification		Active ingredient	Maximum concentration (%)
Column I	Group 1	Cortisone acetate	0.5
		Dexamethasone acetate	0.025
		Dexamethasone	0.025
		Hydrocortisone acetate	0.5
		Hydrocortisone	0.5
		Prednisolone acetate	0.25
		Prednisolone	0.25
	Group 2	Hydrocortisone butyrate	0.05
		Prednisolone valerate acetate	0.15
Column II	Group 1	Isothipendyl hydrochloride	0.75
		Chlorpheniramine	0.5
		Chlorpheniramine maleate	1
		Diphenhydramine	1
	Group 2	Diphenhydramine hydrochloride	2
Column III		Crotamiton	10
Column IV		Glycyrrhizic acid and its salts	1
		Glycyrrhetic acid	1
Column V		Glycol salicylate	2
		Methyl salicylate	5
Column VI		Allantoin	1
Column VII		Isopropyl methylphenol	0.5
		Benzalkonium chloride	0.3
		Benzethonium chloride	0.1
Column VIII		Calamine	8
		Zinc oxide	37 (1.5)
Column IX		Ethyl aminobenzoate	5
		Oxy polyethoxy dodecane	3
		Dibucaine	0.5
		Dibucaine hydrochloride	0.5
		Lidocaine	2
		Lidocaine hydrochloride	2
Column X	Group1	*d*-Camphor	7 (0.1)
		dl-Camphor	7 (0.1)
	Group 2	Mentha oil	2
		dl-Menthol	5 (0.1)
		l-Menthol	5 (0.1)
	Group 3	*d*-Borneol	0.3
Column XI		Ammonia water	15
Column XII	Group 1	Tocopherol	2 (0.1)
		Tocopherol acetate	2 (0.1)
	Group 2	Panthenol	5
	Group 3	Vitamin A oil	500,000 I.U./100 g as vitamin A
		Retinol palmitate	500,000 I.U./100 g as vitamin A