(19) DANMARK

(10) DK/EP 2501384 T4

Patent- og Varemærkestyrelsen

(12) Oversættelse af ændret europæisk patentskrift

(51) Int.Cl.: *A 61 K 31/506 (2006.01)* *A 61 K 9/00 (2006.01)* *A 61 P 35/00 (2006.01)*
C 07 D 239/69 (2006.01)

(45) Oversættelsen bekendtgjort den: **2024-01-02**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om opretholdelse af patentet i ændret form: **2023-11-01**

(86) Europæisk ansøgning nr.: **10781781.9**

(86) Europæisk indleveringsdag: **2010-11-17**

(87) Den europæiske ansøgnings publiceringsdag: **2012-09-26**

(86) International ansøgning nr.: **US2010056926**

(87) Internationalt publikationsnr.: **WO2011062927**

(30) Prioritet: **2009-11-17 US 261812 P**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

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(54) Benævnelse: **Fremgangsmåde til behandling af proliferative lidelser og andre patologiske tilstande formidlede af BCR-ABL, C-KIT, DDR1, DDR2, eller PDGF-R-kinaseaktivitet**

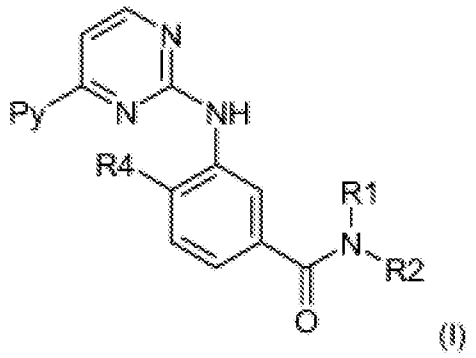
(56) Fremdragne publikationer:
WO-A1-2004/005281
WO-A1-2006/119154
HAZARIKA MAITREYEE ET AL: "Tasigna for chronic and accelerated phase Philadelphia chromosome--positive chronic myelogenous leukemia resistant to or intolerant of imatinib.", CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH 1 SEP 2008 LNKD-PUBMED:18765523, vol. 14, no. 17, 1 September 2008 (2008-09-01), pages 5325-5331, XP002621031, ISSN: 1078-0432
C. TANAKA, T. SMITH, H. KANTARJIAN, F. GILES, O. OTTMANN, K. BHALLA, K. GROUSS, V. SETHURAMAN, K. THOMAS AND H. SCHRAN: "Clinical pharmacokinetics (PK) of AMN107, a novel inhibitor of Bcr-Abl, in healthy subjects and patients with imatinib resistant or intolerant chronic myelogenous leukemia (CML) or relapsed/refractory Ph+ acute lymphocytic leukemia (Ph+ALL)", J. CLIN. ONCOL. 2006 ASCO ANNUAL MEETING PROCEEDINGS PART. I, vol. 24, no. 18S, 2006, page 3095, XP009144277,
VAN ERP N P ET AL: "Clinical pharmacokinetics of tyrosine kinase inhibitors", CANCER TREATMENT REVIEWS, SAUNDERS, US, vol. 35, no. 8, 5 September 2009 (2009-09-05), pages 692-706, XP026774941, ISSN: 0305-7372 [retrieved on 2009-09-05]
YIN OPHELIA Q P ET AL: "Effect of Grapefruit Juice on the Pharmacokinetics of Nilotinib in Healthy

Fortsættes ...

Participants", JOURNAL OF CLINICAL PHARMACOLOGY, LIPPINCOTT CO, HAGERSTOWN, MD, US, vol. 50, no. 2, 1 February 2010 (2010-02-01), pages 188-194, XP009144100, ISSN: 0091-2700, DOI: DOI:10.1177/0091270009336137
YIN O ET AL: "EFFECT OF YOGURT AND APPLESAUCE ON THE ORAL BIOVAILABILITY OF NILOTINIB IN HEALTHY SUBJECTS", JOURNAL OF CLINICAL PHARMACOLOGY, LIPPINCOTT CO, HAGERSTOWN, MD, US, vol. 50, no. 9, 1 September 2010 (2010-09-01), page 1089, XP009144158, ISSN: 0091-2700
Ophelia Q. P. Yin ET AL: "Effects of Yogurt and Applesauce on the Oral Bioavailability of Nilotinib in Healthy Volunteers", The Journal of Clinical Pharmacology, vol. 51, no. 11, 1 November 2011 (2011-11-01), pages 1580-1586, XP055121223, ISSN: 0091-2700, DOI: 10.1177/0091270010384116
Robert G. Strickley ET AL: "Pediatric drugs-a review of commercially available oral formulations", Journal of Pharmaceutical Sciences, vol. 97, no. 5, 1 May 2008 (2008-05-01), pages 1731-1774, XP055121290, ISSN: 0022-3549, DOI: 10.1002/jps.21101
Yady Manrique ET AL: "Crushed Tablets: Does the Administration of Food Vehicles and Thickened Fluids to Aid Medication Swallowing Alter Drug Release?", J Pharm Pharm Sci, 1 May 2014 (2014-05-01), pages 207-219, XP055121285, Retrieved from the Internet: URL:http://eprints.qut.edu.au/71945/1/2102 0-54199-1-PB_Crushing.pdf [retrieved on 2014-06-03]
European Medicines Agency, publication of a decision on a Paediatric Investigation Plan covering nilotinib (Tasigna, 18 May 2009 (2009-05-18), Retrieved from the Internet: URL:http://www.ema. europa .eu/ema/index.jsp?curl=pages/includes/docu ment/docu ment_deta.jsp?webContentId=WC500005412&mid =WCOb01ac058009a3dc [retrieved on 2016-10-05]

Description

[0001] The present invention relates to a regimen for the administration of a pyrimidylaminobenzamide of formula I



(I)

wherein
Py denotes 3-pyridyl,
R_1 represents hydrogen,
R_2 represents 5-(4-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)-phenyl; and
R_4 represents methyl;
or of a pharmaceutically acceptable salt thereof,
for use in the treatment of chronic myeloid leukemia (CML).

[0002] The compound of formula I, wherein Py denotes 3-pyridyl, R_1 represents hydrogen, R_2 represents 5-(4-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)-phenyl and R_4 represents methyl, is known under the International Non-proprietary Name "nilotinib". Nilotinib (4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-*N*-[5-(4-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)phenyl] benzamide) is approved and marketed in the form of its monohydrochloride monohydrate salt under the brand name Tasigna™. Nilotinib is an ATP-competitive inhibitor for Bcr-Abl and also inhibits c-Kit, DDR1, DDR2 and PDGF-R kinase activity at clinically relevant concentrations (see M. Hazarika et al., Clin. Cancer Res. 2008; 14(17): 5325-5331, and N. P. van Erp et al., Cancer Treatment Reviews 2009; 35: 692-706). Tasigna™ is available as 200 mg hard gelatin capsule for oral administration for the treatment of Philadelphia-positive chronic myeloid leukaemia (CML) in the chronic phase (CP) and accelerated phase (AP) in patients resistant to or intolerant of at least one prior therapy including imatinib. For the treatment of CML a daily dose of 800 mg of nilotinib is applied in two doses of 400 mg each.

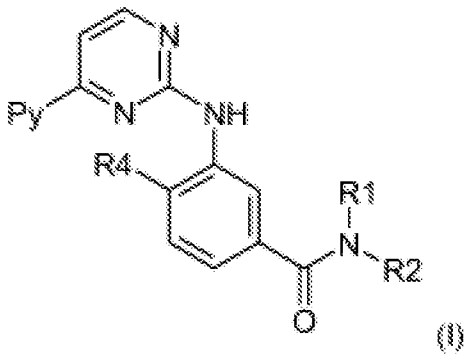
[0003] The effect of food on the pharmacokinetic parameters of 400 mg oral dose of nilotinib in the capsule formulation mentioned above was studied in human subjects. The concomitant administration of nilotinib with food significantly increased subjects exposure. In said study the total exposure (AUC_{0-t}) was 82 % (see C. Tanaka et al., J. Clin. Oncol. 2006 ASCO Annual Meeting Proceedings, vol. 24, no. 18S, p. 3095) and C_{max} was 112 % after a high fat breakfast, whereas the increase in total exposure (AUC_{0-t}) was 29 % and C_{max} was 55 % after a light breakfast given 30 minutes prior to dosing. In view of these findings, it is recommended that nilotinib shall not be taken with a meal in order to minimize the effect of food on nilotinib bioavailability. A statement in this regard is, for instance, included in sections 4.2, 4.4 and 4.5 of the SPC (Summary of Product Characteristics) of the marketing authorization for Tasigna™ issued by the European Medicines Agency (EMEA). Concurrent intake of grapefruit juice also resulted in a modest increase in nilotinib absorption; C_{max} increased by 60% and AUC increased by 29% (Yin OQ, Gallagher N, Li A, et al. J Clin Pharmacol. 2010; 50:188-194).

[0004] Certain patients, for instance elderly patients and pediatric patients, sometimes have difficulties to swallow hard gelatin capsules as a whole. For those patients, suffering from a proliferative disorder, particularly a solid and liquid tumor disorder, or other pathological conditions mediated by Bcr-Abl, c-Kit, DDR1, DDR2 or PDGF-R kinase activity, an alternative dosage form for nilotinib is required. For pediatric patients also dosage flexibility is desirable in order to allow dosage adjustment in accordance with body weight.

[0005] It was now surprisingly found that the problem described above can be resolved by oral administration of nilotinib dispersed in a fruit preparation.

[0006] More specifically, as shown in the Examples, a single oral administration of 400 mg nilotinib (contents of two 200 mg nilotinib capsules), each dispersed in one teaspoon of applesauce is bioequivalent to a single oral administration of 400 mg nilotinib given as intact capsules. However, the same amount dispersed in plain non-fat yogurt is not found to be bioequivalent.

[0007] Hence, disclosed herein is a method of treating chronic myeloid leukemia (CML) comprising oral administration of an effective dose of a pyrimidylaminobenzamide of formula I



(I)

wherein the radicals have the meanings as provided above, or of a pharmaceutically acceptable salt thereof, and, optionally, other pharmaceutically acceptable carriers, dispersed in apple sauce, to a human patient in need thereof.

[0008] The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings, unless otherwise indicated:
Where the plural form is used for compounds, salts, and the like, this is taken to mean also a single compound, salt, or the like.

[0009] Pyrimidylaminobenzamides within the scope of formula I, wherein py is 3-pyridyl and the process for their manufacture, pharmaceutical compositions containing the same as well as the use for treatment of neoplastic diseases, in particular leukemia, are disclosed in WO 04/005281. WO 2006/119154 discloses the use of said compound for the treatment of systemic mastocytosis.

[0010] Pharmaceutically acceptable salts of pyrimidylaminobenzamides of formula I, wherein py is 3-pyridyl, are especially those disclosed in WO2007/015871. In one preferred embodiment nilotinib is employed in the form of its monohydrochloride monohydrate. WO2007/015870 discloses certain polymorphs of nilotinib and pharmaceutically acceptable salts thereof useful for the present invention. A suitable formulation for the administration of nilotinib monohydrochloride monohydrate is described in WO2008/037716.

[0011] As used herein, the expression "a proliferative disorder or other pathological conditions mediated by Bcr-Abl, c-Kit, DDR1, DDR2 or PDGF-R kinase activity" activity means melanoma, especially melanoma harboring c-KIT mutations, breast cancer, cancer of the colon, lung cancer, cancer of the prostate or Kaposi's sarcoma, gastrointestinal stromal tumors (GIST), acute myeloid leukemia (AML), leukemia which responds to an inhibition of the Abl tyrosine kinase activity, such as chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL), mesothelioma, systemic mastocytosis, hypereosinophilic syndrome (HES), fibrosis, especially hepatic fibrosis and renal fibrosis, rheumatoid arthritis, polyarthritis, scleroderma, lupus erythematosus, graft-versus host diseases, neurofibromatosis, pulmonary hypertension, especially, pulmonary arterial hypertension, Alzheimer's disease, seminomas and dysgerminomas and psoriasis. Preferably, the regime described herein is applied in the following disorders and conditions: GIST, CML, Ph+ ALL, systemic mastocytosis, HES, fibrosis, scleroderma, neurofibromatosis and pulmonary arterial hypertension.

[0012] As used herein, the expression "C_{max}" means maximum peak concentration in plasma.

[0013] As used herein, the expression "AUC" means area under the plasma concentration curve.

[0014] The language "oral administration of a pyrimidylaminobenzamide of formula I dispersed in a fruit preparation" as used herein preferably means that the compound of formula I alone or together with at least one suitable pharmaceutical carrier is dispersed in a fruit preparation and administered, preferably manually, to the mouth of the human patient with a suitable device, e.g. a spoon. If desired, 100 to 250 ml of water can be consumed together with the fruit preparation.

[0015] As used herein, the term "fruit preparation" means a juice, sauce or puree prepared from apples. In one preferred embodiment of the invention, the fruit preparation employed is applesauce. Suitable applesauce is available under the brands Andros® applesauce, Mott's® applesauce and Odenwald Apfelmus (Odenwald-Früchte GmbH, Germany). Grapefruit is known to affect the kinetics of drug up-take in human patients. Hence, the term "fruit preparation" does not encompass any juice, sauce or puree prepared from grapefruit.

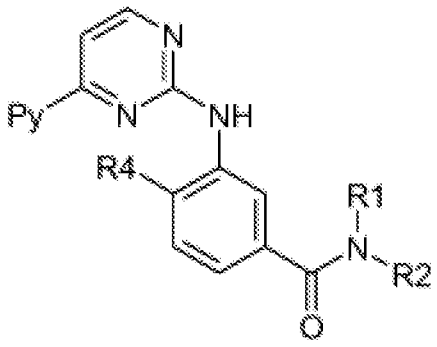
[0016] For the purposes of the present invention, the total daily dose of nilotinib can be adjusted to the needs of the patients depending, in particular on the disease to be treated and the disease status of the patient under treatment, but in any event will not exceed a total daily dose of 800 mg.

[0017] In one embodiment of the invention, the content of two 200 mg nilotinib capsules as disclosed in WO2008/037716 are each dispersed in one teaspoon of applesauce resulting in a single oral administration of 400 mg nilotinib.

[0018] Preferably, the mixture of the compound of formula I dispersed in fruit preparation should be taken immediately after its preparation, wherein "immediately" for the purpose of the present invention means within a time frame of 30 minutes, preferably within 15 minutes, more preferably within 5 minutes and most preferably within 2 minutes after

preparation.

[0019] The instant invention relates to a pyrimidylaminobenzamide of formula I

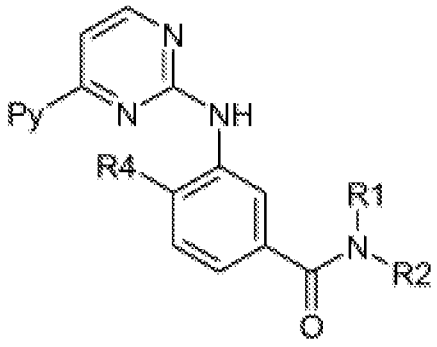


(I),

wherein

Py denotes 3-pyridyl,
R_1 represents hydrogen,
R_2 represents 5-(4-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)-phenyl; and
R_4 represents methyl;
or a pharmaceutically acceptable salt thereof, for use in the treatment of chronic myeloid leukemia CML wherein the compound of formula (I) or a pharmaceutically acceptable salt thereof and, optionally, pharmaceutically acceptable carriers, is orally administered dispersed in apple sauce.

[0020] Furthermore, disclosed herein is the use of a pyrimidylaminobenzamide of formula I



(I),

wherein

Py denotes 3-pyridyl,
R_1 represents hydrogen,
R_2 represents 5-(4-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)-phenyl; and
R_4 represents methyl;
or a pharmaceutically acceptable salt thereof,
for the manufacture of a medicament for the treatment of chronic myeloid leukemia (CML)
wherein the medicament is designated to be dispersed in apple sauce, optionally together with pharmaceutically acceptable carriers, and orally administered to a human patient in need thereof.

EXAMPLES

Example 1: In vitro stability tests

[0021] The content of nilotinib capsules prepared as disclosed in WO2008/037716 is dispersed in yogurt or applesauce. It is shown that nilotinib is stable at room temperature for 15 minutes with mean nilotinib recovery between 97.6 to 99.9 %.

Example 2: Randomized, open label, three-period crossover single-center study in 48 healthy subjects comparing the bioavailability of nilotinib when administered as intact capsule or the capsule content mixed with yogurt or applesauce in healthy volunteers (HV)

[0022] The HV between 18 and 65 years obtain under fasted conditions either a single oral administration of 400 mg nilotinib with two intact 200 mg nilotinib capsules (treatment A); a single oral administration of 400 mg nilotinib with the content of two 200 mg nilotinib capsules each dispersed in one teaspoon of non-fat plain yogurt (treatment B); or a single oral administration of 400 mg nilotinib with the content of two 200 mg nilotinib capsules each dispersed in one teaspoon of applesauce (treatment C). Serial blood samples for serum nilotinib concentration determination are collected for up to 72 hous after each nilotinib administration. All treatments were administered with 240 mL of water, in the morning, after an overnight fast of at least 10 hours. Subjects continued to fast until 4 hours after administration. Standardized meals were served at 4 hours (lunch) and 10 hours (dinner) after nilotinib administration. Consumption of grapefruit, grapefruit juice, or any caffeinated beverages within 48 hours of study initiation was prohibited.

[0023] Serum nilotinib concentrations were determined from blood samples collected at pre-dose (0 hour) and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, and 72 hours post-nilotinib administration on days 1, 13, and 25. At each time point, 2.5 mL of whole blood was drawn using a Serum Separator Vacutainer® (Becton, Dickinson and Company, Franklin Lakes, New Jersey, USA) tube. The tube was allowed to stand vertically at room temperature for 30 minutes prior to centrifugation at 5°C for 10 minutes at 1100 g. Immediately after centrifugation, the upper serum sample was transferred and stored frozen at ≤ -15°C until shipped to the analytical site for sample analyses.

[0024] Serum concentrations of nilotinib were measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay as described previously, with slight modifications (Larson RA, le Coutre PD, Reiffers J et al. J Clin Oncol 28:7s, 2010 (suppl; abstr 6501)). Nilotinib and the internal standard, [M+4]nilotinib, were extracted from a 100 μL serum sample with 700 μL of methyl tertiary-butyl ether (MTBE). The MTBE layer was transferred, evaporated to dryness, and reconstituted with 400 μL of an acetonitrile and 0.2% formic acid mixture (40:60, v/v). Chromatography was carried out using a Phenomenex Synergi™ Polar-RP column (particle size 4 μm, 50 mm x 2 mm i.d.) (Phenomenex, Inc, Torrance, California) held at room temperature. Elution of the analytes was performed using a isocratic elution at a flow rate of 0.5mL/min with mobile phases of 0.2% formic acid in 10 mM aqueous ammonium formate : 0.2% formic acid in acetonitrile (60:40, v/v). Detection was performed by MS/MS in positive ion mode on a Sciex API4000 mass spectrometer (Applied Biosystem, USA) with multiple reaction monitoring of m/z 530→289 for nilotinib and 534→293 for the internal standard. The lower limit of quantification for nilotinib was 2.50 ng/mL using a 100 μL serum sample. Precision of the assay at each QC level was <11% and the accuracy ranged from 95.2% to 104.3%.

[0025] Following the administration of a single oral dose of 400-mg nilotinib as two 200-mg intact capsules, the peak serum concentration of nilotinib occurred at a median time (t_{max}) of 4.0 hours, and the C_{max} values averaged 398 ng/mL. The mean $t_{1/2}$ of nilotinib was found to be 19.8 hours. These results are in agreement with those observed in previous studies in healthy volunteers who received a same 400-mg oral dose of nilotinib as intact capsules. Compared with the administration of 400-mg nilotinib as two 200-mg intact capsules (Treatment A), the systemic exposure of nilotinib was found to be generally higher following the administration of nilotinib as two capsule contents (400 mg) mixed with yogurt (Treatment B). The geometric mean values of C_{max}, $AUC_{0\text{-tlast}}$, and $AUC_{0\text{-inf}}$ of nilotinib were increased by 31%, 11%, and 8% respectively. The 90% CIs of the geometric mean ratio (Treatment B vs A) of nilotinib C_{max}, $AUC_{0\text{-t}}$ and $AUC_{0\text{-}\infty}$ were 1.22-1.41, 1.05-1.06, and 1.02-1.15, respectively.

[0026] Administration of the contents of two nilotinib capsules (400 mg) dispersed in applesauce (Treatment C), showed similar exposure compared with administration of nilotinib as intact capsules (Treatment A). The geometric mean ratio (Treatment C vs A) of nilotinib C_{max}, $AUC_{0\text{-tlast}}$, and $AUC_{0\text{-inf}}$ was 0.95, 0.99, and 0.97 respectively, and the corresponding 90% CIs were 0.88-1.02, 0.94-1.04, and 0.90-1.03 respectively.

[0027] The results are summarized in Table 1.

Table 1: Study Results

PK Parameter	Geometric mean		Ratio and 90% CIs BvsA
	Treatment A (intact capsule)	Treatment B (mixed with yogurt)	
Tmax (h)	4.0	4.0	-0.02 (-8.0, 6.0)
Cmax (ng/mL)	398	525	1.31 (1.22 - 1.41)
AUC0-t (ng*h/mL)	11 223	12 559	1.11 (1.05 - 1.16)
AUC0-∞ (ng*h/mL)	11 965	13 655	1.08 (1.02 - 1.15)
$t_{1/2}$ (h)	19.7	21.0	NA

(continued)

	Treatment A (intact capsule)	Treatment C (mixed with applesauce)	Ratio and 90% CIs C vs A
Tmax (h)	4.0	3.0	-0.02 (-6.00, 6.07)
Cmax (ng/mL)	398	378	0.95 (0.88 - 1.02)
AUC0-t(ng*h/mL)	11 223	11 214	0.99 (0.94 - 1.04)
AUC0-∞ (ng*h/mL)	11 965	12 105	0.97 (0.90 - 1.03)
$t_{1/2}$ (h)	19.7	20.6	NA

[0028] The studies allow the following conclusions:

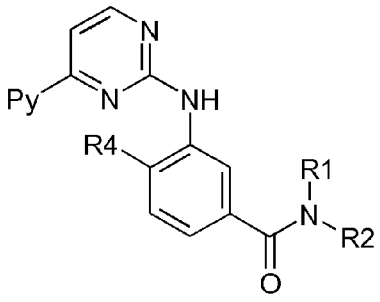
- Single oral administration of 400 mg nilotinib, with two 200 mg nilotinib capsules content, each dispersed in one teaspoon of non-fat plain yogurt is not bioequivalent to a single oral administration of 400 mg nilotinib given as intact capsules.

- Single oral administration of 400 mg nilotinib, with two 200 mg nilotinib capsules content, each dispersed in one teaspoon of applesauce is bioequivalent to a single oral administration of 400 mg nilotinib given as intact capsules.

[0029] The studies also show that the administration of nilotinib in a fruit preparation is safe and well tolerated by human subjects.

PATENTKRAV

1. Pyrimidylaminobenzamid af formlen (I)



(I),

hvor

Py betegner 3-pyridyl,

R_1 repræsenterer hydrogen,

R_2 repræsenterer 5-(4-methyl-1H-imidazol-1-yl)-3-(trifluor-methyl)-phenyl; og

R_4 repræsenterer methyl;

eller et farmaceutisk acceptabelt salt deraf, til anvendelse til behandling af kronisk myeloid leukæmi (CML), hvor forbindelsen af formel (I) eller et farmaceutisk acceptabelt salt deraf og eventuelt, farmaceutisk acceptable bærere, indgives oralt dispergeret i æblemos.

2. Pyrimidylaminobenzamid af formlen (I) til anvendelse i overensstemmelse med krav 1 i form af dets monohydrochlorid-monohydratsalt.