NEW CRYSTALLINE MODIFICATION OF 2-(3,5-BIS-TRIFLUOROMETHYL-PHENYL)-N-[6-(1,1-DIOXO-1,2\textsuperscript{a},THIOMORPHOLIN-4-YL)-(4-FLUORO-2-METHYL-PHENYL)-PYRIDIN-3-YL]-N-METHYL-ISOBUTYRAMIDE

Abstract: The present invention relates to a new crystalline modification of 2-(3,5-bis-trifluoromethylphenyl)-N-[6-(1,1-dioxo-1,2\textsuperscript{a},thiomorpholin-4-yl)-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide characterized by the following X-ray diffraction pattern obtained with a Cu\textsubscript{kα} radiation at 2\textTheta= 4.5, 6.4, 7.5, 7.7, 8.0, 8.2, 10.0, 10.2, 10.9, 11.1, 12.9, 13.4, 14.0, 14.5, 15.1, 15.6, 16.2, 16.5, 17.3, 17.5, 18.0, 18.9, 19.3, 19.5, 19.9, 20.1, 20.6, 21.0, 21.4, 22.7, 23.1 and 23.6 and an infrared spectrum having sharp bands at 2925, 2845, 1637, 1604, 1484, 1395, 1375, 1285, 1230, 1172, 1125, 1082, 999, 943, 893, 863, 860, 782, 705, 684 cm\textsuperscript{-1}, and wherein the extrapolated melting point (DSC) is 137.2°C.
New crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1$\lambda^6$-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide

The present invention relates to a novel crystalline form of

![Chemical Structure](image)

2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1$\lambda^6$-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide (modification A).

It has been found that 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1$\lambda^6$-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide can be isolated, depending upon the method of preparation, in 3 different crystalline modifications (A, B and C) and in amorphous form which are distinguishable by their infra-red spectra, X-ray powder diffraction patterns and their melting behaviour.

2-(3,5-bis-Trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1$\lambda^6$-thiomorpholin-4-yl)-4-(4-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide in its modification B is known and described in PCT/EP02/08311.

2-(3,5-bis-Trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1$\lambda^6$-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide has been described as active on the NK1 receptor for the treatment of diseases, related to this receptor, such as migraine, rheumatoid arthritis, asthma, bronchial hyperreactivity, inflammatory bowel disease or for the treatment of disorders including Parkinson’s disease, anxiety, depression, pain, headache, Alzheimer’s disease, multiple sclerosis, oedema, allergic rhinitis, Crohn’s disease, ocular injury, ocular inflammatory diseases, psychosis, motion
sickness, induced vomiting, emesis, urinary incontinence, psychoimmunologic or psychosomatic disorders, cancer, withdrawal symptoms of addictive drugs from opiates or nicotine, traumatic brain injury or benign prostatic hyperplasia.

Now it has been found that the A modification of the above mentioned compound has an improved pharmaceutical profile, especially in the case of oral administration. The compound can be formulated at high concentrations in a composition further comprising certain selected adjuvants. Such formulations have a better substance resorption and thus an improved bioavailability compared with formulations which contain 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide in its B or C modification.

Amorphous material has also an improved bioavailability in an micro-suspension form, but this form is not suitable for oral administration in human.

2-(3,5-bis-Trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide in its modification B may be prepared in accordance with PCT/EP02/08311 or in its modifications A, B and C or amorphous form via the new higher yielding route as described below:
**N-tert-Butyl-6-chloro-4-(4-fluoro-2-methyl-phenyl)-nicotinamide**

3.4 g Magnesium (137.5 mmol) was suspended under argon in 12.0 ml tetrahydrofuran and treated under reflux with a solution of 17.6 ml (137.3 mmol) 2-bromo-5-fluorotoluene in 20 ml tetrahydrofuran. After the addition of the first 3 ml of this solution, the mixture was warmed to start the Grignard reaction. The reaction mixture was stirred for 30 minutes under reflux, cooled to 50 °C and added within 10 minutes to a solution of 10.0 g (97 %, 45 mmol) N-tert-butyl-6-chloronicotinamide in 50 ml tetrahydrofuran (exothermic reaction). The mixture was stirred at 70 °C for 2 hours, cooled to room temperature and a solution of 17.4 g (68.6 mmol, 1.5 eq.) iodine in 100 ml tetrahydrofuran was added slowly (exothermic reaction). The resulting suspension was stirred for 1.7 hours at 50 °C, treated at room temperature with 50 ml water, poured onto 150 ml 2 N aqueous sulfuric acid and treated with 150 ml tert-butyl-methyl-ether. After vigorous stirring, the phases were separated and the organic phase was washed with half-saturated aqueous sodium bicarbonate and with half-saturated aqueous sodium chloride. The aqueous phases were extracted with tert-butyl-methyl-ether. The combined organic extracts were dried, concentrated in a rotary evaporator and dried under high vacuum at room temperature to provide 17.3 g of a yellow oil. This oil was dissolved in
dichloromethane and filtered through silica gel eluting with hexane and then with dichloromethane. The fractions with the product were collected and concentrated under reduced pressure to a volume of ca. 200 ml to which 400 ml hexane was added. The solution was concentrated in a rotary evaporator to a volume of ca. 150 ml, the suspension obtained was treated with 200 ml hexane and stirred for 2 hours at 4 °C. The precipitate was filtered off, washed with cold hexane/ethyl acetate 19/1(-20°C) and dried under high vacuum to yield 8.0 g (55 %) N-tert-butyl-6-chloro-4-(4-fluoro-2-methyl-phenyl)-nicotinamide as a light beige powder. The mother liquors were concentrated in a rotary evaporator providing 8.5 g of an orange solid, which was purified by chromatography on silica gel eluting with hexane and then with hexane/ethyl acetate 9/1. The fractions with the product were collected, concentrated and dried under high vacuum to yield 3.8 g (25 %) N-tert-butyl-6-chloro-4-(4-fluoro-2-methyl-phenyl)-nicotinamide as a light beige powder.

MS (ISP):m/e = 321 (M+H+, 36), 273 (M-tBu, 100).

N-tert-Butyl-4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-nicotinamide

9.3 g (29.0 mmol) N-tert-Butyl-6-chloro-4-(4-fluoro-2-methyl-phenyl)-nicotinamide was dissolved in 28.0 ml dimethylsulfoxide and 7.0 g (50.7 mmol) potassium carbonate followed by 4.2 ml (43.5 mmol) thiomorpholine was added. The resulting suspension was stirred at 130 °C for 17 hours, cooled to room temperature and partitioned between120 ml ethyl acetate and 250 ml half-saturated aqueous sodium chloride solution. The phases were separated and the organic phase was washed with half-saturated aqueous sodium chloride. The aqueous phases were extracted with ethyl acetate. The combined organic extracts were dried and concentrated in a rotary evaporator to give 21.4 g of a yellow oil. This oil was heated to 80 °C and 214 ml n-hexane was added dropwise to obtain a refluxing suspension, which was let to cool to room temperature and further stirred at 0 °C for one hour. The precipitate was filtered off, washed with cold n-hexane/ethyl acetate 9:1 and dried in a vacuum oven to yield 10.1 g (90 %) N-tert-Butyl-4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-nicotinamide as a light beige powder of m.p. = 163.7-168.7 °C.

MS (ISP):m/e = 388 (M+H", 100).

4-(4-Fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-nicotinamide

9.7 g (25 mmol) N-tert-Butyl-4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-nicotinamide suspended in 48.5 ml toluene was heated to 95 °C and 24.0 g
methanesulfonic acid was added dropwise giving an emulsion, which was stirred at 100 °C for two hours. After cooling to room temperature, the phases were separated and the organic phase was washed with deionized water. The combined aqueous phases were cooled to 0 °C and 28 % aqueous sodium hydroxide was slowly added to increase the pH to ca. 12.5. The suspension obtained was extracted with dichloromethane. The combined organic extracts were dried and concentrated in a rotary evaporator. 100 ml Propyl acetate was added and the solution was concentrated in a rotary evaporator. A second portion of 100 ml propyl acetate was added and the solution was concentrated to ca. 23 g, forming a suspension to which 8.3 ml n-hexane was added. The suspension was stirred at 0 °C for one hour. The precipitate was filtered off, washed with n-hexane/propyl acetate 9:1 and dried in a vacuum oven to yield 8.0 g (97 %) 4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-nicotinamide as a light yellow powder of m.p. = 198-202 °C.

MS (ISP): m/e = 332 (M+H⁺, 100).

[4-(4-Fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-pyridin-3-yl]-carbamic acid methyl ester

10.5 g (31.7 mmol) 4-(4-Fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-nicotinamide were added to a solution of 5.8 g (88.9 mmol) potassium hydroxide in 60 ml methanol cooled to 0 °C. 40 ml Methanol was further added and 11.5 g (35 mmol) (diacetoxyiodo)benzene was added in one portion (exothermic). After two hours at 0 °C, the reaction mixture was allowed to warm to room temperature, diluted with 250 ml deionized water and concentrated in a rotary evaporator. The residue was diluted with 200 ml ethyl acetate, the phases were separated and the aqueous phase was extracted further with ethyl acetate. The organic phases were washed with half-saturated aqueous sodium chloride. The combined organic extracts were dried, concentrated under reduced pressure and dried under high vacuum to yield 14.9 g [4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-pyridin-3-yl]-carbamic acid methyl ester as a brown sticky oil which was used in the next step without purification.

MS(ISP): m/e = 362 (M + H⁺, 100).

Methyl-[4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-pyridin-3-yl]-amine

43.7 ml Red-Al (3.5 M in toluene) was diluted in 25 ml toluene and added dropwise to a solution of 13 g (30.6 mmol) [4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-pyridin-3-yl]-carbamic acid methyl ester in 55 ml toluene at 10 °C (the addition was exothermic). The yellow solution obtained was stirred for 40 minutes at room
temperature and 1.5 hours at 50 °C. It was cooled to 0 °C and poured slowly onto a mixture of 150 ml 4 N aqueous sodium hydroxide and 50 ml ice (very exothermic). After 10 minutes stirring, the phases were separated, the aqueous phase was extracted with tert-butyl-methyl-ether and the organic phases were washed with brine. The combined organic extracts were dried and concentrated under reduced pressure to yield 10 g methyl-\[4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-pyridin-3-yl]-amine as a brown oil which was used in the next step without further purification.

MS (ISP): m/e = 350 (M + Na⁺, 17), 318 (M+H⁺, 100).

2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N\[4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-pyridin-3-yl]-isobutyramide

A solution of 8.5 g (26.6 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride in 12 ml dichloromethane was added dropwise at room temperature to a solution of 8.0 g (24.2 mmol) methyl-\[4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-pyridin-3-yl]-amine and 4.7 ml (33.9 mmol) triethylamine in 65 ml dichloromethane. The reaction mixture was stirred for 1 hour and poured onto 50 ml 1 N aqueous sodium hydroxide. After extraction the phases were separated, the aqueous phase was extracted with dichloromethane and the organic phases were washed with water. The combined organic extracts were concentrated under reduced pressure and the solvent was exchanged for 150 ml ethanol. The solution was seeded at 40 °C with some crystals, 30 ml water were slowly added and the system was stirred for 1 hour at room temperature and for 1 hour at 0 °C. The precipitate was filtered off, washed with cold ethanol (0 °C) and dried under high vacuum to yield 13.0 g (76 % over 3 steps) 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N\[4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-pyridin-3-yl]-isobutyramide as an off-white powder of m.p.= 168–170 °C.

MS (ISP): m/e = 600 (M+H⁺, 100), 279 (31).

2-(3,5-Bis-trifluoromethyl-phenyl)-N\[6-(1,1-dioxo-1λ₆-thiomorpholin-4-yl)]-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide

5.0 g (8.3 mmol) 2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N\[4-(4-fluoro-2-methyl-phenyl)-6-thiomorpholin-4-yl-pyridin-3-yl]-isobutyramide was suspended in 50 ml methanol and treated at room temperature with 6.4 g (10.4 mmol) oxone. The suspension was stirred for 16 hours at room temperature, cooled to 0 °C and 3.4 ml (16.7 mmol) sodium hydrogen sulfite solution was added dropwise. The stirring was pursued
for 30 minutes at room temperature and the pH adjusted to ca. 8.5 with saturated aqueous sodium carbonate. The methanol was evaporated under reduced pressure and the residue was extracted with dichloromethane. The organic phase was washed with half-saturated aqueous sodium chloride. The solvent was exchanged under reduced pressure in a rotary evaporator with 60 ml isopropanol and the volume reduced to ca. 40 ml. The solution was cooled to room temperature under stirring within 2 hours and stirred further for 1 hour. The precipitate formed was filtered off, washed with 5 ml isopropanol and dried under high vacuum to yield 4.4 g (83.5%) 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxothiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide as a white powder of m.p. = 135-138 °C.

$^{1}$H-NMR (CDCl$_3$, 300 MHz): 8.02 [s, 1H], 7.78 [s, 1H], 7.65 [s, 2H], 6.97 [s, 3H], 6.58 [s, 1H, 8 $H_{aom}$]; 4.17 [m, 4H, CH$_2$-N-CH$_2$]; 3.07 [t, 4H, CH$_2$-SO$_2$-CH$_2$]; 2.60 – 2.12 [m, 6H], 1.52 – 1.20 [m, 6H, 4 CH$_3$.]

MS (ISP): m/e = 673 (M+CH$_3$CN+H$^+$, 36), 650 (29), 649 (M+NH$_3$+, 94), 633 (34), 632 (M+H$,^+$, 100), 279 (73).

The different modifications A, B and C and the amorphous form may be prepared from 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxothiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide as follows:

Preparation of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1$\lambda^6$-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide

(Modification A):

10.0 g of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1$\lambda^6$-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide were dissolved in 78.5 g of 2-propanol at reflux conditions. After polishing filtration, the solution was stirred and linearly cooled from 75 °C to 10 °C over a period of 6 h. The slurry was stirred for additional 4 h at 10 °C, before the crystals were harvested by filtration. The colorless solid was rinsed with 8.0 g of cold 2-propanol (10 °C) and dried in vacuum (5 mbar) at 80 °C for 12 h, yielding 9.1 g (91%) of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxothiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide in crystal modification A.

Crystal modification A can also be prepared using 1-propanol instead of 2-propanol, but otherwise following the protocol above. Alternatively, crystal modification A is obtained
from any other modification known by digestion with 1-propanol, 2-propanol or a mixture of ethanol/dichloromethane/water.

**Preparation of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide**

(Modification B):

4.0 g of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide were dissolved in 19.8 g of ethanol at 75 °C. After polishing filtration, the solution was stirred and linearly cooled from 75 °C to 20 °C over a period of 48 h. After filtration, the colorless solid was rinsed with 4.75 g of ethanol and dried in vacuum (5 mbar) at 60 °C for 6 h, yielding 3.4 g (84%) of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide in crystal modification B.

Alternatively, crystal modification B is obtained by digestion of any other modification known with acetonitrile, cyclohexane, ethanol, n-hexane, methanol, methyl t-butyl ether or water.

**Preparation of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide**

(Modification C):

3.0 g of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide in modification A were incubated at 120 °C in vacuum (5 mbar) for 3 days. After cooling to ambient temperature 2.9 g (97%) slightly beige crystals of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide in crystal modification C were obtained.

**Preparation of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide**

(Amorphous):

A solution of 40 g 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide in 400 g dichloromethane was rapidly vacuum concentrated at room
temperature using a rotary evaporator. The resulting slightly beige foam was further
dried in vacuum (5 mbar) at ambient temperature for 12 h, yielding 39 g (98 %) 2-(3,5-
bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1,6-thiomorpholin-4-yl)-4-(4-fluoro-2-
methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide in amorphous state.

Alternatively, amorphous material is obtained by fast evaporation of solutions in
dioxane, ethyl acetate, isopropyl acetate, methyl ethyl ketone or tetrahydrofurane.

The crystal modifications and the amorphous material may clearly be distinguished
by their physicochemical data as described below:

Physicochemical characterization of the different crystal modifications:

**XRPD (X-Ray Powder Diffraction)**

XRPD patterns were recorded on a Bruker D8 diffractometer in reflexion mode.
Measuring time 1 second per step, step size 0.02 degree and copper K-Alpha 1 radiation
(1.54056 Å) at 40 KV, 50 mA. The samples were measured between 2 and 42 2Theta (2θ).
The crystal modifications A, B and C and the amorphous material can clearly be
distinguished by their X-ray powder diffraction patterns.
Figure 1: XRPD patterns of typical lots of different crystal modifications and amorphous state of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1\(\lambda^6\)-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide.

The X-ray diffraction pattern for modification A shows peaks at 4.5, 6.4, 7.5, 7.7, 8.0, 8.2, 10.0, 10.2, 10.9, 11.1, 12.9, 13.4, 14.0, 14.5, 15.1, 15.6, 16.2, 16.5, 17.3, 17.5, 18.0, 18.9, 19.3, 19.5, 19.9, 20.1, 20.6, 21.0, 21.4, 22.7, 23.1 and 23.6 2Theta (20).

Infrared Spectroscopy (IR)

The IR-spectra of the samples are recorded as film of a Nujol suspension consisting of approximately 15 mg of sample and approximately 15 mg of Nujol between two sodium chloride plates, with an FT-IR spectrometer in transmittance. The Spectrometer is a Nicolet 20SX or equivalent (resolution 2 cm\(^{-1}\), 32 or more coadded scans, MCT detector).

The crystal modifications A, B, C and amorphous state can also clearly be distinguished by solid state IR.

Figure 2: IR spectra of typical lots of different crystal modifications and amorphous state of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1\(\lambda^6\)-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide.
Figure 3: IR spectra of modification A, IR bands: 2925, 2854, 1637, 1604, 1484, 1395, 1375, 1285, 1230, 1172, 1125, 1082, 999, 943, 893, 868, 860, 782, 705, 684 cm⁻¹.

Differential Scanning Calorimetry (DSC)
The DSC-thermograms were recorded using a Mettler-Toledo differential scanning calorimeter (DCS-820, DSC-821, respectively, with FR505 sensors, calibrated using Biphenyl, Benzoic acid, Indium and Zinc).

For the measurements of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1H)-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide approximately 2 mg to 6 mg of the sample were placed in aluminium pans, accurately weighed and hermetically closed with perforation lids. Prior to measurement, the lids were automatically pierced resulting in approximately 1.5 mm pin holes. The samples were then heated under a flow of nitrogen of about 100 mL/min using a heating rate of 5 K/min to a maximum temperature of 180 °C.

The crystal modifications A, B and C can be distinguished by their melting behavior. Amorphous material exhibits a glass transition.
Figure 4: DSC thermograms of typical lots of different crystal modifications and amorphous state of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1\(\lambda^6\)-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methylisobutyramide.

Table 1
Thermoanalytical properties of typical lots of modification A, B, C and of the amorphous form of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1\(\lambda^6\)-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methylisobutyramide.
<table>
<thead>
<tr>
<th>Crystall Modification</th>
<th>Modification A</th>
<th>Modification B</th>
<th>Modification C</th>
<th>Amorphous state</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting Temperature (extrapolated peak [°C] from DCS)</td>
<td>137.2</td>
<td>166.7</td>
<td>166.0</td>
<td>-</td>
</tr>
<tr>
<td>Glass Transition Temperature (midpoint of 2nd heating) [°C]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>81.5</td>
</tr>
<tr>
<td>Enthalpy of fusion [J/g]</td>
<td>43.0</td>
<td>60.8</td>
<td>46.4</td>
<td>-</td>
</tr>
<tr>
<td>Weight loss (TGA) [% of w/w]</td>
<td>1.3</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>0.21</td>
</tr>
</tbody>
</table>

The melting temperatures of single lots of modification A may vary within 128.3 – 148.5 °C, of modification B within 161.8-171.3 and of modification C within 164.8-169.7, depending on their content of residual solvent.

**Dynamic Vapor Sorption (DVS)**

The crystal modifications B and C show very similar DVS behavior (reversible uptake of <0.1 %-w/w of water from 0 to 90 % RH) which is different from amorphous material (reversible uptake of 0.8 %-w/w of water from 0 to 90 % RH) and crystal modification A (reversible uptake of 3.1 %-w/w of water from 0 to 90 % RH).
**Figure 5:** DVS isotherms of typical lots of different crystal modifications and amorphous state of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1\(\lambda\)^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide

It has been shown that the different physicochemical properties lead to different pharmacological properties, especially to different pharmacokinetic parameter as shown below:

**Material and Methods**

**Crystalline material, Forms A, B, and C:**

Four male beagle dogs (age 5 to 6 years, body weight 11 to 14 kg) received single oral doses of 2 mg/kg of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1\(\lambda\)^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide form A and form B (cross-over study design). The formulation was a granulate of the finely milled compound with 20 % sodium dodecyl sulfate (SDS) in gelatine capsules.

In addition, four male beagle dogs (age 4 to 7 years, body weight 11 to 14 kg) received a single oral dose of 2 mg/kg of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1\(\lambda\)^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide form C as finely milled compound with 10 % SDS in gelatine capsules.

The dogs received 200 g commercial dog chow (Pal®, approx. 7 % fat content) about 30 minutes before administration of the compound.

**Amorphous material:**

Two dogs (age 8 years, body weight 12 to 14 kg) received 5 mg/kg of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1\(\lambda\)^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide as amorphous material orally by gavage as microsuspension. The dogs were fed before and during the experiment.

Plasma samples were drawn at several time points. 2-(3,5-bis-Trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1\(\lambda\)^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide plasma concentrations were determined using a selective LC-MS method with a quantification limit of 10 ng/mL. Pharmacokinetic parameters (e.g. AUC, Cmax) were estimated by non-compartmental analysis using WinNonlin 3.1®.
Results

Mean $C_{\text{max}}$ and oral bioavailability were 1.7- and 1.9-fold higher after administration of form A as compared to form B. Looking at individual animals, 3 out of 4 animals showed a significant difference in 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1H-6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide plasma exposure after administration of form A (2.1- to 3.8-fold difference in terms of oral bioavailability between form A and form B).

Form C led to approximately the same mean $C_{\text{max}}$ and AUC(0-24h) values as form A.

After administration of the amorphous material (as microsuspension), mean exposure to 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1H-6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide was higher than after administration of the crystalline material in gelatine capsules (approximately 1.3- to 2-fold).

Table 2:

<table>
<thead>
<tr>
<th>Dog</th>
<th>$C_{\text{max}}$ [ng/mL]</th>
<th>C(24h) [ng/mL]</th>
<th>AUC(0-24h) [h-ng/mL]</th>
<th>F [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Form A</td>
<td>Form B</td>
<td>Form A</td>
<td>Form B</td>
</tr>
<tr>
<td>Charly</td>
<td>391</td>
<td>122</td>
<td>47.6</td>
<td>17.7</td>
</tr>
<tr>
<td>Lars</td>
<td>744</td>
<td>631</td>
<td>28.2</td>
<td>51.7</td>
</tr>
<tr>
<td>Lupo</td>
<td>424</td>
<td>216</td>
<td>40.3</td>
<td>23.2</td>
</tr>
<tr>
<td>Mickey</td>
<td>496</td>
<td>251</td>
<td>29.8</td>
<td>21.4</td>
</tr>
<tr>
<td>Mean</td>
<td>514</td>
<td>305</td>
<td>36.5</td>
<td>28.5</td>
</tr>
<tr>
<td>SD%</td>
<td>31</td>
<td>73</td>
<td>25</td>
<td>55</td>
</tr>
</tbody>
</table>

Table 3: Mean pharmacokinetic parameters of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1H-6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide after single oral administration of 2 mg/kg Form C (n = 4).
Table 4: Mean pharmacokinetic parameters of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide after single oral administration of 5 mg/kg amorphous material (n = 2, compound administered by gavage as microsuspension).

<table>
<thead>
<tr>
<th></th>
<th>C_max [ng/mL]</th>
<th>C(24h) [ng/mL]</th>
<th>AUC(0-24h) [h-ng/mL]</th>
<th>F [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>510</td>
<td>29.2</td>
<td>2660</td>
<td>13.3</td>
</tr>
<tr>
<td>SD%</td>
<td>29</td>
<td>24</td>
<td>28</td>
<td>30</td>
</tr>
</tbody>
</table>

Table 5: Mean pharmacokinetic parameters of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide after single oral administration of 2 mg/kg form A, B, C, and amorphous material to fed male beagle dogs.

<table>
<thead>
<tr>
<th></th>
<th>C_max [ng/mL]</th>
<th>C(24h) [ng/mL]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>3050</td>
<td>123</td>
</tr>
<tr>
<td></td>
<td>10400</td>
<td>24.5</td>
</tr>
</tbody>
</table>

*values normalized to 2 mg/kg

<table>
<thead>
<tr>
<th></th>
<th>Form A</th>
<th>Form B</th>
<th>Form C</th>
<th>Amorphous*</th>
<th>Form A</th>
<th>Form B</th>
<th>Form C</th>
<th>Amorphous*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>514</td>
<td>305</td>
<td>510</td>
<td>1220</td>
<td>36.5</td>
<td>28.5</td>
<td>29.2</td>
<td>49.2</td>
</tr>
</tbody>
</table>

Figure 6: Mean of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide plasma concentrations (n = 4) after single oral administration of 2 mg/kg form A and form B to fed male beagle dogs (cross-over study).
Figure 7: Mean of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ8-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide plasma concentrations (n = 4) after single oral administration of 2 mg/kg form A, B, and C to fed male beagle dogs.

Figure 8: Mean of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ8-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide plasma concentrations (n = 4 for form A, B, and C; n = 2 for amorphous) after single oral
administration of 2 mg/kg fed male beagle dogs (for amorphous 5 mg/kg, curve normalized to 2 mg/kg).

In summary it can be said, that as expected, amorphous material administered as a microsuspension led to the highest 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1\(\lambda^6\)-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide exposure after oral administration of the compound to beagle dogs.

Form A demonstrated the highest bioavailability among the three crystalline polymorphs A, B, and C after administration of the compound as powder in gelatine capsules (containing sodium dodecyl sulfate).

For oral administration the crystalline modification A is preferred.

The modification A of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1\(\lambda^6\)-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide and the pharmaceutically acceptable salts of this compound can be used as medicament, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions.

The modification A can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch
or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules.

The pharmaceutical preparations can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

Medicaments containing the modification A or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also an object of the present invention, as is a process for their production, which comprises bringing the modification A into a galenical administration form together with one or more therapeutically inert carriers.

In accordance with the invention the modification A as well as their pharmaceutically acceptable salts is useful in the control or prevention of illnesses based on the NK1 receptor, such as migraine, rheumatoid arthritis, asthma, bronchial hyperreactivity, inflammatory bowel disease or for the treatment of disorders including Parkinson’s disease, anxiety, depression, pain, headache, Alzheimer’s disease, multiple sclerosis, oedema, allergic rhinitis, Crohn’s disease, ocular injury, ocular inflammatory diseases, psychosis, motion sickness, induced vomiting, emesis, urinary incontinence, psychoimmunologic or psychosomatic disorders, cancer, withdrawal symptoms of addictive drugs from opiates or nicotine, traumatic brain injury or benign prostatic hyperplasia.

The most preferred indications in accordance with the present invention are those, which include disorders of the central nervous system, for example the treatment or prevention of certain depressive disorders.

The dosage can vary within wide limits and will, of course, have to be adjusted to the individual requirements in each particular case. In the case of oral administration the dosage for adults can vary from about 0.01 mg to about 1000 mg per day of a compound of general formula I or of the corresponding amount of a pharmaceutically acceptable salt thereof. The daily dosage may be administered as single dose or in divided doses and, in addition, the upper limit can also be exceeded when this is found to be indicated.
Tablet Formulation (Wet Granulation)

<table>
<thead>
<tr>
<th>Item</th>
<th>Ingredients</th>
<th>mg/tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 mg</td>
</tr>
<tr>
<td>1.</td>
<td>modification A</td>
<td>5</td>
</tr>
<tr>
<td>2.</td>
<td>Lactose Anhydrous DTG</td>
<td>125</td>
</tr>
<tr>
<td>3.</td>
<td>Sta-Rx 1500</td>
<td>6</td>
</tr>
<tr>
<td>4.</td>
<td>Microcrystalline Cellulose</td>
<td>30</td>
</tr>
<tr>
<td>5.</td>
<td>Magnesium Stearate</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>167</td>
</tr>
</tbody>
</table>

Manufacturing Procedure

1. Mix items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50 °C.
3. Pass the granules through suitable milling equipment.
4. Add item 5 and mix for three minutes; compress on a suitable press.

Capsule Formulation

<table>
<thead>
<tr>
<th>Item</th>
<th>Ingredients</th>
<th>mg/capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 mg</td>
</tr>
<tr>
<td>1.</td>
<td>modification A</td>
<td>5</td>
</tr>
<tr>
<td>2.</td>
<td>Hydrous Lactose</td>
<td>159</td>
</tr>
<tr>
<td>3.</td>
<td>Corn Starch</td>
<td>25</td>
</tr>
<tr>
<td>4.</td>
<td>Talc</td>
<td>10</td>
</tr>
<tr>
<td>5.</td>
<td>Magnesium Stearate</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>200</td>
</tr>
</tbody>
</table>

Manufacturing Procedure

1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.
Claims

1. New crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-
dioxo-1λ⁶-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-
isobutryramide characterized by the following X-ray diffraction pattern obtained with a
CuKα radiation at 2θ (2Theta) = 4.5, 6.4, 7.5, 7.7, 8.0, 8.2, 10.0, 10.2, 10.9, 11.1, 12.9, 13.4,
14.0, 14.5, 15.1, 15.6, 16.2, 16.5, 17.3, 17.5, 18.0, 18.9, 19.3, 19.5, 19.9, 20.1, 20.6, 21.0,
21.4, 22.7, 23.1 and 23.6 and an infrared spectrum having sharp bands at 2925, 2854,
1637, 1604, 1484, 1395, 1375, 1285, 1230, 1172, 1125, 1082, 999, 943, 893, 868, 860, 782,
705, 684 cm⁻¹, and wherein the extrapolated melting point (DSC) is 137.2 °C.

2. The use of crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-
(1,1-dioxo-1λ⁶-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-
methyl-isobutryramide according to claim 1 for the manufacture of medicaments for the
Treatment of central nervous system disorders.

3. The use of crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-
(1,1-dioxo-1λ⁶-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-
methyl-isobutryramide according to claim 2 for the treatment of migraine, rheumatoid
Arthritis, asthma, bronchial hyperreactivity, inflammatory bowel disease or for the
treatment of disorders including Parkinson’s disease, anxiety, depression, pain, headache,
Alzheimer’s disease, multiple sclerosis, oedema, allergic rhinitis, Crohn’s disease, ocular
injury, ocular inflammatory diseases, psychosis, motion sickness, induced vomiting,
emesis, urinary incontinence, psychoimmunologic or psychosomatic disorders, cancer,
withdrawal symptoms of addictive drugs from opiates or nicotine, traumatic brain injury
or benign prostatic hyperplasia.

4. The use of crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-
(1,1-dioxo-1λ⁶-thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-
methyl-isobutryramide according to claims 2 and 3 for the treatment of depression.

5. A pharmaceutically acceptable composition comprising the crystalline
Modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ⁶-thiomorpholin-
4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutryramide according to
claim 1 and a pharmaceutically acceptable carrier.

6. A pharmaceutically acceptable composition according to claim 5, wherein the
crystalline modification of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(1,1-dioxo-1λ⁶-
thiomorpholin-4-yl)-4-(4-fluoro-2-methyl-phenyl)-pyridin-3-yl]-N-methyl-isobutyramide is administered as powder in gelatine capsules.

7. The invention as herein before described.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

<table>
<thead>
<tr>
<th>IPC</th>
<th>A61K31/54</th>
<th>A61P25/00</th>
<th>C07D213/75</th>
</tr>
</thead>
</table>

According to International Patent Classification (IPC) or to both national classification and IPC.

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

<table>
<thead>
<tr>
<th>IPC</th>
<th>C07D</th>
<th>A61K</th>
<th>A61P</th>
</tr>
</thead>
</table>

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>WO 02/085458 A (HOFFMANN LA ROCHE) 31 October 2002 (2002-10-31) page 31, line 2-8</td>
<td>1-6</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of box C. Patient family members are listed in annex.

<table>
<thead>
<tr>
<th>Special categories of cited documents:</th>
<th><strong>&quot;&quot;</strong> later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&quot;A&quot;</strong> document defining the general state of the art which is not considered to be of particular relevance</td>
<td></td>
</tr>
<tr>
<td><strong>&quot;E&quot;</strong> earlier document but published on or after the international filing date</td>
<td></td>
</tr>
<tr>
<td><strong>&quot;L&quot;</strong> document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td>
<td></td>
</tr>
<tr>
<td><strong>&quot;O&quot;</strong> document referring to an oral disclosure, use, exhibition or other means</td>
<td></td>
</tr>
<tr>
<td><strong>&quot;P&quot;</strong> document published prior to the international filing date but later than the priority date claimed</td>
<td></td>
</tr>
</tbody>
</table>

Date of the actual completion of the International search

22 April 2004

Date of mailing of the international search report

07/05/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5618 Patentlaan 2 NL - 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Tx: 31 651 epo nl, Fax: (+31-70) 340-3016

Authorized officer

Johnson, C

Form PCT/04/210 (second sheet) (January 2004)
**INTERNATIONAL SEARCH REPORT**

**Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

   Although claims 3,4 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. **X** Claims Nos.: because they relate to parts of the international Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

   see FURTHER INFORMATION sheet PCT/ISA/210

3. **☐** Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. **☐** As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. **☐** As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. **☐** As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. **☐** No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- **☐** The additional search fees were accompanied by the applicant’s protest.
- **☐** No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)
Continuation of Box II.2

Claims Nos.: 7

The scope of claim 7 is not clear — either it refers to subject matter already encompassed by claims 1-6, or it refers to undefined subject matter in the description. If the former meaning is intended, then this claim is redundant. If the intention is to claim certain subject matter disclosed in the description, but not in claims 1-6, then the scope is unclear, as no indication is given as to what part of the description is meant. For these reasons, claim 7 does not fulfil the requirements of Article 6 PCT and has not been searched.

The applicant’s attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>WO 02085458 A</td>
<td>31-10-2002</td>
<td>CA 2444395 A1</td>
<td>31-10-2002</td>
</tr>
<tr>
<td>WO 02085458 A</td>
<td>31-10-2002</td>
<td>EP 1385577 A2</td>
<td>04-02-2004</td>
</tr>
<tr>
<td>US 200304157 A1</td>
<td>02-01-2003</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Form PCT/ISA/20 (patent family annex) (January 2004)