acetic acid and the mixture was heated under reflux for 2 hr. After cooling, the mixture was neutralized using aq. potassium carbonate solution, and the yellow solid thus obtained was filtered, washed with water, and dried. Purification by column chromatography (SiO_2;$CHCl_3$/CH_3OH) gave 6-carboxamido-3-phthalimido-1,2,3,4-tetrahydrocarbazole (2.8 g).

The above product (1.0 g) was suspended in ethanol (10 ml) and hydrazine hydrate (5 ml) was added. A clear solution was obtained, and the mixture was left to stir overnight, to yield a precipitate. The whole mixture was evaporated to dryness, washed with aq. K_2CO_3 solution, and water, to leave the title compound 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (0.44 g), as the monohydrate, mp. 146°–148° C.

^{1}H NMR [250 MHz. DMSO-d^6]δ 1.49–1.77 (1H,m), 1.83–2.03 (1H,m), 2.17–2.40 (1H,m), 2.62–2.80 (2H,m), 2.90 (1H,dd), 1 signal obscured by H_2O at ca. 3.1, 7.03 (1H,brd.s), 7.18 (1H,d), 7.58 (1H,d), 7.83 (1H,brd.s), 7.98 (1H,s).

Preparation 2

(+)- and (−)-3-Amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride

Method 1

(±)-3-t-Butyloxycarbonylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole was separated into its enantiomers using chiral HPLC: (chiralcel OD 4.6 mm column, eluting with hexane/ethanol 85:15). The (+)-enantiomer was collected first and had mp=150°–152° C. and $[\alpha]_D^{25}$=+70.1 (in methanol, 0.41% w/v). The (−)-enantiomer had mp =150°–152° C. and $[\alpha]_D^{25}$=−79.4 (in methanol, 0.40% w/v) The (+)-enantiomer was convened to the parent amine hydrochloride by treating with HCl gas in dioxane, to furnish the (+)-enantiomer of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride, mp=248°–251° C., $[\alpha]_D^{25}$=+26.2 (in methanol, 0.50% w/v). The (−)-enantiomer of 3-t-butyloxycarbonylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole was similarly convened into the (−)-enantiomer of 3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride, mp=248°–251° C., $[\alpha]_D^{25}$=−28.6 (in methanol, 0.50% w/v).

Method 2

(±)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole was treated with one equivalent of 2,3:4,6-di-O-isopropylidene-2-keto-L-gulonic acid in methanol to give the salt of the (+)-enantiomer, in 38% yield (with respect to racemate) and 84% enantiomeric excess (ee). This material was recrystallized twice from methanol to give the salt of the (+)-enantiomer in 25% overall yield (with respect to racemate), and>98% ee. This product was convened to the hydrochloride salt first by treatment with aqueous alkali, and the precipitated free base treated with 2M aq. HCl in ethanol, to give (+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole hydrochloride.

Preparation 3

(±)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hydrochloride

4-Cyanophenyl hydrazine hydrochloride (20.2 g) and 4-benzoyloxycyclohexanone (25.9 g) were dissolved in glacial acetic acid (400 ml) and the mixture was heated under reflux for 1.5 hr. After allowing to cool, the mixture was filtered, and the filtrate was evaporated to dryness, and neutralized with aqueous sodium bicarbonate solution to give a solid precipitate, which was purified by chromatography (SiO_2; hexane/ethyl acetate) to give 3-benzoyloxy-6-cyano-1,2,3,4-tetrahydrocarbazole (18 g). This product (11.6 g) was suspended in ethanol (230 ml) and treated with 2.5% aqueous potassium hydroxide solution (120 ml), and heated under reflux for 1 hr. The cooled mixture was neutralized with glacial acetic acid and evaporated to a solid residue, which was washed with water, and dried to give 3-hydroxy-6-cyano-1,2,3,4-tetrahydrocarbazole (6.6 g).

The above product (3.57 g) was dissolved in dry pyridine (35 ml) and treated with tosyl chloride (3.51 g) in dry pyridine (35 ml), and the mixture was stirred at 100° C. for 2 hr. After cooling, the solution was poured into water (500 ml), extracted with ethyl acetate, and the latter extract was washed with 2M HCl, dried ($MgSO_4$) and evaporated to dryness. Purification by chromatography (SiO_2; hexane/ethyl acetate) gave 3-tosyloxy-6-cyano-1,2,3,4-tetrahydrocarbazole (0.53 g).

This product (0.40 g) was dissolved in 33% methylamine in alcohol (25 ml) and heated at 100° C. in a sealed steel vessel for 1.5 hr. After cooling, the mixture was evaporated to dryness and purified by chromatography (SiO_2; chloroform/methanol) to give 3-methylamino-6-cyano-1,2,3,4-tetrahydrocarbazole (0.13 g).

The above product (0.12 g) was dissolved in THF (10 ml) and reacted with di-tert-butyl dicarbonate (0.36 g) in THF (3 ml) at room temperature overnight. The reaction mixture was evaporated to dryness, partitioned between 2M sodium bicarbonate solution and ethyl acetate, and the organic extract dried and evaporated to give a white solid. This was triturated with ether/hexane to give 3-t-butyloxycarbonylmethylamino-6-cyano-1,2,3,4-tetrahydrocarbazole (0.14 g).

This product (0.14 g) was dissolved in methanol (15 ml) and treated with a mixture of 20% aqueous sodium hydroxide (0.20 ml) and 30% hydrogen peroxide (0.20 ml), and the whole mixture was stirred at room temperature overnight. Sodium metabisulphite (38 mg) was added, and the solution was evaporated to dryness, and chromatographed (SiO_2; chloroform/10% NH_4OH in methanol) to give 3-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (0.12 g). The above compound (0.11 g) was dissolved in methanol (10 ml), and treated with 3M hydrochloric acid at room temperature. The mixture was evaporated to dryness, azeotroping with ethanol to give a solid, which was recrystallized from methanol/ether to give the title compound, mp 327°–328° C. (80 mg).

1H NMR [250 MHz, MeOH-d^4]d 1.98–2.20 (1H, m), 2.29–2.49 (1H, m), 2.75–2.90(5H, s+m), 2.90–3.09 (2H, m), 3.52–3.69 (1H, m), 7.31 (1H, d), 7.63 (1H, d), 8.05 (1H,s).

Preparation 4

(±)-6-Carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole oxalate

1,4-Cyclohexanedione mono-2',2'-dimethyl trimethylene ketal (2.00 g) was mixed with anhydrous ethylamine (10.0 g) and benzene (10 ml), and the mixture was cooled to 5° C. A solution of titanium tetrachloride (0.95 g) in benzene (10 ml) was added, dropwise, then the mixture was stirred at room temperature for 1 hr. The mixture was To this solution was added palladium-on-carbon catalyst (100 mg), and the mixture was hydrogenated at 50 psi pressure overnight. The catalyst was filtered off and the ethanol evaporated to leave 4-ethylamino-cyclohexanone 2',2'-dimethyl trimethylene ketal as an oil (2.0 g).

This compound (0.80 g) was dissolved in formic acid (20 ml) and the solution was heated to 90° C. for 1 hr. Formic acid was evaporated, and the residue was partitioned

between chloroform and 1M hydrochloric acid. The aqueous layer was evaporated to dryness to give 4-ethylaminocyclohexanone (0.40 g).

A mixture of the above product (0.40 g) and 4-carboxamidophenyl hydrazine hydrochloride (0.60 g) in glacial acetic acid (20 ml) was heated under reflux for 1 hr. The acid was evaporated in vacuo to an oil, which was purified by chromatography (SiO_2; $CHCl_3$/10% NH_3 in MeOH) to give an oil (0.50 g). Part of this product (150 mg) was dissolved in methanol and treated with oxalic acid. The solution was treated with ether to give the title compound as a crystalline solid, mp 165°–170° C. (100 mg).

1H NMR [250 MHz, DMSO-d^6]67 1.25 (3H, t), 1.81–2.05 (1H, m), 2.20–2.38 (1H,m), 2.61–2.79 (1H, m), 2.79–2.94 (2H, m), 2.98–3.28(3H, dd +s), 3.41–3.60 (1H, m), 7.08(1H, brd. s), 7.28 (1H, d), 7.60 (1H, d), 7.82(1H, brd. s), 8.00 (1H, s), 11.12 (1H, s).

Preparation 5

(±)-6-Carboxamido-3- N-methylamino-1,2,3,4-tetrahydrocarbazole

A solution of (±)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hydrochloride salt (6.0 g) in water (60 ml) at 68° C. was basified to pH 10.5 with 5M aqueous sodium hydroxide. The resultant mixture was extracted with butan-1-ol (30 ml, 15 ml). These extracts were combined and evaporated to give the title compound as a dark oil (6.96 g) containing ca. 46% w/w butan-1-ol.

1H NMR[400 MHz, d^6-DMSO]δ 1.40–2.00 (1H,br), 1.62 (1H,m), 2.06 (1H,m), 2.33 (1H,m) 2.39 (3H,s), 2.77 (3H,m), 2.97 (1H,dd), 7.02 (1H,s), 7.24 (1H,d), 7.59 (1H,dd), 7.80 (1H,s), 7.99 (1H,d), 10.93 (1H,s) +peaks due to butan-1-ol.

Preparation 6

4-Methylaminocyclohexanone (2',2'-dimethyltrimethylene) ketal hydrochloride

1,4-Cyclohexanedione (mono-2'2'-dimethyltrimethylene) ketal (50 g) was dissolved in dry toluene (500 ml) in a flask fitted with a dry ice trap and flushed with nitrogen with stirring. Methylamine (47.0 g) was then added dropwise to the reaction mixture, at 20° C. slowly to allow dissolution in the toluene. Molecular sieves (32.0 g) were then added and the reaction mixture stirred at 20° C. under an air lock. The reaction was complete after ca. 4 h (>97%). The sieves were then filtered off and the clear amber filtrate evaporated to a volume of 160 ml. The concentrated solution of iminoketal was diluted with ethanol (340 ml) and degassed with argon. Palladium catalyst (palladium on charcoal, 3.55 g) was added and the mixture hydrogenated at atmospheric pressure and 20° C. for 24 h. When hydrogen uptake was complete the reaction mixture was filtered through Celite and the Celite bed washed with a little ethanol (2×25 ml). The solvent was then removed under reduced pressure to give the ketal amine as an amber oil. (49.12 g, 92%).

The ketal amine (80 g, 0.375 Mol) was dissolved in isopropyl ether with stirring. A solution of HCl in isopropyl ether (prepared by bubbling a known weight of gas into a known volume of solvent) was added dropwise causing the formation of an immediate white precipitate, which became very thick as the addition was completed. The thick suspension was stirred for a further 30 minutes, filtered off, and the product washed with a little fresh isopropyl ether and then dried under vacuum to give the title compound as a white, free flowing powder (84.01 g).

1H NMR: -[270 MHz, $CDCl_3$]δ 9.51 (2H,bs), 3.48 (4H, d), 3.00 (1H,m), 2.73 (3H,t), 2.32 (2H,d), 2.15 (2H,d), 1.85, (2H,dq), 1.41 (2H,dt), 0.96 (6H,s).

Preparation 7

(±)-6-Carboxamide-3-methylamino-1,2,3,4-tetrahydrocarbazole hydrochloride

4-Aminobenzamide (3.0 g) was dissolved in 5N HCl (20 ml) cooled to −5° to 0° C. with stirring and the mixture further cooled to around −15° C. Sodium nitrite (1.98 g) in water (4.4 ml) was added dropwise with stirring at such a rate that the temperature was maintained at between −10° to −15° C. The mixture was then stirred at around −8° C. for 30 min. Ice cold water (40 ml) was then added followed by solid sodium dithionite (7.7 g) in a single portion, the means of cooling removed and the mixture stirred at around 15° C. for 30 min. To the resulting yellow suspension was added conc. HCl (30 ml) followed by 4-methylaminocyclohexanone (2'2'-dimethyltrimethylene) ketal hydrochloride (5.488 g) and the mixture heated to around 70° C., not allowing the reaction temperature to rise above 75° C. After ca. 2 h, the reaction mixture was cooled to 20° C. and the dark solution then carefully neutralised with caustic (aq., 40%) to pH 10 maintaining the temperature between 15°–20° C., whereupon a thick precipitate formed to give the title compound. The reaction mixture was then left to stir overnight and the precipitate filtered off and dried (3.88 g, 63%).

^{1}H nmr [250 MHz, d_6DMSO]δ=11.21 (1H,s), 8.06 (1H,s), 7.89 (1H, bs), 7.63 (1H,d), 7.28(1H,d), 7.10 (1H,bs), 3.50–3.15 (2H,m), 2.95–2.70 (3H,m), 2.62 (3H,s), 2.33 (1H,m), 1.97 (1H,m).

4-Methylaminocyclohexanone (2',2'-dimethyltrimethylene) ketal hydrochloride

1,4-Cyclohexanedione mono-2,2-dimethyltrimethylene ketal (20.0 g, 0.101 mol) was dissolved in ethanol (200 ml) containing methylamine (8.0 g, 0.258 mol). The resultant solution was hydrogenated at 30 psi over 10% Pd/C catalyst (2.0 g) for 4 hrs at room temperature. The reaction mixture was filtered through a celite pad and the filtrate evaporated under reduced pressure to give an oil (21.4 g).

The oil was dissolved in tetrahydrofuran (210 ml) and the resultant solution cooled in an ice/water bath while conc. HCl (10.5 ml) was added to the stirred solution in two portions such that the temperature did not rise above 15° C. and then filtered. The solid was washed with THF (50 ml) and air dried overnight to give the title compound (22.80 g). mp 245.1° C. (EtOH).

^{1}H nmr (250 MHz, d_6DMSO)δ 0.9 (t,6H), 1.3 (q,2H), 1.45 (q,2H), 1.9 (brd,2H), 2.25 (brd,2H), 2.5 (s,3H), 3.0 (m, 1H), 3.5 (d,4H).

EXAMPLE 1

(+) and (−)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hydrochloride

(a) To a stirred solution of (±)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hydrochloride (0.3 g) in propan-2-ol/saturated aqueous potassium hydrogen carbonate (20:1 21 ml), di-ten-butyl dicarbonate (0.425 g) was added and stirring continued for 1 hour. The mixture was diluted with ethyl acetate (50 ml) washed with water (2×20 ml), dried ($MgSO_4$) and solvent removed at reduced pressure to give (±) 3-N-tert-butoxycarbonyl-N-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (0.36 g).

^{1}H NMR (d_6-DMSO)δ 1.47 (s,9H), 1.84–2.08 (m,2H), 2.71–2.94 (m,4H), 2.80 (s,3H), 4.26 (m,1H), 7.02 (br.s,1H), 7.25 (d,1H), 7.57 (d,1H), 7.76 (br.s,1H), 7.97 (s,1H) and 10.96 (s,1H).

(b) The (+) and the (−) enantiomers of (±)-3-N-tert-butoxycarbonyl-N-methylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (0.3) were separated by chiral HPLC: (chiralpak AD 20 mm column, hexane:ethanol 9:1 eluant).

Treatment of the first eluting enantiomer (0.02 g) with 3N aqueous hydrochloric acid/methanol 1:1 (4 ml) for16 hours, filtration and removal of solvent gave, after recrystallisation from methanol/diethyl ether, the (+) enantiomer of the title compound (0,009 g) m.p.219°–225° C., $[\alpha]_D^{25°\ C}$=+25.4 (methanol 0.063% w/v).

Treatment of the second eluting enantiomer (0.03 g) under similar conditions gave the (−) enantiomer or the title compound (0.02 g), m.p. 219°–225° C. $[\alpha]_D^{25°\ C}$=−23.3 (methanol 0.116% w/v).

EXAMPLE 2

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole

(a) To a solution of (±)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.77 g) in dimethylformamide (70 ml), triethylamine (0.62 g) and benzyl chloroformate (0.47 g) were added. The solution was stirred overnight, further triethylamine (0.27 g) and benzyl chloroformate (0.26 g) added and the mixture stirred for 4 hours. The reaction mixture was poured into water.(500 ml), and extracted with ethyl acetate (2×50 ml). The combined extracts were dried ($MgSO_4$) and solvent was removed at reduced pressure. The residue was recrystallized from methanol/water to give (±)-3-N-benzyloxycarbonyl-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.62 g) m.p. 103°–110° C.

(b) The (+) and (−) enantiomers of (±)-3-N-benzyloxycarbonyl-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole were separated by chiral HPLC (OD column, eluant hexane/ethanol 4:1).

The first eluting enantiomer (0.23 g) m.p. 105°–106° C., $[\alpha]_D^{25°\ C}$=+157.2. (ethanol, 0.39% w/v).

The second eluting enantiomer (0.23 g) m.p. 105°–106° C., $[\alpha]_D^{25°\ C}$=−163.1 (ethanol, 0.23% w/v).

(c) A solution of (+)-3-N-benzyloxycarbonyl-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.23 g) in ethanol (20 ml) containing 10% palladium/charcoal (0.23 g) was shaken under a hydrogen atmosphere (50 psi) for 3 hours. Catalyst was removed by filtration and solvent removed at reduced pressure to give the (+) enantiomer of the title compound (free base) as a foam m.p. 98°–102° C.,.$[\alpha]^{o25°\ C}$=+61.2.

EXAMPLE 3

(±)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole camphor-sulphonate

To a solution of (±)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (3 g) in methanol (20 ml), a solution of (1 S)-(+)-10-camphorsulphonic acid (2.86 g) in methanol was added. Solvent was removed at reduced pressure and the residue recrystallised ten times to give the (+) enantiomer of the title compound as the camphorsulphonate salt m.p. 177°–180° C. This was treated with 2 equivalents of triethylamine and 10 equivalents of 2,3,4,6-tetra-o-acetyl-beta-D-glucopyranosylisothiocyanate in dimethylformamide at room temperature for 30 minutes. Aliquots of the reaction mixture wre removed from the mixtue for HPLC analysis. Analytical HPLC of the 2,3,4,6-tetra-O-acetyl-beta-D-glucopyranosylthiourea derivative (C18 Novapak, eluant derivative prepared from the (+) enantiomer of Example 1 and showed the material was 99% ee.

EXAMPLE 4

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole succinate (1:1)

(a) Benzaldehyde (10.6 g) was added to a suspension of (+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (12.35 g) in methanol (100 ml).The mixture was stirred for 1 hour, sodium cyanoborohydride (9.3 g) added over 1 hour and the clear solution stirred for 24 hours. The solution was cooled (ice bath) and formaldehyde (37% aqueous methanolic, 9:1 solution, 5.5 ml) added. After 30 minutes stirring at room temperature water (100 ml) was added, stirring continued for 30 minutes followed by extraction with dichloromethane (3×150 ml). The combined organic extracts were washed with water (2×200 ml), dried (Na_2SO_4), filtered and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, dichloromethane—10% ethanol/dichloromethane) to give 3-N-benzyl-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (9.4 g) as a foam. The succinate salt (1:1) was recrystallised from methanol m.p. 175°–182° C.

^{1}H NMR (d_6-DMSO)δ 1.81–1.96 (m, 1H), 2.09–2.21(m, 1H), 2.29 (s,3H), 2.44 (s,4H), 2.66–3.11(m,5H), 3.76 (q,2H), 7.05 (br. s1H), 7.22–7.43(m,6H), 7.59 (d, 1H), 7.79 (br. ,s,1H), 8.03 (s,1H), and 10.94 (s,1H).

(b) To a solution of 3-N-benzyl-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (1.0 g) in ethanol (1 00 ml) containing succinic acid (0.39 g), Pearlmans catalyst (1.0 g) was added and the mixture shaken under an atmosphere of hydrogen at 45 psi and 50° C. for 2 hours. The mixture was filtered (celite pad) and the pad washed thoroughly with ethanol. The combined filtrate and washings were evaporated to dryness, co-evaporated with ethanol (3×100 ml) and recrystallised from methanol to give the title compound [(1:1) succinate salt]. m.p. 148°–155° C.

^{1}H NMR (d_6-DMSO)δ 1.84 (m,1H), 2.15–2.34 (m,1H), 2.28 (s,4H), 2.57 (m,1H), 2.61 (s,3H), 2.83 (m,2H), 3.13 (dd,1H), 3.29 (m,1H), 7.08 (br s,1H), 7.26 (d,1H), 7.60 (dd,1H), 7.82 (br s,1H), 8.01 (d,1H) and 11.08 (s,1H).

EXAMPLE 5

(+)-6-Carboxamido-3-N-methylamino-1,.2,3,4-tetrahydrocarbazole

(a) To a solution of (+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (5 g) in pyridine (150 ml), dicyclohexylcarbodiimide (4.13 g) was added followed by carbon disulphide (1.67 g). The solution was stirred for 1 hour, solvent removed at reduced pressure and the residue co-evaporated with toluene (3×100 ml). The residue was recrystallised from methanol to give 6-carboxamido-3-isothiocyanato-1,2,3,4-tetrahydrocarbazole (5.06 g) m.p.245°–248° C.

(b) A solution of 6-carboxamido-3-isothiocyanato-1,2,3,4-tetrahydrocarbazole (0.25 g) in ethanol (40 ml) was treated with sodium borohydride (0.17 g) in one portion and stirred for 18 hours. Acetone (5 ml) was added the mixture stirred for a further 1 hour and solvent removed at reduced pressure. The residue was column chromatographed (basic alumina, 5% methanol/dichloromethane eluant) to give the title compound (0.11 g) having the same physico chemical characteristics as the product of Example 2.

EXAMPLE 6

(+)- and (−)-6-Carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole hydrochloride

(a) From (±)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole (0.26 g), (±)-3-N-tert-butoxycarbonyl-N-ethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (0.27 g) isolated as an oil was prepared according to the procedure of Example 1.

^{1}H NMR (d_6-DMSO)δ 1.1 (t,3H), 1.23 (s,9H), 1.92 (m,1H), 2.09 (m,1H), 2.78–2.92 (m,4H), 3.21–3.62 (m,2H), 4.21 (m,1H), 7.04 (br.s, 1H), 7.24 (d,1H), 7.58 (d,1H), 7.76 (br.s, 1H), 7.99 (s,1H) and 10.99 (s,1H).

(b) From (±)-3-N-tert-butoxycarbonyl-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole (0.25 g), the (+)- and the (−)-enantiomers of 3-N-tert butoxycarbonyl-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole were prepared by chiral HPLC (chiralcel OD 4.67 mm, eluant hexane/ethanol 92/8).

Treatment of the enantiomer eluting first, (0.06 g) $[\alpha]_D^{25°}$ *c.*=+108.2 (ethanol 0.9% w/v) with hydrochloric acid/methanol according to the method of Example 1 gave (+)-6-carboxamido-N-ethylamino-1,2,3,4-tetrahydrocarbazole hydrochloride (0.04 g) m.p. 211°–221° C. $[60\ ]_D^{25°}$ *c.*=+37.2 (methanol, 0.12% w/v).

Treatment of the second eluting enantiomer (80 mg) $[\alpha]^{p25°}$ *c.*=−103.5 (ethanol, 0.19% w/v) with hydrochloric acid/methanol according to the method of Example 1 gave (−)-6-carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole hydrochloride (0.05 g) m.p. 211°–221 ° C. after recrystallisation from methanol/diethyl ether $[\alpha]_D^{25°}$ *c.*=−33.6 (methanol, 0.11% w/v).

(+)-6-Carboxamido-3-N-ethylamino-1,2,3,4-tetrahydrocarbazole succinate (1:1)

(a) From (+)-3-amino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (1.15 g), (+)-3-N-benzyl-N-ethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole (1.26 g) was obtained according to the procedure of Example 4 replacing formaldehyde with acetaldehyde (0.44 g). The succinate salt (1:1) was prepared by addition of succinic acid (0.4 g) to the free base (1.08 g) and recrystallisation from propan-2-ol m.p. 130°–140° C.

^{1}H NMR (d_6-DMSO)δ 1.05 (t,3H), 1.85 (m,1H), 2.10 (m,1H), 2.40 (s,4H), 2.58–2.91(m,5H), 3.06 (m,1H), 3.77 (q,2H), 7.03 (br.s,1H), 7.17–7.47(m,5H), 7.58 (d,1H), 7.78 (br.s,1H), 8.00 (s,1H), 10.90 (s,1H) and 12.28 (br.s2H).

(b) Recrystallisation of (+)-3-N-benzyl-N-ethylamino-6-carboxamido-1,2,3,4-tetrahydrocarbazole succinate (1.36 g), from methanol, according to the procedure of Example 4 gave the title compound (1.04 g) m.p. 165°–167° C.

1H NMR (d6-DMSO)δ 1.19 (t,3H), 1.86 (m,1H), 2.23 (m,1H), 2.30 (s,4H), 2.62 (m,1H), 2.85 (m,2H), 3.02 (q,2H), 3.14 (m,1H), 3.38 (m,1H), 7.08 (br.s,1H), 7.26 (d,1H), 7.59 (d,1H), 7.80 (br.s,1H), 8.00 (s,1H) and 11.08 (s,1H).

EXAMLPE 8

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole L (+)-tartrate salt (1:1)

to a hot solution of (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.25 g) in methanol/water (11:1, 24 ml) L (+)-tartaric acid (0.15 g) was added and the solution allowed to stand for 3 hours. The crystalline title compound (0.30 g) was isolated by filtration. m.p. 195°–197° C.

^{1}H NMR (d_6-DMSO)δ 1.92 (m,1H), 2.25 (m,1H), 2.67 (s,3H), 2.68 (m,1H), 2.84 (m,2H), 3.17 (dd, 1H), 3.43 (m,1H), 3.87 (s,2H), 7.07 (br.s, 1H), 7.27 (d,1H), 7.61 (d,1H), 7.82 (br.s, 1H), 8.01 (s,1H) and 11.11 (s,.1H).

EXAMPLE 9

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole D (−)-tartrate salt (1:1)

To a hot solution of (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.25 g) in methanol (9 ml) D (−)-tartaric acid (0.15 g) was added and the solution allowed to stand for 3 hours. The crystalline title compound (0.32 g) was isolated by filtration m.p. softens above 147° C.

^{1}H NMR (d_6-DMSO)δ 1.92 (m,1H), 2.25 (m,1H), 2.67 (s,3H), 2.68 (m,1H), 2.84 (m2H), 3.17 (dd,1H), 3.43 (m,1H), 3.87 (s,2H), 7.07 (br.s,1H), 7.27 (d,1H), 7.61 (d,1H), 7.82 (br.s,1H), 8.02 (s,1H) and 11.09 (s,1H).

EXAMPLE 10

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hemisuccinate (2:1)

To a hot solution of (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.30 g) in propan-2-ol was added succinic acid (0.07 g) and the solution allowed to stand for 3 hours. The title compound (0.21 g) was isolated by filtration. m.p. 220°–235° C.

^{1}H NMR (d_6-DMSO)δ 1.77 (m,1H), 2.14 (m,1H), 2.26 (s,2H), 2.54 (s,3H), 2.55 (m,1H), 2.79 (m;2H), 3.10 (dd,1H), 3.43 (m,1H), 7.06 (br.s,1H), 7.25 (d,1H), 7.59 (d,1H), 7.82 (br.s,1H), 7.99 (s,1H) and 11.01 (s,1H).

EXAMPLE 11

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole methanesulphonate

To a hot solution of (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.30 g) in propan-2-ol/ethyl acetate methanesulphonic acid (0.12 g) was added and the solution allowed to stand for 3 hours. The title compound (0.33 g) was isolated as a gum.

^{1}H NMR (d_6-DMSO)δ 1.93 (m,1H), 2.25 (m,1H), 2.35 (s,3H), 2.70 (m,4H), 2.86 (m,2H), 3.10 (dd,1H), 3.50 (m,1H), 7.11 (br.s,1H), 7.27 (d, 1H), 7.61 (d,1H), 7.82 (br.s,1H), 8.02 (s,1H), 8.65 (br.s,2H) and 11.12 (s,1H).

EXAMPLE 12

(+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hydrobromide

Hydrogen bromide gas was passed through a solution of (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (0.30 g) in ethanol(50 ml) for 15 seconds. After 30 minutes the title compound (0.03 g) m.p. 205°–208° C. was separated by filtration and washed with ethanol.

^{1}H NMR (d_6-DMSO)δ 1.94 (m,1H),2.25 (m,1H),2.26 (s,2H), 2.70 (m,4H),2.85 (m,2H), 3.17 (dd,1H),7.10 (br.s, 1H),7.27 (d,1H),7.61 (d,1H), 7.82 (br.s,1H),8.02 (s,1H) 8.67 (br.s,2H) and 11.01 (s,1H).

a) (+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole-R-2-pyrrolidone-5-carboxylic acid salt

To a solution of (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole (6.96 g containing ca. 46% w/w butan-1-ol, prepared as in Preparation 5) in ethanol (50 ml), stirred at ambient temperature, was added a solution of R-2-pyrrolidone5-carboxylic acid (1.00 g, e.e. >99%) in hot ethanol (33 ml). The resultant mixture was stirred at ambient temperature for 40 h. The crystalline product was filtered off under nitrogen, washed with a small volume of ethanol, then dried in vacuo at 60° C. (Yield=2.63 g).

This product was dissolved in water (2.6 ml), and the solution was then diluted with ethanol (130 ml) and stirred at ambient temperature for 40 h. The crystalline product was filtered off, washed and dried as before. (Yield=1.72 g).

This product was recrystallised from ethanol (90 ml)/water (1.8 ml) as described above to give the title compound (1.44 g; e.e.=>99%).

^{1}H NMR [250 MHz,d_6-DMSO]δ 1.90 (2H,m), 2.06 (2H,m),2.19 (2H,m),2.57 (3H,s), 2.62 (1H,m),2.82 (2H,m),3.15 (2H,m), 3.80 (1H,dd),7.07 (1H,s),7.26 (1H,d),7.59(1H,s), 7.62 (1H,s),7.84 (1H,s),8.00 (1H,s),11.10 (1H,s) +peaks due to ethanol.

b) (+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole succinate salt, monohydrate

A solution of (+)-6-carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole R-2-pyrrolidone-5-carboxylic acid salt (1.34 g) in water (5.4 ml) was basified to pH 13.2 with 5M aqueous sodium hydroxide. The resultant mixture was extracted with butan-1-ol (5.4 ml). This extract was evaporated to give (+)-6-carboxamido-3-N-methylamino1,2,3,4-tetrahydrocarbazole as an oil/solid (735 mg) containing ca. 2% w/w butan-1-ol.

A portion of this product (232 mg) was dissolved in ethanol (1.45 ml). This solution was filtered, and added dropwise to a stirred solution of succinic acid (110 mg) in ethanol (1.45 ml)/water (0.48 ml). The mixture was seeded before the addition was complete. Stirring was continued for 30 min at ambient temperature, then 30 min at 0° C. The crystalline product was filtered off, washed with a small volume of ethanol, then dried in vacuo at 60° C. Yield=233 mg.

^{1}H NMR [250 MHz,d_6-DMSO]δ 1.87 (1H,m), 2.25 (1H,m),2.29 (4H,s),2.62 (3H,s), 2.65 (1H,m),2.83 (2H,m),3.15 (1H,dd), 3.34 (1H,m),7.09 (1H,s),7.27 (1H,d),7.61(1H,dd), 7.84 (1H,s),8.02 (1H,s),11.10 (1H,s).

We claim:

1. (+)-6-Carboxamido-3-methylamino-1,2,3,4-tetrahydrocarbazole or a salt, solvate or hydrate thereof.

2. (+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole L (+)-tartrate salt (1:1) or a solvate or hydrate thereof.

3. (+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole D (−)-tartrate salt (1:1) or a solvate or hydrate thereof.

4. (+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hemisuccinate (2:1) or a solvate or hydrate thereof.

5. (+)-6-Carboxamido-3-N-methylamino 1,2,3,4-tetrahydrocarbazole methanesulphonate or a solvate or hydrate thereof.

6. (+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole succinate (1:1) or a solvate or hydrate thereof.

7. (+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole hydrochloride or a solvate or hydrate thereof.

8. (+)-6-Carboxamido-3-N-methylamino1,2,3,4-tetrahydrocarbazole hydrobromide or a solvate or hydrate thereof.

9. (+)-6-Carboxamido-3-N-methylamino-1,2,3,4-tetrahydrocarbazole succinate monohydrate.

10. A method of treatment of a condition wherein a 5-HT_1-like agonist is indicated, which comprises administering to a subject in need thereof an effective amount of the compound of claim 1 or a physiologically acceptable salt, solvate or hydrate thereof.

11. A method of treating migraine, which comprises administering to a subject in need thereof an effective amount of a compound according to claim 1 or a physiologically acceptable salt, solvate or hydrate thereof.

12. A pharmaceutical composition comprising a compound according to claim 1 or a physiologically acceptable salt, solvate or hydrate thereof and a physiologically acceptable carrier.

* * * * *

Vanguard Medica

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14.0 PATENT CERTIFICATION

The undersigned declares that Patent Nos. 5,464,864, 5,827,871, 5,637,611, 5,618,947, 5,618,948, and 5,616,603 cover the synthetic process, formulation, composition of matter, and/or use in the treatment of migraine for frovatriptan succinate monohydrate. This product is the subject of this application for which this approval is being sought.

Patricia B.A. Barclay

Patricia BA Barclay
Head of Legal Affairs
Vanguard Medica Limited

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ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 21-006 SUPPL # ____
Trade Name _____ Generic Name Frovatriptan _____
Applicant Name ——— for Vanguard _____ HFD-120
Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/__x_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /___/

   If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES /x__/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

   d) Did the applicant request exclusivity?

   YES /__x_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_x__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No – Please indicate as such).

YES /___/ NO /_x__/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /__x_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

APPEARS THIS WAY
ON ORIGINAL

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /x/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____.

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /x/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the

clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/NO /___/

If yes, explain: _____

_____

APPEARS THIS WAY
ON ORIGINAL

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # ___ YES /___/ ! NO /___/ Explain: ___

! _____

! _____

Investigation #2 !

IND # ___ YES /___/ ! NO /___/ Explain: ___

! _____

! _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

/S/ 4/17/00

Signature of Preparer Date

Title: PM

/S/ 4/25/00

Signature of Office or Division Director Date

cc:
Archival NDA
HFD-120/Division File
HFD- 120 /Chen

HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

EXCLUSIVITY SUMMARY for NDA # 21-006 SUPPL # ____
Trade Name ___Frovelan_____Generic Name Frovatriptan_____
Applicant Name Elan_____ HFD-120
Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/__x_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /___/

   If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES /x__/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

   d) Did the applicant request exclusivity?

   YES /__x_/ NO /___/

   If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_x__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No – Please indicate as such).

YES /___/ NO /_x__/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /__x_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

APPEARS THIS WAY
ON ORIGINAL

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /x/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /x/

APPEARS THIS WAY
ON ORIGINAL

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__/ NO /__/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

APPEARS THIS WAY
ON ORIGINAL

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

APPEARS THIS WAY
ON ORIGINAL

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # ___ YES /___/ ! NO /___/ Explain: ___

! _____

! _____

Investigation #2 !

IND # ___ YES /___/ ! NO /___/ Explain: ___

! _____

! _____

APPEARS THIS WAY
ON ORIGINAL

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /__/ NO /__/

If yes, explain: _____

_____

_____

/S/ 10/31/01

Signature of Preparer Date

Title:_____

_____ _____

Signature of Office or Division Director Date

cc:
Archival NDA
HFD-120/Division File
HFD- 120 /Chen

APPEARS THIS WAY
ON ORIGINAL

HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

EXCLUSIVITY SUMMARY for NDA # 21-006 SUPPL # ____
Trade Name ____Frovelan_____Generic Name Frovatriptan_____
Applicant Name Elan_____ HFD-120
Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/__x_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /___/

   If yes, what type(SE1, SE2, etc.)?_____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES /x__/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

   d) Did the applicant request exclusivity?

   YES /__x_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_x__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No – Please indicate as such).

YES /___/ NO /_x__/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /__x_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

APPEARS THIS WAY
ON ORIGINAL

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /x/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /x/

APPEARS THIS WAY
ON ORIGINAL

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/NO /___/

If yes, explain: _____

_____

APPEARS THIS WAY ON ORIGINAL

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # ____ YES /___/ ! NO /___/ Explain: ____

Investigation #2 !

IND # ____ YES /___/ ! NO /___/ Explain: ____

APPEARS THIS WAY
ON ORIGINAL

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____ _____

Signature of Preparer Date

Title:_____

_____ _____

Signature of Office or Division Director Date

cc:
Archival NDA
HFD-120/Division File
HFD- 120 /Chen

APPEARS THIS WAY
ON ORIGINAL

HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
11/9/01 04:49:13 PM

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 021006
Trade Name: ——— (FROVATRIPTAN SUCCINATE)2.5MG TAB
Generic Name: FROVATRIPTAN SUCCINATE
Supplement Number: 000 **Supplement Type**: N
Dosage Form:
Regulatory Action: ~~AE~~ AP **Action Date**: 4/28/00
COMIS Indication: TREATMENT OF ACUTE MIGRAINE

Indication #1: Treatment of Migraine Headache
Label Adequacy: Does not apply
Formulation Needed: No new formulation is needed
Comments (if any) 10/31/01 Pediatric studies will be deferred w/ AP letter.

Lower Range	Upper Range	Status	Date
12 years	17 years	Deferred	11/8/03

This page was last edited on ~~10~~/31/01

/S/ 10/31/01

Signature Date

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DATE: November 2, 2001

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-006

SUBJECT: Division's Recommendation for Action on NDA 21-006, for the use of frovatriptan succinate for the acute treatment of migraine

NDA 21-006, for the use of frovatriptan succinate for the acute treatment of migraine, was submitted by ——— on 1/29/99. It was the subject of an Approvable letter dated 4/28/00. The letter requested the following additional data:

1) the results of a p53 mouse carcinogenicity study
2) additional long-term safety data
3) a proposal for a new trade name
4) updated stability data
5) the adoption of specific dissolution specifications
6) a commitment to revise immediate container labels

In addition, we informed the sponsor that they would receive an expiry of 24 months.

The sponsor responded to the Approvable letter with a submission dated 8/21/00. It is worth noting that the results of the requested p53 mouse study were uninterpretable, as the positive control was not distinguished from the control group. As a result, the sponsor performed and submitted a second p53 mouse study, which was considered acceptable. That report, which initiated the PDUFA clock, was submitted on 5/7/01.

The sponsor's response has been reviewed by Dr. Eric Bastings, medical officer (review dated 10/25/01), Dr. Martha Heimann, chemist (reviews dated 7/17/01 and 10/9/01), Dr. Raman Baweja, Office of Clinical Pharmacology and Biopharmaceutics (e-mail dated 10/31/01), Dr. Yeh-Fong Chen, statistician (review of carcinogenicity study dated 9/7/01), Dr. Aisar Atrakchi, pharmacologist (review dated 10/2/01), and Dr. Armando Oliva, Neurology Drugs Team Leader (memo dated 11/1/01).

Dr. Oliva's memo comprehensively summarizes the sponsor's responses, the division's position, and the important labeling changes. In brief, the sponsor has responded to all the issues raised in the Approvable letter. There is now sufficient long-term exposure presented (over 300 patients who treated at least 2

headaches/month for at least 6 months) with no adverse events of concern noted. The CMC concerns have been addressed, and the sponsor has adopted our proposed dissolution specifications.

The issues surrounding our original request for a p53 mouse study were somewhat complex, and I will not repeat them here (see my memo of 4/24/00 for a brief summary of the issues). The second p53 mouse study demonstrated a dose-related increase in sarcomas at the site of implantation of transponders. The transponders are manufactured by ——— and there are no historical data for the occurrence of such tumors in p53 mice implanted with these specific transponders. There are data on the occurrence of such tumors in association with ——— implanted transponders in traditional mice, and the incidence seen here was greater than this historical rate. The incidence seen here was also greater than that seen in the control group of the uninformative p53 mouse study, which used transponders by a different company.

As a result of these findings, the application was presented to the Executive Committee of the CAC on 10/2/01. They concluded that frovatriptan is not carcinogenic, and that additional studies did not need to be performed.

One point remains to be addressed.

We have learned, in a telephone conversation with OPDRA staff on 11/2/01, that they find the sponsor's proposed tradename, ——— While they have not issued a formal recommendation yet, they have determined that this name raises the potential for medication errors.

Specifically, as noted above, we objected to the sponsor's initial proposed tradename. They then proposed ——— and, on 11/2/00, OPDRA found this name acceptable. According to current policy, though, OPDRA re-assessed the name just prior to approval. At this re-assessment, they have discovered another drug product, also indicated for acute headache relief, called Phrenelin. Phrenelin is a combination of acetaminophen and butalbital that comes in a single fixed combination. A study performed by OPDRA revealed some confusion between these 2 products based on the similarity in the sound of the 2 names. The similarity in the names and indications, as well as the fact that each only exists in a single dosage strength (predisposing to prescribers **not** being expected to state a dosage strength when calling in a prescription) all suggest that medication errors may occur. We are particularly concerned that patients who may have contraindications to ——— who may be prescribed Phrenelin may receive ——— in error. For these reasons, we recommend that the name ——— not be permitted.

We called the sponsor today, 11/2/01, and spoke with ——— of Regulatory Affairs. We explained the issue, and the bases for our concerns, as outlined in the previous paragraph. We explained that, if the Agency determines that

——— is problematic, prudence would dictate that this name should not be approved. We further explained that, in that circumstance, we could approve the application without a tradename, and we would work closely with the sponsor to rapidly evaluate any proposed new tradename.

We and the sponsor have otherwise agreed to the labeling included in the package (for the record, I agree with Dr. Oliva that labeling may state that a maximum of 3 doses in a 24 hour period is acceptable, with language making clear that there is no evidence that doses given subsequent to 1) a failed first dose or 2) a headache recurrence after a successful first dose, are effective).

For the reasons stated, we recommend that the included Approval letter, with the appended agreed-to labeling, be issued. In particular, we recommend that the tradename ——— not be accepted.

Russell Katz, M.D.

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
11/5/01 12:41:16 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 21006/000
Stamp: 29-JAN-1999 Regulatory Due: 29-NOV-1999
Applicant: VANGUARD MEDICA
CHANCELLOR CT, SURREY GU2 5SF
GUILDFORD, , UK

Priority: 1S Org Code: 120
Action Goal: District Goal: 30-SEP-1999
Brand Name: MIGUARD(FROVATRIPTAN SUCCINATE)2.5MG TAB
Established Name:
Generic Name: FROVATRIPTAN SUCCINATE
Dosage Form: TAB (TABLET)
Strength: 2.5 MG

FDA Contacts:

L. CHEN	(HFD-120)	301-594-5529	, Project Manager
M. HEIMANN	(HFD-120)	301-594-2850	, Review Chemist
M. GUZEWSKA	(HFD-120)	301-594-5571	, Team Leader

Overall Recommendation:

ACCEPTABLE on 09-NOV-1999 by M. EGAS(HFD-322)301-594-0095

Establishment: 9616676
GALEN GROUP
SEAGOE INDUSTRIAL ESTATE
CRAIGAVON, NORTHERN IRELAND.

DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 15-JUN-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment: [redacted]

DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 09-NOV-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Establishment: [redacted]

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Milestone Date: 24-FEB-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	1215	HFD#	120	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION:	Lana Chen				frovatriptan succinate tablets
RE:	NDA #	21-006			

A. Look-alike/Sound-alike

	Potential for confusion:
Cardura	___ Low XXX Medium ___ High
Midrin	___ Low ___ Medium XXX High
Midamor	___ Low XXX Medium ___ High
Midol	XXX Low ___ Medium ___ High
Maduramycin (USAN)	___ Low ___ Medium XXX High
Miglitol	XXX Low ___ Medium ___ High

B. Misleading Aspects:

C. Other Concerns:

D. Established Name

___ Satisfactory
___ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

___ ACCEPTABLE XXX UNACCEPTABLE

F. Signature of Chair/Date /S/ 8/11/99

ORIG AMENDMENT

CENTER FOR DRUG EVALUATION AND RESEARCH

N (BM)

APR 11 2000

DUPLICATE

RECEIVED HFD-120

Confidential

April 10, 2000

Russell Katz, M.D.
Acting Director, Division of Neuropharmacological Drug Products (HFD-120)
Food and Drug Administration
Center for Drug Evaluation and Research
Attention: Document Control Room 4008
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-006 – [redacted] (frovatriptan succinate) tablets
Response to Request for Information - List of Clinical Investigators

Dear Dr Katz:

This letter is in response to a request for information in a telephone conversation between Lana Chen of your division and [redacted] on April 10, 2000. During that telephone call, Lana Chen requested a copy of the list of investigators from the original frovatriptan original NDA submission of NDA 21-006. A copy of the list of investigators as it appeared in the original submission is provided as an attachment to this cover letter. Please note that page numbers are as they appeared in the NDA and encompass pages 31 through 90.

If you have any questions concerning this communication or should you require further information, please call me at (858) 646-2467.

Yours truly,

[redacted]

cc. Lana Chen, HFD-120

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page

FOR FDA USE ONLY

APPLICATION NUMBER
NDA 21-006

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Vanguard Medica Limited	April 10, 2000
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number *(Include Area Code)***
011-44-1483-787878	011-44-1483-787811

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code), and U.S. License number if previously issued):*

Vanguard Medica Limited
Chancellor Court, Surry Research Park
Guildford, Surrey GU2 5SF, UK

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

[ ]

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
frovatriptan succinate	Miguard™ Tablets

CHEMICAL/BICCHEMICAL/BLOOD PRODUCT NAME *(if any)*	CODE NAME *(if any)*
(+) 3-methylamine-6-carboxamido-1,2,3,4-tetrahydrocarbazole succinate monohydrate	VML 251

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	2.5 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Treatment of Acute Migraine

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGIC APPLICATION (21 CFR part 601)

IN AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION X AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) X PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS X PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Previously submitted

Cross References (list related License Application, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Drug Substance: DMF ——

Drug Product: DMFs ——

This application contains the following items *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c)) *Section 3.1 only*
	4. Chemistry section
	A. Chemistry, manufacturing, and control information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) - Response to Request for Information

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
		April 10, 2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number

8.1.2 List of Investigators

A complete alphabetical listing of all physicians involved in the frovatriptan clinical studies is provided in this section. This table also includes the investigators' addresses and a designation of the study they conducted.

APPEARS THIS WAY
ON ORIGINAL

PANEL 8.1.2:1 -- LIST OF INVESTIGATORS

Investigator	Address	PK/PD Studies	Controlled	Uncontrolled
Judith Abdalla, M.D., FRCP	450 Central Avenue, Suite 208 London, Ontario N6B 2E8 Canada		251/96/07	
James Adelman, M.D.	Adelman Headache Center 510 North Elam Avenue, Suite 302 Greensboro, North Carolina 27403 USA		251/95/02 251/96/14 251/97/03	
H. Allain, M.D.	Höpital de Pontchaillou Service de Pharmacologie 1, rue Henri ie Guitloux 35000 Rennes France		251/96/09	
A. Autret, M.D.	CHU-Höpital Bretonneau Service de Neurologia 2 boulevard Tonnellé 37044 Tours, Cedex France		251/96/09	
Ricardo Ayala, M.D.	Affiliated Research Centers 1401 Centerville Road, Suite 300 Tallahassee, Florida 32308 USA		251/96/07	

PANEL 8.1.2:1 -- LIST OF INVESTIGATORS

Investigator	Address	PK/PD Studies	Controlled	Uncontrolled
Jeffrey Baggish, M.D.	Innovative Medical Research, Inc. 1001 Cromwell Bridge Road, Suite 302 Baltimore, Maryland 21286 USA			251/96/08
C. Camak Baker, M.D.	Headache Institute of Minnesota, Inc. 800 East 28th Street, Suite 307 Minneapolis, Minnesota 55407-3700 USA		251/96/06	
I. Barone-Kaganas, M.D.	Neurologisch Praxis Hirschgaesslein 21 4010 Basel Switzerland		251/96/09	
Richard Bath, M.D.	Hill Top Research/Future HealthCare 7720 Montgomery Road Cincinnati, Ohio 45236-4202 USA		251/95/02 251/96/14	
R. Beran, M.D.	6th Floor, 12 Thomas Street Chatswood, New South Wales 2067 Australia		251/96/09	

PANEL 8.1.2:1 -- LIST OF INVESTIGATORS

Investigator	Address	PK/PD Studies	Controlled	Uncontrolled
G. Berecz, M.D.	Kenezi Gyula Korhaz Rendelointezet Neurologiai Bartok Bela u. 2-26 4043 Debrecen Hungary		251/96/09	
M. Berki, M.D.	Magyar Honvedseg Kozponti Katonai Korhaz Neurologia Robert Karoly krt 44 1134 Budapest Hungary		251/96/09	
L. Biermann, M.D.	P.O. Box 95861 Waterkloof 0145 South Africa		251/96/09	
O. Blin, M.D.	Höpital La Timone Centre de Pharmacologie Clinique et D'Evaluations Therapeutiques (CPCET) 264, rue Saint-Pierre 13385 Marseille, Cedex France		251/96/09	

PANEL 8.1.2:1 -- LIST OF INVESTIGATORS

Investigator	Address	PK/PD Studies	Controlled	Uncontrolled
Harvey Blumenthal, M.D.	Kelly Professional Building 6565 South Yale, Suite 312 Tulsa, Oklahoma 74136 USA		251/95/02 251/96/14	251/96/08
Roger Bobowick, M.D.	Connecticut Clinical Research Center 160 Robbins Street Waterbury, Connecticut 06708 USA		251/96/07	
F. Boureau, M.D.	Höpital Saint-Antoine Centre d'evaluations et de traitement de la douleur 184, rue du Faubourg Saint-Antoine 75571 Cedex 12 France		251/96/09	
W. Boyd, M.D.	73 First House First Road, Grassy Park Capetown South Africa		251/96/09	
L. Brattström, M.D.	Tjarhovsgatan 1 392 81 Kalmar Sweden		251/96/09	

PANEL 8.1.2:1 -- LIST OF INVESTIGATORS

Investigator	Address	PK/PD Studies	Controlled	Uncontrolled
T. Breuer, M.D.	St. Annaziekenhuis Bogardeind 2 5664 EH Geldrop Netherlands		251/96/09	
Paul Brownstone, M.D.	Alpine Clinical Research Center 1000 Alpine Avenue, Suite 200 Boulder, Colorado 80304 USA		251/96/07	
G. Bueherz, M.D.	Hopital Moliere Longchamp Department of Neurology Rue Marconi 142 1190 Brussel Belgium		251/96/09	
Roger Cady, M.D.	Headache Care Center 1230 East Kingsley Street Springfield, Missouri 65804 USA		251/97/03 251/96/06	251/96/08
Fredric Cantor, M.D.	Rx Trials, Inc. 8807 Colesville Road, 3rd Floor Silver Spring, Maryland 20910 USA		251/96/07	

PANEL 8.1.2:1 -- LIST OF INVESTIGATORS

Investigator	Address	PK/PD Studies	Controlled	Uncontrolled
David Capobianco, M.D.	Mayo Clinic Jacksonville 4500 San Pablo Road Jacksonville, Florida 32224 USA		251/96/07	
James Claghorn, M.D.	Claghorn and Lesem Research Clinic 6750 West Loop South, Suite 1050 Bellaire, Texas 77401-4103 USA		251/95/02	
[redacted]	[redacted]	251/97/02		
M. Collard, M.D.	Höpitaux Universitaires Clinique Neurologique 67091 Strasbourg, Cedex France		251/96/09	
David Cook, M.D.	Raleigh Neurology C/o Carolina Physicians Research 23 Sunnybrook Road Raleigh, North Carolina 27610 USA			251/96/08

PANEL 8.1.2:1 -- LIST OF INVESTIGATORS

Investigator	Address	PK/PD Studies	Controlled	Uncontrolled
Clinton Corder, M.D.	Oklahoma Foundation for Cardiovascular Research, Inc. 1000 North Lincoln Boulevard, Suite 440 Oklahoma City, Oklahoma 73104 USA		251/96/06	
Bruce Corser, M.D.	Hartford Research Group Cincinnati, Ohio 45242 USA		251/97/03	
R. Corston, M.D.	New Cross Hospital, Medical Research The Ashes Wolverhampton WV10 0QP United Kingdom		251/96/09	
James Couch, M.D. Ph. D. FACP	University of Oklahoma Health Science Center 800 Northeast 13th Street, Room 6E238 Oklahoma City, Oklahoma 73104 USA		251/96/07	