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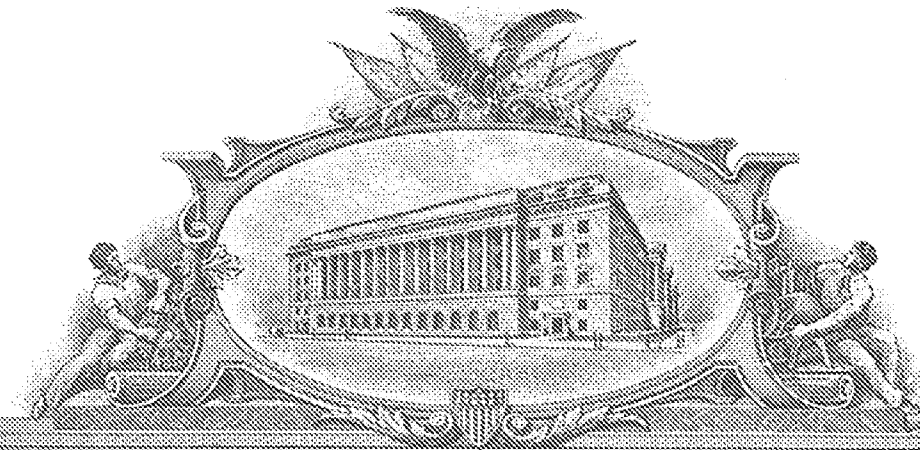
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**PROVISIONAL APPLICATION FOR
UNITED STATES PATENT**

for

**COMBINED ORAL DOSAGE FORMS OF
PALONOSETRON AND NETUPITANT**

by:

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COMBINED ORAL DOSAGE FORMS OF PALONOSETRON AND NETUPITANT

FIELD OF THE INVENTION

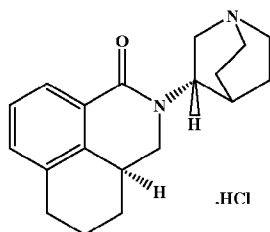
The present invention relates to combined oral dosage forms of palonosetron and netupitant.

BACKGROUND OF THE INVENTION

The nausea and emetogenic side effects of anti-cancer chemotherapy and radiotherapy are a widespread and longstanding problem. Perhaps less well known but no less important are post-operative nausea and emesis, which may have physiological mechanisms related to the effects seen for chemotherapy.

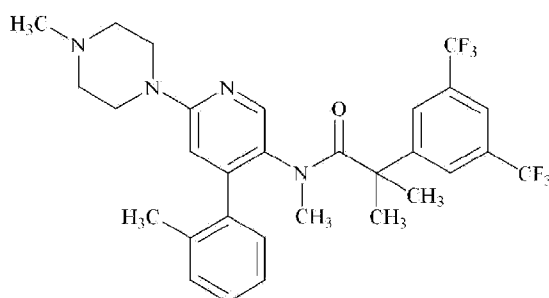
Palonosetron hydrochloride has recently emerged as a highly efficacious anti-nauseant and anti-emetic against these conditions. See PCT publications WO 2004/045615 and 2004/073714 from Helsinn Healthcare. Palonosetron hydrochloride is sold in the United States as a sterile injectable liquid under the ALOXI[®] brand, in sterile unit dose vials containing 0.075 or 0.25 mg. of palonosetron hydrochloride. Palonosetron hydrochloride also is also sold as an orally administered soft-gel dosage form containing 0.5 mg. of palonosetron hydrochloride.

The official chemical name for palonosetron hydrochloride is (3aS)-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1H-beriz[de] isoquinoline hydrochloride (CAS No. 119904-90-4); its empirical formula is C₁₉H₂₄N₂O·HCl, and its molecular weight is 332.87. The compound is represented by the following chemical structure:



Methods of synthesizing palonosetron are described in U.S. Patent Nos. 5,202,333 and 5,510,486. Pharmaceutically acceptable dosage forms are described in PCT publications WO 2004/067005 and WO 2008/049552 from Helsinn Healthcare.

Netupitant is a selective NK₁ receptor antagonist of the formula 2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethyl-N-[4-(2-methylphenyl)-6-(4-methylpiperazin-1-yl)pyridin-3-yl]propanamide, or Benzeneacetamide, N, α , α -trimethyl-N-[4-(2-methylphenyl)-6-(4-methyl-1-piperazinyl)-3-pyridinyl]-3,5-bis(trifluoromethyl)-. The compound has a molecular weight of 478.61, CAS registry number 290297-26-6, and the below chemical structure:



Methods of synthesizing netupitant are described in U.S. Patent Nos. 6,297,375, 6,479,483, and 6,303,790. U.S. Patent No. 6,719,996 described methods of formulating netupitant to overcome the molecule's low bioavailability.

Merck & Co. markets another NK₁ antagonist, aprepitant, as EMEND[®] in the United States. The product is approved in a capsule dosage form, and is marketed for the prevention of CINV (acute and delayed) in combination with other anti-emetic agents such as ondansetron and metoclopramide. The product reportedly has a terminal half-life of from 9 to 13 hours.

SUMMARY OF THE INVENTION

The present invention is premised on the discovery that netupitant is a remarkably potent anti-emetic in spite of its low bioavailability, and that the combination of netupitant and palonosetron in oral dosage forms has improved anti-emetic effects over either ingredient alone. Based on these discoveries, solid oral dosage forms have been developed that combine netupitant and palonosetron for the treatment of acute and delayed emesis.

The dosage forms are extremely versatile and stable owing to their unique design and formulation. This versatility and stability is accomplished by formulating the netupitant and palonosetron in separate dosage forms and combining the dosage forms in one capsule. Thus, for example, the palonosetron can be formulated in a small gel-cap at a dose of around 0.5 mg., and the netupitant formulated in a tablet at a dose of about 150 mg. A capsule can then be filled with one or more palonosetron gel-caps and one or more netupitant tablets, depending on the

therapeutic objective for the product. Because the palonosetron and netupitant are in separate dosage units, they can be formulated without regard to the stability of the other, and without degradation to by-products, for instance (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate, a degradation by-product of palonosetron.

Thus, in one embodiment the invention provides an orally administered dosage form comprising a combination of palonosetron and netupitant, or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides an orally administered capsule dosage form comprising (a) an outer shell; (b) one or more tablets housed within said outer shell, each comprising netupitant or a pharmaceutically acceptable salt or prodrug thereof and one or more pharmaceutically acceptable excipients; and (c) one or more soft-gel capsules housed within the outer shell, each comprising palonosetron or a pharmaceutically acceptable ester or prodrug thereof and one or more pharmaceutically acceptable excipients; wherein said dosage form comprises (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate in an amount that does not exceed 3 wt.%.

In still other embodiments the invention provides methods of treating acute and delayed-onset emesis by administering the dosage forms of the present invention to a human in need thereof, preferably shortly before the emesis inducing event.

Additional embodiments and advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The embodiments and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description, serve to explain the principles of the invention.

FIG. 1 is an illustration depicting a capsule containing one soft-gel capsule of palonosetron and three tablets of netupitant.

FIG. 2 is a graph depicting the pharmacokinetic profile of netupitant in humans following oral administration of netupitant alone and netupitant together with palonosetron.

FIG. 3 is a graph depicting the pharmacokinetic profile of palonosetron in humans following oral administration of palonosetron alone and palonosetron together with netupitant.

DETAILED DESCRIPTION OF THE INVENTION

The present invention may be understood more readily by reference to the following definitions and detailed description of preferred embodiments of the invention and the non-limiting Examples included therein.

Definitions and Use of Terms

As used in this specification and in the claims which follow, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “an ingredient” includes mixtures of ingredients, reference to “an active pharmaceutical agent” includes more than one active pharmaceutical agent, and the like.

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises," means "including but not limited to," and is not intended to exclude, for example, other additives, components, integers or steps.

The terms “treating” and “treatment,” when used herein, refer to the medical management of a patient with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes active treatment, that is, treatment directed specifically toward the improvement of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes palliative

treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the associated disease, pathological condition, or disorder.

“Pharmaceutically acceptable” means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use. Pharmaceutically acceptable salts of palonosetron include palonosetron hydrochloride. Pharmaceutically acceptable pro-drugs of netupitant include those described in U.S. Patent Nos. 6,593,472, 6,747,026 and 6,806,370, including the N-oxide of netupitant. The contents of these publication are incorporated herein by reference.

When ranges are given by specifying the lower end of a range separately from the upper end of the range, it will be understood that the range can be defined by selectively combining any one of the lower end variables with any one of the upper end variables that is mathematically possible.

When used herein the term “about” or “ca.” will compensate for variability allowed for in the pharmaceutical industry and inherent in pharmaceutical products, such as differences in product strength due to manufacturing variation and time-induced product degradation. The term allows for any variation which in the practice of pharmaceuticals would allow the product being evaluated to be considered bioequivalent to the recited strength of a claimed product.

When doses or weight percentages of active ingredient are expressed herein, it will be understood that the doses or weight percentages are based on the free base of the active ingredient when the active ingredient is present as a pharmaceutically acceptable salt or prodrug.

Combined Oral Dosage Forms

As discussed above, the invention provides versatile combined oral dosage forms of palonosetron and netupitant that can be readily modified depending on the therapeutic objective, and that do not present issues of stability and degradation. In a preferred embodiment, the invention provides a capsule for oral administration made from a hard outer shell that houses one

or more netupitant tablets and one or more palonosetron soft-gel capsules. The finished capsule and the tablet(s) and soft-gel capsule(s) housed within the capsule shell are all preferably formulated as immediate release dosage forms. The invention further provides a method of treating emesis comprising orally administering to a patient suffering from emesis, or at risk for suffering emesis, a dosage form of the present invention.

While the netupitant is preferably formulated in a solid tablet, it will be understood that it can be formulated in any solid form that is suitable for oral administration including, for example, a tablet or capsule (hard or soft-gel). In a preferred embodiment, the netupitant is formulated in a tablet. The number of netupitant units contained within the combined dosage form can be, for example, from 1 to 10, 1 to 5, or 1 to 3. The netupitant units within the combined dosage form can provide anywhere from 50 to 500 mg. of netupitant on an aggregate basis, preferably from 100 to 350 mg. Each netupitant unit preferably comprises from 50 to 200 mg. of netupitant, more preferably 100 to 150 mg. of netupitant, and most preferably 100 or 150 mg. of netupitant.

The palonosetron can also be formulated in any solid form that is suitable for oral administration, although it is preferably formulated as a soft-gel capsule. The number of palonosetron units within the combined dosage form can be, for example, from 1 to 5, from 1 to 3 or just 1. Each of the palonosetron units within the combined dosage form can provide anywhere from 0.01 to 5.0 mg. palonosetron, preferably from 0.1 to 1.0 mg. palonosetron on an aggregate basis. Each palonosetron unit will preferably comprise from 0.1 to 1.0 mg. of palonosetron, most preferably about 0.25, 0.5, 0.75 or 1.0 mg. of palonosetron.

Figure 1 illustrates an exemplary embodiment of a combined oral dosage form of palonosetron and netupitant. The dosage form 10 comprises a two piece hard outer shell that includes a body 20 and a cap 22. The dosage form 10 contains one palonosetron soft-gel capsule 30 and three netupitant tablets 40.

Hard Outer Shell

The hard outer shell of the present invention can be made of any pharmaceutically acceptable material that dissolves in gastric fluids. Preferred materials for the hard outer shell include, for example, gelatin, cellulose, starch, or hydroxypropyl methylcellulose (HPMC). In a particular embodiment of the invention, the hard outer shell has a maximum oxygen

permeability. Preferably, the oxygen permeability is less about 1.0×10^{-3} , 5.0×10^{-4} , 1.0×10^{-4} , 5.0×10^{-5} , or even 2.0×10^{-5} ml-cm/(cm²·24 hr. atm).

The hard outer shell can be a continuous structure. Alternatively, the hard outer shell can be a two-piece hard capsule.

Soft-Gel Capsule

The soft-gel capsule used for the palonosetron preferably comprises a soft outer shell and a liquid inner fill composition comprising palonosetron hydrochloride. Non-limiting examples of suitable palonosetron soft-gel capsules are provided in PCT publication WO 2008/049552, the contents of which are hereby incorporated by reference.

The soft outer shell of the soft-gel capsule can contain any type of material that dissolves in gastric fluids. Preferred materials for the soft outer shell include, for example, gelatin, cellulose, starch, or hydroxypropyl methylcellulose (HPMC). The soft-gel capsule can further comprise shell excipients such as glycerin, sorbitol, and colorants/opacifiers such as titanium dioxide. The soft-gel capsule can further include solvents such as purified water. In particular embodiments of the invention, the outer shell has a maximum oxygen permeability, preferably of no more than 1.0×10^{-3} , 5.0×10^{-4} , 1.0×10^{-4} , 5.0×10^{-5} , or even 2.0×10^{-5} ml-cm/(cm²·24 hr. atm). Suitable soft-gel capsules include the 1.5-oval gelatine capsule shell manufactured by Catalent Pharma Solutions.

The liquid fill is preferably composed predominantly of one or more lipophilic components in an amount of from 50 wt.% to 99 wt.%, preferably from 75 wt.% to 98 wt.%. Preferred lipophilic components include, for example, mono- and di-glycerides of fatty acids, especially including the mono- and di-glycerides of capryl/capric acid. The liquid fill may also contain glycerin, preferably in an amount of from 1 to 15 wt.%, more preferably from 2 to 10 wt.%. In one preferred embodiment, both the shell and the inner fill composition comprise glycerin. In another preferred embodiment, the liquid fill comprises about 0.25, 0.50, 0.75 mg., or more of palonosetron as palonosetron hydrochloride.

The fill composition may comprise various means to facilitate the transition of palonosetron from the dosage form to the gastrointestinal fluids of the GI tract, so that the palonosetron may be more readily absorbed into the bloodstream. For example, the liquid fill composition may contain a surfactant, optimally in an amount of from 0.1 wt.% to 6 wt.%, from

0.5 wt.% to 5 wt.%, or from 1.0 wt.% to 3.0 wt.%. The liquid fill composition preferably comprises greater than 0.1, 0.5, or 1.0 wt.% of surfactant, and less than 10, 8, 5, 4, or even 4 wt.% of surfactant. A particularly preferred surfactant is polyglyceryl oleate.

Alternatively or in addition, the transitioning means for a liquid filled capsule may comprise water that forms a single phase or microemulsion with the other liquid ingredients in the excipient base. The liquid fill composition preferably comprises from 0.05 wt.% to 30 wt.% water, from 1 wt.% to 20 wt.% water, or from 2 wt.% to 10 wt.% water. The liquid fill preferably comprises greater than 0.1, 0.5 or 1.0 wt.% water, and less than 20, 15, 10, 8 or 5 wt.% water.

The active agent, which is preferably palonosetron hydrochloride, is preferably present in the fill composition in an amount ranging from 0.01 to 10.0 wt.%, from 0.05 to 5.0 wt.%, or from 0.1 wt.% to 2.0 wt.%. Alternatively, particularly stable formulations have been found where the concentration of palonosetron exceeds 0.3%, preferably at a concentration no greater than 1 wt.%.

Tablet

The tablets of the present invention can include from 20 to 95 wt.% of netupitant, and preferably comprises from 60 to 80 wt.% of netupitant. In addition, the tablets can contain diluents, disintegrants, surfactants, binders, glidants, and/or lubricants. In a particular embodiment, the tablet comprises from 5 to 25 wt.% of microcrystalline cellulose. The microcrystalline cellulose can function as a diluent and disintegrant, and preferably comprises 15 wt.% of the tablet. Another suitable disintegrant is sodium croscarmellose, which can be present in the tablet in an amount of from 1 to 5 wt.%, preferably 2 wt.%.

A suitable binder for use in the tablet is polyvinylpyrrolidone, which can be present in the tablet in an amount from 1 to 10 wt.% of the tablet, and preferably 5 wt.%. A suitable glidant for use in the tablet is colloidal silicon dioxide, which can be present in the tablet in an amount of 2 wt.%. Suitable lubricants for use in the tablet include sodium stearyl fumarate and magnesium stearate, which can be present in the tablet in an amount of 0.7 wt.% and 0.35 wt.%, respectively.

Methods of Treatment

In still further embodiments, the invention provides methods of treating emesis by administering one or more of the dosage forms described herein. The dosage form is preferably

administered shortly before the emesis inducing event (i.e. no more than 2 hours before the event). The emesis may be acute phase emesis (i.e. emesis experienced within about 24 hours of an emesis inducing event), or delayed emesis (i.e. emesis experienced after the acute phase, but within seven, six, five or four days of an emesis inducing event). The emesis may constitute chemotherapy induced nausea and vomiting (“CINV”), from moderately or highly emetogenic chemotherapy, radiation therapy induced nausea and vomiting (“RINV”), or post-operative nausea and vomiting (“PONV”).

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.) but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at room temperature, and pressure is at or near atmospheric.

EXAMPLE 1 -- REPRESENTATIVE SOFT-GEL FORMULATION

Table 1 below describes representative formulations for a soft-gel capsule containing 0.5 mg. of palonosetron.

Table 1: Representative Soft-Gel Formulation

Ingredient	Approximate Amount (mg./Capsule)	Function
<i>Fill Solution</i>		
Palonosetron HCl	0.56 ¹	Active
Mono- and di-glycerides of Capryl/Capric Acid (Capmul MCM)	62.19	Solvent vehicle
Glycerin, anhydrous, USP/Ph Eur	3.37	Plasticizer
Polyglyceryl oleate (Plurol Oleique CC 497)	0.87	Surfactant
Purified water, USP/Ph Eur	2.94	Co-solvent
Butylated hydroxyanisole (BHA), NF/Ph Eur	0.07	Antioxidant
Nitrogen	-	
Theoretical fill weight	70.00 mg.	
<i>Gelatine Capsule Shell, 1.5-oval (Catalent Pharma Solutions)²</i>		
Gelatine (type 195), NF/Ph Eur	-	Shell
Sorbitol Special/Glycerin Blend 50/50	-	Plasticizer
Titanium dioxide, USP/Ph Eur	-	Colorant/Opacifier
Purified water, USP/Ph Eur	-	Solvent

¹Corresponds to 0.50 mg. free base

²Quantitative composition of capsule shell is proprietary to Catalent Pharma Solutions

EXAMPLE 2 -- REPRESENTATIVE TABLET FORMULATION

Table 2 below describes a representative formulation for a tablet containing 100 mg. of netupitant.

Table 2: Representative Tablet Formulation

Ingredient	Approximate Amount (mg./Tablet)	Function
Netupitant, milled	100	Active
Microcrystalline cellulose pH 101	20.5	Diluent and disintegrant
Sucrose Lauric Acid Esters	10.0	Surfactant
Polyvinylpyrrolidone K30	7.0	Binder
Sodium croscarmellose	3.0	Disintegrant
Colloidal Silicon Dioxide	3.0	Glidant
Sodium Stearyl Fumarate	1.0	Lubricant
Magnesium Stearate	0.5	Lubricant
Total weight	145 mg.	

EXAMPLE 3 – PHARMACOKINETICS OF COMBINED DOSAGE FORM

Objective

The effects of palonosetron on the pharmacokinetics (PK) of netupitant and the effects of netupitant on the PK of palonosetron were examined in healthy volunteers.

Methods

A randomized, open, 3-way crossover study was conducted. Each subject participated in 3 treatment periods, each lasting approximately 12 days (Day -1 to Day 11). The treatment periods were separated by wash-out periods of no less than 14 days (between Day 1 of any 2 consecutive treatment periods).

The following treatments were investigated:

Treatment A: oral netupitant 450 mg administered as single dose of three 150 mg capsules.

Treatment B: oral palonosetron 0.75 mg and oral netupitant 450 mg administered simultaneously as three capsules of 150 mg netupitant followed by 1 capsule of 0.75 mg palonosetron.

Treatment C: oral palonosetron 0.75 mg administered as single dose as one 0.75 mg capsule.

Doses were administered under fasting conditions. Subjects fasted over-night for approximately 10 hours. Water, however, was permitted up to 1 hour pre-dose. Food intake was permitted 4 hours post-dose, and water was allowed ad lib 1 hour post-dose.

Doses were administered with the subject in an upright position. The subjects remained in an upright position for 4 hours post-dose. The capsules were swallowed whole with 250 mL of room-temperature tap water. Repeated PK blood sampling (for netupitant and/or palonosetron) was performed.

Results

The primary PK variables assessed for netupitant and palonosetron were the maximum plasma concentration observed (C_{max}), the area under the plasma concentration versus time curve from time zero to the last quantifiable sampling time point (t) (AUC_{0-t}), and the area under the plasma concentration versus time curve from time zero to infinity (AUC_{0-inf}). The secondary PK

variables assessed were the terminal elimination half-life ($t_{1/2,z}$), and the time at which the maximum plasma concentration was observed (t_{max}). Results are reported below in Tables 3 and 4, and in Figures 2 and 3.

Table 3: Summary of Netupitant Pharmacokinetic Parameters

Parameter	Netupitant 450 mg	Palonosetron 0.75 mg + Netupitant 450 mg
AUC _{0-t} [h* μ g/L]	22808 (7270)	22775 (10064)
AUC _{0-inf} [h* μ g/L]	25927 (10156)	26241 (13219)
C _{max} [μ g/L]	650.2 (257.8)	659.7 (325.7)
t _{max} (h)	4.50 (3.00 ; 24.00)	4.50 (3.00 ; 23.95)
t _{1/2,z} (h)	71.81 (37.10 ; 261.61)	78.31 (50.17 ; 196.13)

Mean and SD are shown, except for t_{max} and t_{1/2,z}, where median and range are shown.

As can be seen in Table 4 below, the median t_{max} was 0.5 hour shorter after administration of palonosetron in combination with netupitant, whereas median apparent t_{1/2,z} was similar after the combination and the single dose administration.

Table 4: Summary of Palonosetron Pharmacokinetic Parameters

Parameter	Palonosetron 0.75 mg	Palonosetron 0.75 mg + Netupitant 450 mg
AUC _{0-t} [h* μ g/L]	67415 (19554)	74230 (24866)
AUC _{0-inf} [h* μ g/L]	70813 (20415)	77254 (25402)
C _{max} [μ g/L]	1638.4 (415.5)	1863.1 (487.1)
t _{max} (h)	5.02 (4.00 ; 8.00)	4.50 (3.00 ; 6.02)
t _{1/2,z} (h)	34.73 (19.61 ; 70.46)	36.91 (20.23 ; 56.08)

Mean and SD are shown, except for t_{max} and t_{1/2,z}, where median and range are shown.

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains. It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of

the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

CLAIMS

What is claimed is:

- 1) An orally administered dosage form comprising a combination of palonosetron and netupitant, or a pharmaceutically acceptable salt or prodrug thereof, comprising:
 - a) an outer shell;
 - b) one or more netupitant units housed within said outer shell, each comprising said netupitant or pharmaceutically acceptable salt or prodrug thereof and one or more pharmaceutically acceptable excipients; and
 - c) one or more palonosetron units housed within said outer shell, each comprising said palonosetron or pharmaceutically acceptable ester or prodrug thereof and one or more pharmaceutically acceptable excipients;wherein said dosage form comprises (3S)-3-[(3aS)-1-oxo- 2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate in an amount that does not exceed 3 wt. %.
- 2) The dosage form of claim 1, comprising about 0.5 mg. of palonosetron hydrochloride and from 100-300 mg. of netupitant, wherein said weight of palonosetron hydrochloride is based on the weight of the free base.
- 3) The dosage form of claim 1, wherein said one or more netupitant units are in the form of one or more orally administered tablets, and said palonosetron units are in the form of one or more orally administered soft-gel capsules.
- 4) The capsule of claim 3, wherein said outer shell of said capsule has an oxygen permeability of less than 1.0×10^{-3} ml·cm/(cm²·24 hr. atm).
- 5) The capsule of claim 3, wherein each of said tablets comprises about 150 mg. of netupitant.
- 6) The capsule of claim 3, wherein each of said soft-gel capsules comprises an inner fill composition comprising from 0.1 to 2.0 mg. of palonosetron hydrochloride.
- 7) The capsule of claim 3, wherein each of said soft-gel capsules comprises an inner fill composition comprising from 75 to 98 wt. % of one or more lipophilic components.
- 8) The capsule of claim 3, wherein each of said soft-gel capsules comprises an outer shell having an oxygen permeability of less than 1.0×10^{-3} ml·cm/(cm²·24 hr. atm).

- 9) An orally administered capsule dosage form comprising:
- a) an outer shell;
 - b) one or more tablets housed within said outer shell, each comprising netupitant or a pharmaceutically acceptable salt or prodrug thereof and one or more pharmaceutically acceptable excipients; and
 - c) one or more soft-gel capsules housed within said outer shell, each comprising palonosetron or a pharmaceutically acceptable ester or prodrug thereof and one or more pharmaceutically acceptable excipients;
- wherein said dosage form comprises (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate in an amount that does not exceed 3 wt.%.
- 10) The capsule of claim 9 comprising about 0.5 mg. of palonosetron hydrochloride and from 100-300 mg. of netupitant, wherein said weight of palonosetron hydrochloride is based on the weight of the free base.
- 11) The capsule of claim 9, wherein said outer shell of said capsule has an oxygen permeability of less than 1.0×10^{-3} ml·cm/(cm²·24 hr. atm).
- 12) The capsule of claim 9, wherein each of said tablets comprises about 150 mg. of netupitant.
- 13) The capsule of claim 9, wherein each of said soft-gel capsules comprises an outer shell having an oxygen permeability of less than 1.0×10^{-3} ml·cm/(cm²·24 hr. atm).
- 14) The capsule of claim 9, wherein said soft-gel capsule comprises an inner fill composition comprising from 0.1 to 2.0 mg. of palonosetron hydrochloride.
- 15) The capsule of claim 9, wherein said soft-gel capsule comprises an inner fill composition comprising from 75 to 98 wt.% of one or more lipophilic components.
- 16) A method of treating emesis comprising administering to a human in need thereof the dosage form of claim 1.
- 17) The method of claim 16 wherein said emesis is delayed-onset emesis.
- 18) A method of treating emesis comprising administering to a human in need thereof the dosage form of claim 9.
- 19) The method of claim 18 wherein said emesis is delayed-onset emesis.

COMBINED ORAL DOSAGE FORMS OF
PALONOSETRON AND NETUPITANT

ABSTRACT

Provided are synergistically effective combinations of netupitant and palonosetron, in the form of capsules that contain netupitant tablets and a palonosetron soft-gel capsule housed within.

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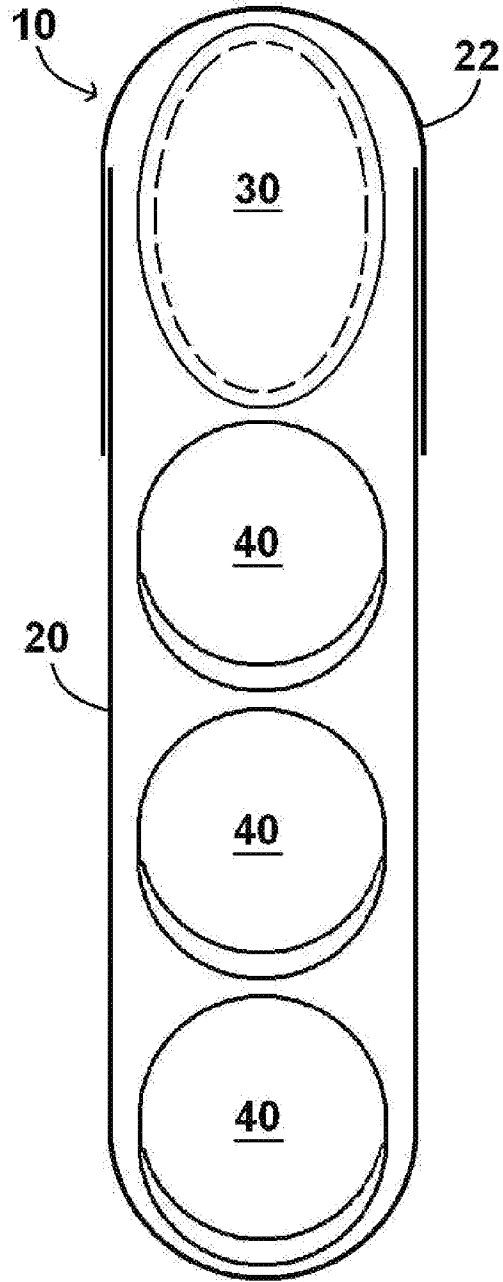


Figure 1

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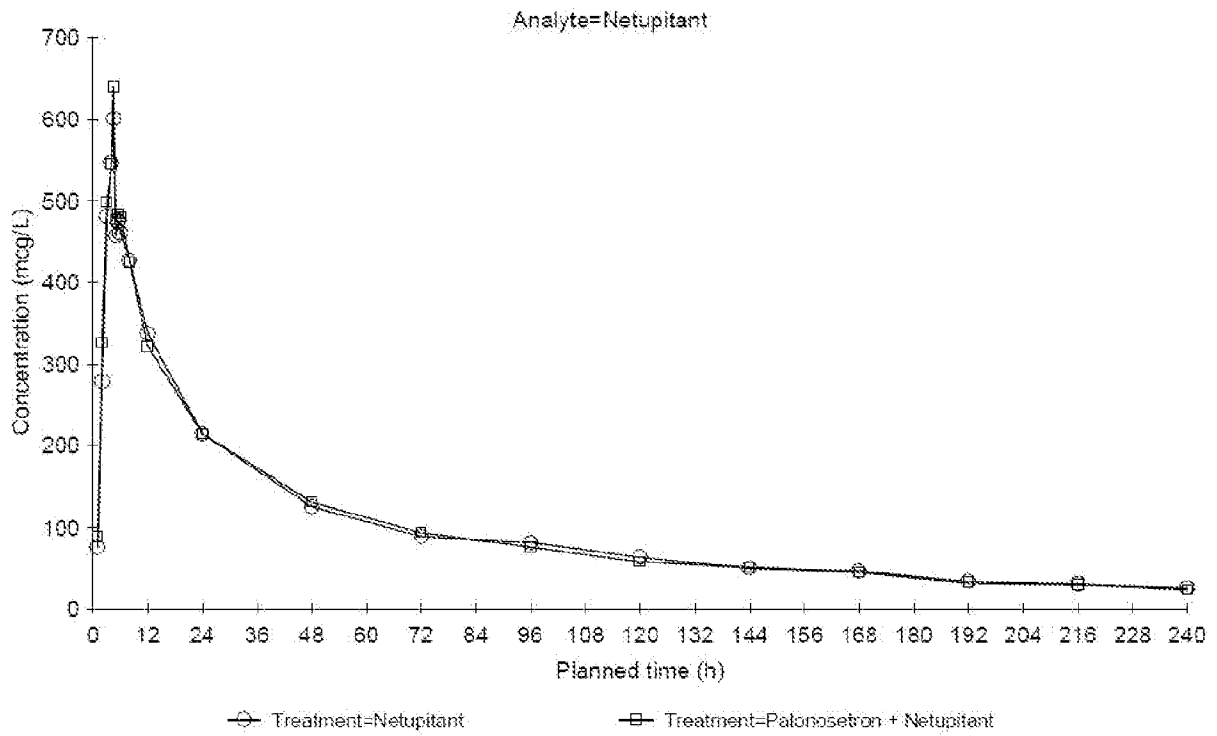


Figure 2

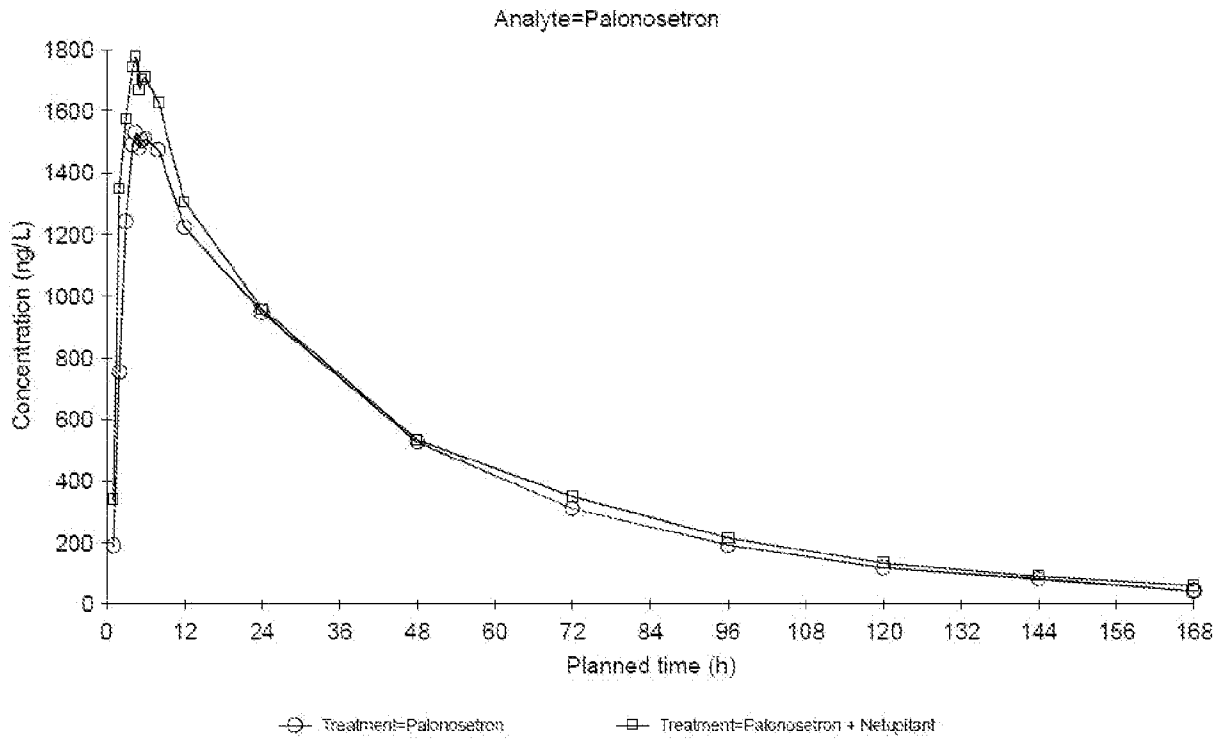


Figure 3

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	23278.11
		Application Number	
Title of Invention	COMBINED ORAL DOSAGE FORMS OF PALONOSETRON AND NETUPITANT		
The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.			

Secrecy Order 37 CFR 5.2

<input type="checkbox"/>	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)
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Applicant Information:

Applicant 1				
Applicant Authority <input checked="" type="radio"/> Inventor		<input type="radio"/> Legal Representative under 35 U.S.C. 117		<input type="radio"/> Party of Interest under 35 U.S.C. 118
Prefix	Given Name	Middle Name	Family Name	Suffix
	Roberta		Cannella	
Residence Information (Select One) <input type="radio"/> US Residency <input checked="" type="radio"/> Non US Residency <input type="radio"/> Active US Military Service				
City	Varese	Country Of Residence	IT	
Citizenship under 37 CFR 1.41(b)				
Mailing Address of Applicant:				
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Address 2				
City	Varese	State/Province		
Postal Code		Country	IT	
Applicant 2				
Applicant Authority <input checked="" type="radio"/> Inventor		<input type="radio"/> Legal Representative under 35 U.S.C. 117		<input type="radio"/> Party of Interest under 35 U.S.C. 118
Prefix	Given Name	Middle Name	Family Name	Suffix
	Daniele		Bonadeo	
Residence Information (Select One) <input type="radio"/> US Residency <input checked="" type="radio"/> Non US Residency <input type="radio"/> Active US Military Service				
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Citizenship under 37 CFR 1.41(b)				
Mailing Address of Applicant:				
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Address 2				
City	Varese	State/Province		
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Applicant 3				
Applicant Authority <input checked="" type="radio"/> Inventor		<input type="radio"/> Legal Representative under 35 U.S.C. 117		<input type="radio"/> Party of Interest under 35 U.S.C. 118
Prefix	Given Name	Middle Name	Family Name	Suffix
	Fabio		Trento	
Residence Information (Select One) <input type="radio"/> US Residency <input checked="" type="radio"/> Non US Residency <input type="radio"/> Active US Military Service				
City	Como	Country Of Residence	IT	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	23278.11
	Application Number	
Title of Invention	COMBINED ORAL DOSAGE FORMS OF PALONOSETRON AND NETUPITANT	

Citizenship under 37 CFR 1.41(b)	IT		
Mailing Address of Applicant:			
Address 1	Via Alla Valle, 20B, Pare'		
Address 2			
City	Como	State/Province	
Postal Code		Country	IT
Applicant 4			
Applicant Authority	<input checked="" type="radio"/> Inventor	<input type="radio"/> Legal Representative under 35 U.S.C. 117	<input type="radio"/> Party of Interest under 35 U.S.C. 118
Prefix	Given Name	Middle Name	Family Name
	Riccardo		Braglia
Residence Information (Select One) <input type="radio"/> US Residency <input checked="" type="radio"/> Non US Residency <input type="radio"/> Active US Military Service			
City	Lugano-Pazzallo	Country Of Residence	CH
Citizenship under 37 CFR 1.41(b)	CH		
Mailing Address of Applicant:			
Address 1	Via Pian Scairolo 9 -- CH-6912		
Address 2			
City	Lugano-Pazzallo	State/Province	
Postal Code		Country	CH
All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button. <input type="button" value="Add"/>			

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).	
<input type="checkbox"/> An Address is being provided for the correspondence information of this application.	
Customer Number	53449
Email Address	<input type="button" value="Add Email"/> <input type="button" value="Remove Email"/>

Application Information:

Title of the Invention	COMBINED ORAL DOSAGE FORMS OF PALONOSETRON AND NETUPITANT		
Attorney Docket Number	23278.11	Small Entity Status Claimed	<input checked="" type="checkbox"/>
Application Type	Provisional		
Subject Matter	Utility		
Suggested Class (if any)		Sub Class (if any)	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	1

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	23278.11
	Application Number	
Title of Invention	COMBINED ORAL DOSAGE FORMS OF PALONOSETRON AND NETUPITANT	

Publication Information:

<input type="checkbox"/>	Request Early Publication (Fee required at time of Request 37 CFR 1.219)
<input type="checkbox"/>	Request Not to Publish. I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

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Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Enter either Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

Please Select One:	<input checked="" type="radio"/> Customer Number	<input type="radio"/> US Patent Practitioner	<input type="radio"/> Limited Recognition (37 CFR 11.9)
Customer Number	53449		

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This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status			<input type="button" value="Remove"/>
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

			<input type="button" value="Remove"/>
Application Number	Country	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			<input type="radio"/> Yes <input checked="" type="radio"/> No

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Assignee Information:

Providing this information in the application data sheet does not substitute for compliance with any requirement of part 3 of Title 37 of the CFR to have an assignment recorded in the Office.

Assignee 1

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	23278.11
	Application Number	
Title of Invention	COMBINED ORAL DOSAGE FORMS OF PALONOSETRON AND NETUPITANT	

If the Assignee is an Organization check here. <input checked="" type="checkbox"/>			
Organization Name	Helsinn Therapeutics SA		
Mailing Address Information:			
Address 1	P.O. Box 357		
Address 2	6915 Pambio-Noranco		
City	Lugano	State/Province	
Country	CH	Postal Code	
Phone Number		Fax Number	
Email Address			
Additional Assignee Data may be generated within this form by selecting the Add button.			

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.					
Signature	//Clark G. Sullivan//		Date (YYYY-MM-DD)	2009-11-18	
First Name	Clark	Last Name	Rogers	Registration Number	36942

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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Electronic Acknowledgement Receipt

EFS ID:	6482222
Application Number:	61262470
International Application Number:	
Confirmation Number:	2370
Title of Invention:	COMBINED ORAL DOSAGE FORMS OF PALONOSETRON AND NETUPITANT
First Named Inventor/Applicant Name:	Roberta Cannella
Customer Number:	53449
Filer:	Clark G. Sullivan/Geoff Rogers
Filer Authorized By:	Clark G. Sullivan
Attorney Docket Number:	23278.11
Receipt Date:	18-NOV-2009
Filing Date:	
Time Stamp:	19:11:36
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$110
RAM confirmation Number	6938
Deposit Account	504667
Authorized User	

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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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		Specification	1	14	
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		Abstract	17	17	
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