Title: DONEPEZIL COMPOSITIONS AND METHOD OF TREATING ALZHEIMER’S DISEASE

Abstract: Oral dosage forms comprising donepezil or a pharmaceutically acceptable salt thereof (e.g., donepezil hydrochloride) alone or in combination with a second active ingredient (e.g., memantine hydrochloride or a pharmaceutically acceptable salt thereof) for the treatment of Alzheimer’s disease are provided. The oral dosage forms comprise donepezil granules that may be sprinkled on food and can significantly improve compliance in patients with swallowing difficulty.
DONEPEZIL COMPOSITIONS AND METHODS OF TREATING ALZHEIMER'S DISEASE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 U.S.C. § 119, based on U.S. Provisional Application Serial No. 61/935,596 filed on February 4, 2014, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to compositions comprising donepezil or a pharmaceutically acceptable salt thereof (e.g., donepezil hydrochloride) alone or in combination with memantine or a pharmaceutically acceptable salt thereof (e.g., memantine hydrochloride) and methods for treating disorders (e.g. Alzheimer's disease) comprising administering donepezil or a pharmaceutically acceptable salt thereof (e.g., donepezil hydrochloride) alone or in combination with memantine or a pharmaceutically acceptable salt thereof (e.g., memantine hydrochloride).

BACKGROUND OF THE INVENTION

Donepezil hydrochloride (Aricept®) is an acetylcholinesterase inhibitor (AChEi) approved for the treatment of dementia of the Alzheimer's type in the United States and is available as 5 mg and 10 mg immediate release tablets, 23 mg sustained release tablets and as 5 mg and 10 mg orally disintegrating tablets.

Memantine (Namenda®) (l-amino-3,5-dimethyl adamantane), which is disclosed, e.g., in U.S. Pat. Nos. 4,122,193; 4,273,774; and 5,061,703, is a systemically-active uncompetitive NMDA receptor antagonist having low to moderate affinity for the receptor and strong voltage dependency and rapid blocking/unblocking kinetics. Memantine hydrochloride is approved for the treatment of moderate to severe dementia of the Alzheimer's type in the United States and is available as Namenda® (5 and 10 mg BID immediate release tablets) and Namenda XR® (28 mg once-daily extended release capsules).

There is an existing and continual need for formulations comprising donepezil that provide reliable delivery and absorption of the active ingredient, while also providing
a dosing regimen that is straightforward and increases patient compliance. The present invention provides novel compositions and dosage forms comprising donepezil hydrochloride alone or in combination with a second active ingredient (e.g., memantine hydrochloride or a pharmaceutically acceptable salt thereof) that can be sprinkled on food and thereby increase patient compliance.

SUMMARY OF THE INVENTION

According to some embodiments, the present invention provides compositions comprising a therapeutically effective amount of donepezil or a pharmaceutically acceptable salt thereof (e.g., donepezil hydrochloride) for oral administration.

According to some embodiments, the present invention provides methods for treating Alzheimer's disease by administering to a patient in need thereof, a therapeutically effective amount of donepezil or a pharmaceutically acceptable salt thereof (e.g., donepezil hydrochloride) alone or in combination with memantine or a pharmaceutically acceptable salt thereof (e.g., memantine hydrochloride).

According to some embodiments, the present invention provides methods of treating moderate to severe dementia of the Alzheimer's type comprising administering an oral dosage form comprising a composition comprising donepezil or a pharmaceutically acceptable salt thereof to a patient in need thereof wherein the composition has an angle of repose of less than about 40 degrees.

According to some embodiments, the present invention provides methods of treating moderate to severe dementia of the Alzheimer's type comprising administering an oral dosage form comprising a composition comprising donepezil or a pharmaceutically acceptable salt thereof to a patient in need thereof wherein the dosage form may be sprinkled on food and more than 80% of the donepezil or pharmaceutically acceptable salt thereof dissolves within 30 minutes of administration to the patient.

According to some embodiments, the present invention provides methods of treating moderate to severe dementia of the Alzheimer's type comprising administering an oral dosage form comprising a composition comprising donepezil or a pharmaceutically acceptable salt thereof to a patient in need thereof wherein the oral
dosage form has a volume of less than 0.70 ml and the composition has a drag loading of about 10%.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows Comparative Dissolution Profiles of donepezil granules filled in capsules 10 mg and Aricept tablets 10 mg.

Figure 2 shows Comparative Dissolution Profiles of Donepezil HCl Capsules (Prepared by Roller Compaction, Containing Lactose and MCC) and Aricept Tablets 10 mg.

Figure 3 shows Comparative Dissolution Profiles of Donepezil HCl 10 mg Capsules and Aricept Tablets in 0.1N HCl.

Figure 4 shows Comparative Dissolution Profiles of Donepezil HCl 10 mg Capsules and Aricept Tablets in pH 4.5 Phosphate Buffer.

Figure 5 shows Comparative Dissolution Profiles of Donepezil HCl 10 mg Capsules and Aricept Tablets in pH 6.8 Phosphate Buffer.

Figure 6 shows Comparative Dissolution Profiles of Donepezil HCl 10 mg Capsules at Different pH (0.1N HCl, pH 4.5 Phosphate Buffer and pH 6.8 Phosphate Buffers).

DETAILED DESCRIPTION OF THE INVENTION

According to some embodiments, the present invention provides compositions comprising a therapeutically effective amount of donepezil or a pharmaceutically acceptable salt thereof (e.g., donepezil hydrochloride) for oral administration.

In exemplary embodiments, the present invention provides compositions comprising a therapeutically effective amount of donepezil or a pharmaceutically acceptable salt thereof (e.g., donepezil hydrochloride) in combination with memantine or a pharmaceutically acceptable salt thereof (e.g., memantine hydrochloride) for oral administration.

In exemplary embodiments, the present invention provides methods for treating Alzheimer's disease by administering to a patient in need thereof, a therapeutically effective amount of donepezil or a pharmaceutically acceptable salt thereof (e.g.,
donepezil hydrochloride) alone or in combination with memantine or a pharmaceutically acceptable salt thereof (e.g., memantine hydrochloride).

In exemplary embodiments, the present invention provides methods of treating moderate to severe dementia of the Alzheimer's type comprising administering an oral dosage form comprising a composition comprising donepezil or a pharmaceutically acceptable salt thereof to a patient in need thereof wherein the composition has an angle of repose of less than about 40 degrees.

In exemplary embodiments, the present invention provides methods of treating moderate to severe dementia of the Alzheimer's type comprising administering an oral dosage form comprising a composition comprising donepezil or a pharmaceutically acceptable salt thereof to a patient in need thereof wherein the dosage form may be sprinkled on food and more than 80% of the donepezil or pharmaceutically acceptable salt thereof dissolves within 30 minutes of administration to the patient.

In exemplary embodiments, the present invention provides methods of treating moderate to severe dementia of the Alzheimer's type comprising administering an oral dosage form comprising a composition comprising donepezil or a pharmaceutically acceptable salt thereof to a patient in need thereof wherein the oral dosage form has a volume of less than 0.70 ml and the composition has a drag loading of about 10%.

The dosage forms of the invention may comprise a composition comprising donepezil as donepezil hydrochloride in an immediate release form (e.g., 5 or 10 mg). The dosage forms may also comprise a composition comprising donepezil as donepezil hydrochloride in a modified release form, e.g., as a 23 mg sustained release dosage.

The dosage forms of the invention may further comprise memantine or a pharmaceutically acceptable salt thereof, e.g., memantine hydrochloride. The memantine may be provided as an immediate release (e.g., 5, 10 or 20 mg) or modified release form (e.g., 7, 14, 21, or 28 mg). For example, in some embodiments the dosage forms may comprise 14 mg memantine or a pharmaceutically acceptable salt thereof. In other embodiments the dosage forms may comprise 28 mg memantine or a pharmaceutically acceptable salt thereof.

In exemplary embodiments, the present invention may comprise an immediate release component and a modified release component. For example, the present
invention may comprise immediate release donepezil and modified release memantine. The amount of each component will depend on the active ingredient that is formulated as either an immediate or modified release component. In some examples, the dosage forms will comprise 10 mg donepezil as an immediate release form and 14 mg memantine as a modified release dosage form. In other examples, the dosage forms will comprise 10 mg donepezil as an immediate release form and 28 mg memantine as a modified release dosage form, or other examples, the dosage forms will comprise 23 mg donepezil as a modified release dosage form and 14 mg memantine as a modified release dosage form. In other examples, the dosage forms will comprise 23 mg donepezil as a modified release dosage form and 28 mg memantine as a modified release dosage form.

For example, the dosage forms comprising an immediate release component and a modified release component may include an amount of donepezil in the immediate release form of approximately 1% to 15% w/w of drug loading, preferably 5% to 15%. An immediate release donepezil content of about 10% w/w is particularly preferred. The composition of the invention may exhibit more than one peak in the plasma concentration/time curve in any one dosing interval depending on a particular active ingredient used, relative amounts of the IR and MR components, and the dissolution properties of the MR component. Thus, compositions may be achieved that have specific release profiles.

In some embodiments, the dosage forms may include an immediate release component and a modified release component that may include beads, granules or combinations thereof. Beads are dose proportional, i.e., the same proportions of beads of different types can be used for different doses without significantly altering the percent drug released over time. Different doses are obtained by using different amounts of beads. Beads also enable a variety of dissolution profiles by mixing one or more types of beads with different dissolution properties or using multi-layer coatings, as additional drug layering over a polymer layer and subsequent coatings to prepare unitary beads. In some embodiments, the dosage forms of the invention may include beads, granules or suspensions filled into capsules, compressed into tablets, or filled into sachets. One or more types of modified release beads can be mixed together and encapsulated, or used as
a sprinkle on the subject’s food. According to the invention, the oral solid dosage form may be any of these forms. Preferably, the dosage form is a capsule.

A suitable immediate release form of donepezil may simply be particles of donepezil admixed with soluble components for example, sugars (e.g., sucrose, mannitol, etc.), polymers (e.g., polyethylene glycol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, etc.), surfactants (e.g., sodium lauryl sulphate, chremophor, tweens, spans, pluronics, and the like), insoluble glidant components (e.g., microcrystalline cellulose, calcium phosphate, talc, fumed silica, and the like), coating material (examples of suitable coating materials are polyethylene glycol, hydroxypropyl methyl cellulose, wax, fatty acids, etc.), dispersions in suitable material (examples are wax, polymers, pharmaceutically acceptable oils, soluble agents, etc.) or combinations of the above.

The angle of repose may be used to characterize the flow properties of solids. Angle of repose is a characteristic related to interparticulate friction or resistance to movement between particles. The angle of repose is the constant, three-dimensional angle (relative to the horizontal base) assumed by a cone-like pile of material formed by any of several different methods. A variety of angle of repose test methods are described in the literature. The most common methods for determining the static angle of repose can be classified on the basis of the following two important experimental variables: (1) The height of the "funnel" through which the powder passes may be fixed relative to the base, or the height may be varied as the pile forms and (2) the base upon which the pile forms may be of fixed diameter or the diameter of the powder cone may be allowed to vary as the pile forms.

In addition to the above methods, the following variations have been used to some extent in the pharmaceutical literature:

*Drained angle of repose* is determined by allowing an excess quantity of material positioned above a fixed diameter base to "drain" from the container. Formation of a cone of powder on the fixed diameter base allows determination of the drained angle of repose.

*Dynamic angle of repose* is determined by filling a cylinder (with a clear, flat cover on one end) and rotating it at a specified speed. The dynamic angle of repose is the angle (relative to the horizontal) formed by the flowing powder. The internal angle of
kinetic friction is defined by the plane separating those particles sliding down the top
layer of the powder and those particles that are rotating with the drum (with roughened
surface).

Although there is some variation in the qualitative description of powder flow
using the angle of repose, much of the pharmaceutical literature appears to be consistent
with the classification shown below.

<table>
<thead>
<tr>
<th>Flow Property</th>
<th>Angle of Repose (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>25–30</td>
</tr>
<tr>
<td>Good</td>
<td>31–35</td>
</tr>
<tr>
<td>Fair—aid not needed</td>
<td>36–40</td>
</tr>
<tr>
<td>Passable—may hang up</td>
<td>41–45</td>
</tr>
<tr>
<td>Poor—must agitate, vibrate</td>
<td>46–55</td>
</tr>
<tr>
<td>Very poor</td>
<td>56–65</td>
</tr>
<tr>
<td>Very, very poor</td>
<td>&gt;66</td>
</tr>
</tbody>
</table>

Experimental Considerations for Angle of Repose

In exemplary embodiments, the present invention provides dosage forms wherein
the angle of repose of the composition comprising donepezil or salt thereof (e.g.,
donepezil HCl) is less than about 40 degrees. In other embodiments, the angle of repose
is less than about 35 degrees. In other embodiments, the angle of repose is less than
about 30 degrees. In some exemplary embodiments, the present invention provides
dosage forms wherein the angle of repose is between about 25 and about 40 degrees.

In some embodiments, the compositions release more than about 80% donepezil
or a pharmaceutically acceptable salt thereof (e.g., donepezil hydrochloride) within 60
minutes upon entry in a use environment, e.g., administration to a patient in need thereof.
For example, the compositions may release more than about 80% donepezil within about
10 minutes, about 15 minutes, about 30 minutes, about 45 minutes or about 60 minutes.
The dissolution rate or release can be measured using the methods provided in FDA
guidance for immediate release and modified release dosage forms.

In some embodiments, entry into a use environment includes but is not limited to
contact of a formulation of the invention with the gastric or enteric fluids of a patient to
whom it is administered, or with a fluid intended to simulate gastric fluid. For example,
the use environment includes, but is not limited to dissolution media (e.g., pH 1.2-6.8) commonly used for testing the dissolution rate of compositions. In some embodiments, use environment refers to the stomach or other portion of the gastrointestinal tract intended as the site of major absorption locus. The donepezil or hydrochloride salt may be released in a dissolution medium with a pH ranging from about 1.2 to 6.8. In exemplary embodiments, a dissolution medium of pH 6.8 is employed to simulate intestinal fluid. In some embodiments, a dissolution medium of pH 4.5 is employed. In still other embodiments, a dissolution medium of pH 1.2 is employed to simulate gastric fluid. In some examples, the dissolution medium may be maintained at about 37°C±1°C. In exemplary embodiments, the compositions are immediate release and provide a dissolution rate of >80% donepezil after about 30 minutes at pH 1.2. In some examples, >80% of donepezil HC1 dissolves within 30 minutes using USP Apparatus I at 100 rpm in a volume of 900 mL in each of the following media: (1) simulated gastric fluid USP without enzymes; (2) a pH 4.5 buffer, and (3) a pH 6.8 simulated intestinal fluid USP without enzymes.

In exemplary embodiments, the present invention provides dosage forms wherein more than 80% of the donepezil or pharmaceutically acceptable salt thereof dissolves within 30 minutes of administration to the patient. In some embodiments, more than 60% of the donepezil or pharmaceutically acceptable salt thereof dissolves within 5 minutes of administration to the patient. In exemplary embodiments, more than 70% of the donepezil or pharmaceutically acceptable salt thereof dissolves within 5 minutes of administration to the patient. In some embodiments, more than 30% of the donepezil or pharmaceutically acceptable salt thereof dissolves within 2.5 minutes of administration to the patient. In other embodiments, more than 20% of the donepezil or pharmaceutically acceptable salt thereof dissolves within 2.5 minutes of administration to the patient.

In exemplary embodiments, the present invention provides dosage forms wherein the oral dosage form has a volume of less than 0.70 ml. In other embodiments, the oral dosage forms have a volume of less than 0.50 ml. In other embodiments, the oral dosage forms have a volume of less than 0.40 ml.
Definitions

As used throughout, "Aricept" means donepezil hydrochloride tablets that are approved in the United States (Aricept®) for the treatment of dementia of the Alzheimer's type and are available as 5 mg and 10 mg immediate release dosage forms.

The term "pharmacologically acceptable" means biologically or pharmacologically compatible for in vivo use in animals or humans, and preferably means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

An "effective amount" means the amount of a composition according to the invention that, when administered to a patient for treating a condition is sufficient to effect such treatment. The "effective amount" will vary depending on the active ingredient, the state or condition to be treated and its severity, and the age, weight, physical condition and responsiveness of the mammal to be treated.

The term "therapeutically effective" applied to dose or amount refers to that quantity of a compound or pharmaceutical composition that is sufficient to result in a desired activity upon administration to a mammal in need thereof.

A "subject or patient in need thereof" means a person that has been diagnosed with Alzheimer's disease. A patient in need thereof may be limited to a "stabilized patient" which means a patient currently stabilized on either memantine HCl (10 mg twice daily or 28 mg extended release once daily and/or donepezil HCl 10 mg.

The term "administering" to a patient means to provide as an oral dosage form whole or sprinkled over food, e.g., on applesauce.

The term "about" or "approximately" means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. For example, "about" can mean within 1 or more than 1 standard deviations, per practice in the art. Alternatively, "about" with respect to the compositions can mean plus or minus a range of up to 20%, preferably up to 10%, more preferably up to 5%.

Alternatively, particularly with respect to biological systems or processes, the term can
mean within an order of magnitude, preferably within 5-fold, and more preferably within 2-fold, of a value.

The following examples are merely illustrative of the present invention and should not be construed as limiting the scope of the invention in any way as many variations and equivalents that are encompassed by the present invention will become apparent to those skilled in the art upon reading the present disclosure.
Example 1

A blend containing donepezil HCl, Microcrystalline cellulose (MCC), and starch was prepared and lubricated with magnesium stearate. The lubricated blend was compacted using a roller compactor. An oscillating granulator with 0.8 mm screen was used for milling of the compacts. After milling, all granules were passed through mesh #30, blended with extragranular excipients and lubricated with magnesium stearate. The lubricated granular blend was filled in size 4 hard gelatin capsule shells using a laboratory scale automated scale encapsulating machine.

Table 1 provides examples of compositions prepared using MCC as the diluent.

| Table 1: Composition and Properties of Donepezil HCl Capsules Prepared by Roller Compaction |
|-------------------------------------|----------|----------|----------|
| Batch Number                        | 1086-135-10 | 1086-135-10 A | 1086-140-10 |
| **Components**                      | mg/unit   | mg/unit   | mg/unit   |
| **Intrgranular**                    |           |           |           |
| Donepezil HCl                       | 10        | 10        | 10        |
| Microcrystalline cellulose NF (Avicel PH102) | 82.3    | 82.3    | 82.1    |
| Corn starch NF                      | 5         | 5         | 5         |
| Magnesium stearate NF              | 0.25      | 0.25      | 0.25      |
| Colloidal silicon dioxide NF (Aerosil 200P) | 0.1      | 0.1      | 0.1      |
| **Extragranular**                  |           |           |           |
| Corn starch NF                      | 2         | 2         | 2         |
| Magnesium stearate NF              | 0.25      | 0.25      | 0.25      |
| Colloidal silicon dioxide NF (Aerosil 200P) | 0.1      | 0.4      | 0.3      |
| Total unit weight for 10 mg capsule | 100 mg    | 100 mg    | 100 mg    |
| Batch size                          | 500 capsules | 500 capsules | 5000 capsules |
| **Characteristics**                |           |           |           |
| Angle of repose                     | ND        | 30.96     | 29.93     |
| Bulk density (g/mL)                 | 0.48      | 0.48      | 0.47      |
| Tap density (g/mL)                  | 0.64      | 0.64      | 0.63      |
| Compressibility (t-b)/t             | 25        | 25        | 25        |
| Hausener ratio (Tap/Bulk)           | 1.33      | 1.33      | 1.34      |

The bulk density of donepezil granules of Batch 1086-135-10 is 0.48 g/mL, but the granules did not flow through the funnel during angle of repose measurements. Hence, colloidal silicon dioxide was also added extragranularly (#1086-135-10A) to the granules to improve the flow. A slightly larger batch (Batch 1086-140-10) was made and
granules were encapsulated in size 4 capsule shells. Weight variation of capsules of this batch was found within acceptable range of ±10%.

Dissolution profile of donepezil granules filled in capsules 10 mg (Batch 1086-140-10) was compared with Aricept tablets 10 mg. See Figure 1.

Tables 2 and 3 show the properties for donepezil Drug Substance and Aricept 10 mg Pulverized Tablets respectively.

<table>
<thead>
<tr>
<th>Table 2: Donepezil Drug Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle of repose (requires tapping)</td>
</tr>
<tr>
<td>Bulk density (g/mL)</td>
</tr>
<tr>
<td>Tap density (g/mL)</td>
</tr>
<tr>
<td>Compressibility (t-b)/t</td>
</tr>
<tr>
<td>Hausener ratio (Tap/Bulk)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3: Aricept 10 mg Tablet Pulverized to powder in a mortar and pastel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle of repose</td>
</tr>
<tr>
<td>Bulk density (g/mL)</td>
</tr>
<tr>
<td>Tap density (g/mL)</td>
</tr>
<tr>
<td>Compressibility (t-b)/t</td>
</tr>
<tr>
<td>Hausener ratio (Tap/Bulk)</td>
</tr>
</tbody>
</table>

Example 2

A blend containing donepezil HCl, Microcrystalline cellulose (MCC), lactose monohydrate, and starch was prepared and lubricated with magnesium stearate. The lubricated blend was compacted using a roller compactor equipped with corrugated rollers at 2 ton roll pressure. An oscillating granulator with 0.8 mm screen was used for milling of the compacts. After milling, all granules were passed through mesh #30, blended with extragranular excipients and lubricated with magnesium stearate. The lubricated granular blend was filled in size 5 hard gelatin capsule shells using a laboratory automated scale encapsulating machine.

In the roller compaction experiments, different ratios of lactose monohydrate and MCC were evaluated as follows: 60:22.3 (Batch 1086-149-10) and 22.3:60 (Batch 1086
In both these experiments, a portion of lactose was also added in the extragranular portion. The bulk density of the blend with higher percentage of lactose (Batch 1086-149-10, 0.49 g/mL) was higher than the granules with lower amount of lactose (Batch 1086-150-10, 0.44 g/mL). Based on these observations, it was decided to use a higher percentage of lactose, all in intragranular portion and Batch 1086-172-10 was manufactured. A small amount of colloidal silicon dioxide was also added intragranularly to improve the flow of blend during roller compaction. A larger batch of granules (#1086-183-10) was manufactured and encapsulated in a smaller (size 5) capsule. Filling in smaller size capsules was possible because of the higher bulk density (0.6 g/mL). Weight variation of capsules was found within acceptable range of ±10%.

Table 4 provides Composition and Properties of Donepezil HCl Capsules Trial Batches (Prepared by Roller Compaction, Containing Lactose and MCC).

<table>
<thead>
<tr>
<th>Batch Number and Characteristics</th>
<th>Composition and Properties of Donepezil HCl Capsules Trial Batches</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1086-149-10</td>
</tr>
<tr>
<td>Components</td>
<td>mg/unit</td>
</tr>
<tr>
<td>Intragranular</td>
<td></td>
</tr>
<tr>
<td>Donepezil HCl</td>
<td>10</td>
</tr>
<tr>
<td>Lactose monohydrate NF (Supertab 11SD)</td>
<td>50</td>
</tr>
<tr>
<td>Microcrystalline cellulose NF (Avicel PH102)</td>
<td>22.3</td>
</tr>
<tr>
<td>Corn starch NF</td>
<td>7.4</td>
</tr>
<tr>
<td>Magnesium stearate NF</td>
<td>0.1</td>
</tr>
<tr>
<td>Colloidal silicon dioxide NF (Aerosil 200P)</td>
<td>-</td>
</tr>
<tr>
<td>Extragranular</td>
<td></td>
</tr>
<tr>
<td>Lactose monohydrate NF (Supertab 11SD)</td>
<td>10</td>
</tr>
<tr>
<td>Magnesium stearate NF</td>
<td>0.2</td>
</tr>
<tr>
<td>Colloidal silicon dioxide NF (Aerosil 200P)</td>
<td>0.2</td>
</tr>
<tr>
<td>Total unit weight for 10 mg capsule</td>
<td>100 mg</td>
</tr>
<tr>
<td>Batch size</td>
<td>500 Capsules</td>
</tr>
<tr>
<td>Characteristics</td>
<td></td>
</tr>
<tr>
<td>Angle of repose</td>
<td>-</td>
</tr>
<tr>
<td>Bulk density (g/mL)</td>
<td>0.49</td>
</tr>
<tr>
<td>Tap density (g/mL)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Dissolution profile of donepezil capsules 10 mg of Batch 1086-183-10 was compared with Ailicept tablets 10 mg. See Figure 2. These granules also had a higher bulk
density (0.6 g/nL) and good flow. Hence, the composition of this batch (1086 183 10) was considered suitable for the combination product (Memantine HCl ER/Donepezil HCl IR Capsules).

A GMP batch of selected formulation of donepezil HCl capsules 10 mg (1086-194-10) was manufactured at laboratory scale (8000 capsules) and Size 5 hard gelatin capsules of white color were used for a clinical study.

The dissolution of capsules of batch # 1086-194-10 were studied as a function of pH using different media i.e., a) 0.1N HCl, b) phosphate buffer (pH 4.5), and c) phosphate buffer (pH=6.8) and compared with Aricept tablets 10 mg (Batch 003865). See Figures 3-5 for the 0.1N HCl, pH 4.5, and pH 6.8 dissolution media, respectively.

The capsule formulation shows a faster initial release of the drug relative to Aricept and then levels off at about 10 minutes. This fast release from capsules shells is attributed to faster disintegration of capsule shells as compared to tablets. The tablet formulation (Aricept) shows a marginally slower initial release and levels off at about 30 minutes, in all instances, quantitative release is seen for all the lots evaluated at all three pH values evaluated.

Figure 6 shows the dissolution profile of a formulation for a BE study using donepezil HCl capsules (Batch 1086-194-10) in media of different pH. The dissolution profile of donepezil HCl capsules was found to be similar in all the media studied.
Example 3

Memantine HC1 ER/Donepezil HC1 capsules were developed as oral capsules containing a fixed dose combination of memantine hydrochloride (HC1) extended release (ER) beads and donepezil HC1 immediate release (IR) granules for the treatment of moderate to severe dementia of the Alzheimer’s type.

The quantitative composition donepezil HC1 granules along with the grade, function, amount per capsule, and percent for each component are shown in Table 5.

<table>
<thead>
<tr>
<th>Component</th>
<th>Function</th>
<th>% w/w of total granules</th>
<th>Amount per capsule (mg/unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrgranular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donepezil Hydrochloride USP</td>
<td>Active</td>
<td>10%</td>
<td>10</td>
</tr>
<tr>
<td>Lactose monohydrate NF (Supertab SD11)</td>
<td>Diluent</td>
<td>60%</td>
<td>60</td>
</tr>
<tr>
<td>Microcrystalline cellulose NF (Avicel PH102)</td>
<td>Diluent</td>
<td>22%</td>
<td>22</td>
</tr>
<tr>
<td>Corn starch NF</td>
<td>Disintegrant</td>
<td>7.2%</td>
<td>7.2</td>
</tr>
<tr>
<td>Magnesium stearate NF</td>
<td>Lubricant</td>
<td>0.3%</td>
<td>0.3</td>
</tr>
<tr>
<td>Colloidal silicon dioxide NF (Aerosil 200P)</td>
<td>Glidant</td>
<td>0.1%</td>
<td>0.1</td>
</tr>
<tr>
<td>Extra granular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colloidal silicon dioxide NF (Aerosil 200P)</td>
<td>Glidant</td>
<td>0.2%</td>
<td>0.2</td>
</tr>
<tr>
<td>Magnesium stearate NF</td>
<td>Lubricant</td>
<td>0.2%</td>
<td>0.2</td>
</tr>
<tr>
<td>Total fill weight of donepezil granules</td>
<td>-</td>
<td>100%</td>
<td>100</td>
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NF = National Formulary.

An immediate release composition of donepezil HCI granules with desired dissolution and density was developed in order to combine with memantine hydrochloride ER beads, in a small size capsule.

For convenient oral administration, size of the dosage form is important to make it easy to swallow. Tablet weight for Aricept® 10 mg tablets is 280 mg containing approximately 3.57% of drug loading. A similar drug loading in the granules was expected to result in high capsule fill weights that could only be accommodated in larger capsule sizes. A large capsule size was deemed undesirable from patient convenience perspective. To facilitate the encapsulation of two drug components in a small capsule, a
higher drug loading and denser formulation of donepezil HCl was desired. Therefore, a
drug loading of 10% w/w donepezil HCl was considered. In addition to Memantine HCl
ER/Donepezil HCl capsules of strengths, 28/10 and 14/10, the strengths of 28/5 mg and
14/5 mg were contemplated. Drug loading of 10% w/w was expected to result in the fill
weights of 100 mg and 50 mg respectively for 10 mg and 5 mg strengths. Drug loading
higher than 10% w/w will result in lower than 50 mg fill weight for the lower strength,
which might compromise fill accuracy using commonly available encapsulation
machines. Hence, it was decided to develop donepezil blend/granule formulation with
10%

Excipients for donepezil HCl granules were selected based on their
chemical/physical compatibility with donepezil, regulatory acceptance, and
processability. A drug excipient compatibility study was performed before selecting the
final composition. Only excipients that were chemically compatible with donepezil HCl
were used in the formulation of donepezil HCl granules. Most of the excipients selected
for donepezil granulation of donepezil HCl granules are similar to those present in
Aricept tablets 10 mg. To improve the density of composition, it was decided to use dry
granulation by roller compaction as described above.

The donepezil HCl granules have higher drug loading (10% w/w) with immediate
release characteristics. The dissolution profile in different pH was comparable to Aricept
tablets. It is bioequivalent to Aricept tablets and stable for more than 24 months at room
temperature.

Memantine HCl ER/Donepezil HCl capsules were developed by combining the
Memantine HCl ER beads and Donepezil HCl granules (14/10 mg and 28/10 mg). Both
memantine strengths are dose-proportional in that they are manufactured from a common
ER beads, differing only in the filled amount of ER beads. Memantine HCl ER bead
formulation was developed since it offered flexibility in achieving the desired memantine
strengths using a common bead formulation.

The memantine HCl ER beads are multi-layered, consisting of sugar spheres
which are layered with an aqueous dispersion of the API, talc, and povidone K30 to form
drug layered beads. The drag layered beads are coated with Surelease® Clear dispersion
to form polymer coated beads. The polymer coated beads are seal coated with Opadry® Clear. The excipients used in the drug product ER capsule formulation were selected based on their compatibility with the memantine HC1 API.

**Example 4**

A Single-Center, Randomized, Open-Label, 3-Way Crossover, Single-Dose Study was conducted to evaluate the effect of food and the effect of administration of capsule contents sprinkled on applesauce in healthy adults.

The approved Namenda XR doses are 7, 14, 21, and 28 mg. The approved Aricept strengths are 5, 10, and 23 mg; the 23-mg once-daily dose can only be administered once subjects have been on a dose of 10 mg once daily for at least 3 months. The proposed highest-dose strength for MDX-8704 is 28 mg memantine HC1 ER/10 mg donepezil HC1. In this food-effect and relative bioavailability study, the MDX-8704 28 mg memantine HC1 ER/10 mg donepezil HC1 capsule was used in accordance with the FDA Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies (US Food and Drug Administration, 2002) to conduct the study with the highest-dose strength.

A total of 36 healthy male and female subjects aged 18 through 45 years, were enrolled in the study. All 36 subjects were included in the safety analysis. Twenty-three subjects were included for the pharmacokinetic (PK) analysis of Treatment A (MDX-8704 intact capsule under fasted conditions), 23 for Treatment B (MDX-8704 intact capsule under fed conditions), and 21 for Treatment C (MDX-8704 capsule contents sprinkled on applesauce under fasted conditions).

Subjects were randomly assigned to 1 of 6 treatment sequences (ABC, ACB, BAC, BCA, CAB, or CBA).

**Table 6 : Treatment sequences**

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</tr>
</tbody>
</table>

25
Each of the following treatments was administered with a 21-day washout period between treatments:

**Treatment A:** A single oral dose of MDX-8704 (memantine HC1 ER/donepezil HC1) 28 mg/10 mg capsule administered under fasted conditions;

**Treatment B:** A single oral dose of MDX-8704 (memantine HC1 ER/donepezil HC1) 28 mg/10 mg capsule administered following a high-fat breakfast; and

**Treatment C:** A single oral dose of MDX-8704 (memantine HC1 ER/donepezil HC1) 28 mg/10 mg administered as capsule contents sprinkled on 30 mL (2 tablespoons) of applesauce under fasted conditions.

Blood samples were collected starting on Day 1 of each period at 0 hour (predose) and at 1, 2, 3, 4, 6, 8, 10, 12, 14, 24, 30, 36, 48, 72, 96, 120, 168, 216, and 264 hours after dosing. Plasma samples were analyzed for nimodantine and donepezil concentrations using a validated liquid chromatography coupled with tandem mass spectrometry method with good accuracy, linearity, reproducibility, and precision.

**Statistical Methodology:**

Descriptive statistics for all PK parameters of memantine and donepezil were provided by treatment for all subjects who completed the study, had no episode of emesis (within 24 hours after administration of MDX-8704 for PK analysis of memantine and within 2 times the median Tmax [time of maximum plasma drug concentration] after administration of MDX-8704 for PK analysis of donepezil), and had evaluable PK parameters. The Cmax (maximum plasma drug concentration), AUCO-t (area under the plasma concentration versus time curve from time 0 to time t), and AUC0-∞ (area under the plasma concentration versus time curve from time 0 to infinity) parameters of memantine and donepezil were compared by means of a linear mixed effects model with sequence, treatment, and period as fixed effects and subjects within sequence as a random effect. Confidence intervals (CIs) of 90% were constructed for the ratio of geometric least squares (LS) means of Cmax, AUCO-t, and AUC0-∞ between MDX-8704 intact capsule under fed conditions (Treatment B) and MDX-8704 intact capsule under fasted conditions (Treatment A), and between MDX-8704 capsule contents sprinkled on
applesauce under fasted conditions (Treatment C) and Treatment A. No food effect would be concluded if the corresponding 90% CIs of the ratio of geometric LS means of Cmax, AUC0-t, and AUC0-∞ between Treatment B and Treatment A for memantine and donepezil were within the range of 0.800 to 1.250. No difference between administrations of MDX-8704 as intact capsule versus capsule contents sprinkled on applesauce would be concluded if the corresponding 90% CIs of the ratio of geometric LS means of Cmax, AUC0-t, and AUC0-∞ between Treatment C and Treatment A for memantine and donepezil were within the range of 0.800 to 1.250. Arithmetic mean ratios of Tmax for memantine and donepezil were presented between Treatment B and Treatment A, and between Treatment C and Treatment A. The Wilcoxon signed-rank test was performed on Tmax. A p-value <0.05 was considered a significant difference between treatments.

Safety parameters (adverse events [AEs], vital sign assessments, clinical laboratory evaluations, electrocardiographic [ECG] parameters, physical examination findings, and results of the Columbia-Suicide Severity Rating Scale [C-SSRS] were summarized for all subjects who took at least 1 dose of investigational product.

Results:

Subject Disposition: Thirty-six subjects were enrolled in the study. Three subjects (8.33%) prematurely discontinued from the study. One subject (2.78%) discontinued due to an AE; 1 subject (2.78%) discontinued due to a protocol violation, and 1 subject (2.78%) discontinued for other reasons.

For subjects in the Safety Population, the mean age (± SD) and body mass index (± SD) were 27.3 (± 5.3) years and 25.41 (± 2.90) kg/m², respectively. Overall, 25 subjects (69.44%) were male and 11 subjects (30.56%) were female.

Pharmacokinetics: The PK Population consisted of all subjects who completed the study and had evaluable PK parameters for Treatments A and B (intact capsule administered with and without food) or Treatments A and C (intact capsule versus capsule contents sprinkled on applesauce under fasted conditions). Subjects who vomited within 24 hours after administration of MDX-8704 were excluded from the PK analysis of memantine. Subjects who vomited within 2 times the median Tmax after
administration of MDX-8704 were excluded from the PK analysis of donepezil. Data from subjects in the PK Population were used for PK analysis and summary statistics of PK parameters.

Twenty-three subjects were included in the food effect analysis (intact capsule administered with and without food) of memantine and donepezil; 21 subjects were included in the comparison of administration of intact capsule under fasted conditions versus capsule contents sprinkled on applesauce under fasted conditions for both memantine and donepezil.

The 90% CIs for the geometric LS means ratios of Cmax, AUCO-t, and AUC0-∞ for memantine in the comparison of MDX-8704 intact capsule under fed conditions (Treatment B) versus administration of MDX-8704 intact capsule under fasted conditions (Treatment A) were within the range of 0.800 to 1.250, indicating no significant food effect. In addition, the 90% CIs for the geometric LS means ratios of Cmax, AUCO-t, and AUC0-∞ for memantine in the comparison of MDX-8704 capsule contents sprinkled on applesauce under fasted conditions (Treatment C) versus Treatment A were within the range of 0.800 to 1.250, indicating no statistically significant difference between administration of MDX-8704 as intact capsule under fasted conditions versus capsule contents sprinkled on applesauce under fasted conditions. The mean terminal elimination half-life of memantine was observed to be 62.07, 59.75, and 62.77 hours for Treatments A, B, and C, respectively. There was a statistically significant difference in the median Tmax for memantine following administration of Treatment A versus Treatment B with a p-value of 0.014; and following administration of Treatment A versus Treatment C with a p-value of 0.012.

The 90% CIs for the geometric LS means ratios of Cmax, AUCO-t, and AUC0-∞ for donepezil in the comparison of MDX-8704 intact capsule under fed conditions (Treatment B) versus administration of MDX-8704 intact capsule under fasted conditions (Treatment A) were within the range of 0.800 to 1.250, indicating no significant food effect. In addition, the 90% CIs for the geometric LS means ratios of Cmax, AUCO-t, and AUC0-oo for donepezil in the comparison of MDX-8704 capsule contents sprinkled on applesauce under fasted conditions (Treatment C) versus Treatment A were within the
range of 0.800 to 1.250, indicating no statistically significant difference between administration of MDX-8704 as intact capsule under fasted conditions versus capsule contents sprinkled on applesauce under fasted conditions. The mean terminal elimination half-life of donepezil was observed to be 67.26, 66.62, and 65.01 for Treatments A, B, and C, respectively. There was a statistically significant difference in the median Tmax for donepezil following administration of Treatment A versus Treatment B with a p-value of < 0.001. There was no statistically significant difference between the median Tmax for donepezil following administration of Treatment A versus Treatment C with a p-value of 0.278.

There was no statistically significant difference in the total exposure and peak concentration of memantine and donepezil following administration of MDX-8704 (memantine ER/donepezil) 28 mg/10 mg capsule with a high-fat meal versus under fasted conditions, suggesting food has no significant effect on the bioavailability of the MDX-8704 capsule. The median Tmax was reduced to 14.0 hours from 24.0 hours for memantine, but was prolonged to 6.0 hours from 3.0 hours for donepezil when administered with the high-fat meal compared to under fasted conditions. The change in the Tmax was statistically significant for both memantine and donepezil.

There was no statistically significant difference in total exposure and peak concentration of memantine and donepezil following administration of an intact MDX-8704 (memantine ER/donepezil) 28 mg/10 mg capsule versus the capsule contents sprinkled on applesauce under fasted conditions, suggesting the 2 treatments are bioequivalent. The median Tmax of memantine was reduced to 14 hours from 24 hours and the Tmax of donepezil was reduced to 2.1 hours from 3.0 hours when administered as an intact capsule under fasted conditions versus as capsule contents sprinkled on applesauce under fasted conditions. The change in the Tmax was statistically significant for memantine, but was not statistically significant for donepezil.

The incidence of TEAEs was similar for MDX-8704 administered under fasted conditions either as an intact capsule or as capsule contents sprinkled on applesauce and lower for MDX-8704 administered after a high-fat meal.
Clinically significant safety signals were not observed in this study. A single oral dose of MDX-8704 (memantine ER/donepezil) 28 mg/10 mg capsule was generally safe and tolerable in the healthy male and female subjects in this study.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims. It is further to be understood that all values are approximate, and are provided for description.

All patents, patent applications, publications, product descriptions, and protocols are cited throughout this application, the disclosures of which are incorporated herein by reference in their entireties for all purposes.
WHAT IS CLAIMED IS:

1. A method of treating moderate to severe dementia of the Alzheimer's type comprising administering an oral dosage form comprising a composition comprising donepezil or a pharmaceutically acceptable salt thereof to a patient in need thereof, wherein the composition has an angle of repose of less than about 40 degrees.

2. The method of claim 1, wherein the composition comprises 10 mg donepezil or a pharmaceutically acceptable salt thereof.

3. The method of claim 1, wherein the dosage form comprises memantine or a pharmaceutically acceptable salt thereof.

4. The method of claim 1, wherein the dosage form comprises 28 mg memantine or a pharmaceutically acceptable salt thereof.

5. The method of claim 1, wherein the angle of repose is less than about 35 degrees.

6. The method of claim 1, wherein the angle of repose is less than about 30 degrees.

7. The method of claim 1, wherein the angle of repose is between about 25 to about 40 degrees.

8. The method of claim 1, wherein the dosage form may be sprinkled on food and more than 80% of the donepezil or pharmaceutically acceptable salt thereof dissolves within 30 minutes of administration to the patient.

9. The method of claim 1, wherein more than 60% of the donepezil or pharmaceutically acceptable salt thereof dissolves within 5 minutes of administration to the patient.

10. The method of claim 1, wherein more than 70% of the donepezil or pharmaceutically acceptable salt thereof dissolves within 5 minutes of administration to the patient.
11. The method of claim 1, wherein more than 30% of the donepezil or pharmaceutically acceptable salt thereof dissolves within 2.5 minutes of administration to the patient.

12. The method of claim 1, wherein more than 20% of the donepezil or pharmaceutically acceptable salt thereof dissolves within 2.5 minutes of administration to the patient.

13. The method of claim 1, wherein the dosage form has a volume of less than 0.70 ml.

14. The method of claim 1, wherein the dosage form has a volume of less than 0.50 ml.

15. The method of claim 1, wherein the dosage form has a volume of less than 0.40 ml.

16. The method of claim 1, wherein the composition has a drug loading of about 10%.

17. A method of treating moderate to severe dementia of the Alzheimer's type comprising administering an oral dosage form comprising a composition comprising donepezil or a pharmaceutically acceptable salt thereof to a patient in need thereof, wherein the dosage form may be sprinkled on food and more than 80% of the donepezil or pharmaceutically acceptable salt thereof dissolves within 30 minutes of administration to the patient.

18. The method of claim 17, wherein the composition comprises 10 mg donepezil or a pharmaceutically acceptable salt thereof.

19. The method of claim 17, wherein the dosage form comprises memantine or a pharmaceutically acceptable salt thereof.

20. The method of claim 17, wherein the dosage form comprises 28 mg memantine or a pharmaceutically acceptable salt thereof.

21. The method of claim 17, wherein the composition has an angle of repose of less than about 40 degrees.

22. The method of claim 17, wherein the composition has an angle of repose of less than about 35 degrees.
23. The method of claim 17, wherein the composition has an angle of repose of less than about 30 degrees.

24. The method of claim 17, wherein the composition has an angle of repose of between about 25 and about 40 degrees.

25. The method of claim 17, wherein the dosage form has a volume of less than 0.70 ml.

26. The method of claim 17, wherein the dosage form has a volume of less than 0.50 ml.

27. The method of claim 17, wherein the dosage form has a volume of less than 0.40 ml.

28. The method of claim 17, wherein the composition has a drug loading of about 10%.

29. The method of claim 17, wherein more than 60% of the donepezil or pharmaceutically acceptable salt thereof dissolves within 5 minutes of administration to the patient.

30. The method of claim 17, wherein more than 70% of the donepezil or pharmaceutically acceptable salt thereof dissolves within 5 minutes of administration to the patient.

31. The method of claim 17, wherein more than 30% of the donepezil or pharmaceutically acceptable salt thereof dissolves within 2.5 minutes of administration to the patient.

32. The method of claim 17, wherein more than 20% of the donepezil or pharmaceutically acceptable salt thereof dissolves within 2.5 minutes of administration to the patient.

33. A method of treating moderate to severe dementia of the Alzheimer's type comprising administering an oral dosage form comprising a composition comprising donepezil or a pharmaceutically acceptable salt thereof to a patient in need thereof, wherein the dosage form has a volume of less than 0.70 ml and the composition has a drug loading of about 10%.
34. The method of claim 33, wherein the dosage form has a volume of less than 0.50 ml and the composition has a drug loading of about 10%.

35. The method of claim 33, wherein the dosage form has a volume of less than 0.40 ml and the composition has a drug loading of about 10%.

36. The method of claim 33, wherein the composition comprises 10 mg donepezil or a pharmaceutically acceptable salt thereof.

37. The method of claim 33, wherein the dosage form comprises memantine or a pharmaceutically acceptable salt thereof.

38. The method of claim 33, wherein the dosage form comprises 28 mg memantine or a pharmaceutically acceptable salt thereof.

39. The method of claim 33, wherein the composition has an angle of repose of less than about 40 degrees.

40. The method of claim 33, wherein the composition has an angle of repose of less than about 35 degrees.

41. The method of claim 33, wherein the composition has an angle of repose of less than about 30 degrees.

42. The method of claim 33, wherein the composition has an angle of repose of between about 25 and about 40 degrees.

43. The method of claim 33, wherein more than 80% of the donepezil or pharmaceutically acceptable salt thereof dissolves within 30 minutes of administration to the patient.

44. The method of claim 33, wherein more than 60% of the donepezil or pharmaceutically acceptable salt thereof dissolves within 5 minutes of administration to the patient.
45. The method of claim 33, wherein more than 70% of the donepezil or pharmaceutically acceptable salt thereof dissolves within 5 minutes of administration to the patient.

46. The method of claim 33, wherein more than 30% of the donepezil or pharmaceutically acceptable salt thereof dissolves within 2.5 minutes of administration to the patient.

47. The method of claim 33, wherein more than 20% of the donepezil or pharmaceutically acceptable salt thereof dissolves within 2.5 minutes of administration to the patient.
Figure 1
Figure 2

![Graph showing drug dissolution over time for two substances: Accept (B.No. 303865) and ADS-4002 (B.No. 1086-183-10).](image-url)
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

USPC - 514/319 (keyword delimited)

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

Orbi, Google Patents, Google Scholar.

Search terms used: donepezil memantine alzheimer" angle repose

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier application or patent but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed
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  "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  "Q" document member of the same patent family

Date of the actual completion of the international search: 06 April 2015

Date of mailing of the international search report: MAY 2015

Name and mailing address of the ISA/US

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PCT OSB: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)