Title: FORMULATIONS FOR CATHEPSIN K INHIBITORS

Abstract: The instant invention relates to pharmaceutical compositions comprising cathepsin K inhibitors as the active ingredient with excipients which include binders, diluents, lubricants, and disintegrants. Also disclosed are processes for making said pharmaceutical compositions for oral and intravenous delivery.
This invention relates to formulations of cathepsin K inhibitors.

A variety of cathepsin K inhibitors have been disclosed for the treatment of various disorders related to cathepsin K functioning, including osteoporosis, glucocorticoid induced osteoporosis, Paget’s disease, abnormally increased bone turnover, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, atherosclerosis, obesity, glaucoma, chronic obstructive pulmonary disease and cancer including metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma. Representative examples of cathepsin K inhibitors include those disclosed in International Publication WO03/075836, which published on September 18, 2003, to Merck & Co., Inc. & Axys Pharmaceuticals, which is hereby incorporated by reference in its entirety.

Cathepsin K inhibitors can be formulated for oral dosing as tablets, by using a direct compression, wet granulation or roller compaction method. Similarly, cathepsin K inhibitors can be formulated for oral dosing as gelatin capsules, being a liquid in a soft capsule, or dry powder or semi-solid in a hard capsule. In addition, cathepsin K inhibitors can be formulated for intravenous dosing.

The instant invention relates to pharmaceutical compositions containing cathepsin K inhibitors. Also disclosed are processes for making said pharmaceutical compositions.

A particularly effective cathepsin K inhibitor is \( N^1-(1\text{-cyanocyclopropyl})-4\text{-fluoro-}N^{2}-\{(15)-2,2,2\text{-trifluoro-1 \,}4'\text{-}(methylsulfonyl)\text{-1',1'-biphenyl-4-yl}]\text{-ethyl}\}-L\text{-leucinamide,} \)

\[
\begin{align*}
\text{CF}_3 & \quad \text{H} \\
\text{O} & \quad \text{N} \\
\text{N} & \quad \text{N}
\end{align*}
\]

which can be prepared by procedures described in: International Publication WO03/075836, which published on September 18, 2003, to Merck & Co., Inc. & Axys Pharmaceuticals; International Publication WO2006/017455, which published on February 16, 2006, to Merck &

The instant invention comprises a pharmaceutical composition comprising by weight, about 0.5 to 40% by weight of a cathepsin K inhibitor, or a pharmaceutically acceptable salt thereof, and from about 60% to 99.5% by weight of excipients selected from diluents, a binder, a lubricant, and a disintegrant.

In an embodiment of the pharmaceutical composition, the excipients comprise a diluent, a binder, and a disintegrant.

In an embodiment of the invention, the cathepsin K inhibitor is \( N^1-(1\text{-cyanocyclopropyl})4\text{-fluoro-7V}-(1\text{5})-2,2,2\text{-trifluoro-} 1\text{-[4\text{'-}(methylsulfonyl)1,1\text{'-biphenyl-4-yl]ethyl}\text{-}L\text{-leucinamide, or a pharmaceutically acceptable salt thereof.}

In an embodiment of the invention, the diluents are selected from the group consisting of lactose anhydrous, lactose monohydrate, mannitol, microcrystalline cellulose, calcium phosphate and starch. In a class of the embodiment, the diluents are lactose monohydrate and microcrystalline cellulose.

In an embodiment of the invention, the binder is hydroxypropyl cellulose, polyvinylpyrrolidone or hydroxypropylmethylcellulose. In a class of the embodiment, the binder is hydroxypropyl cellulose.

In an embodiment of the invention, the lubricant is magnesium stearate or sodium stearyl fumarate. In a class of the embodiment, the lubricant is magnesium stearate.

In an embodiment of the invention the disintegrant is croscarmellose sodium, starch or sodium starch glycolate. In a class of the embodiment, the disintegrant is croscarmellose sodium.

The instant invention includes a process for the preparation of a tablet containing a cathepsin K inhibitor, which process comprises:

(a) forming a powder blend of the cathepsin K inhibitor with excipients,
(b) wet granulating the powder blend with hydroxypropyl cellulose to form granules,
(c) drying the granules, and
(d) compressing the dried granules in to a tablet.
In an embodiment of the process, the cathepsin K inhibitor is \( N^1-(1\text{-cyanocyclopropyl})\text{-fluoro-N}^2-\{(1S)-2,2,2\text{-trifluoro-1-}[4'-(methylsulfonyl)\text{-1',1'-biphenyl-4-yl}]\text{ethyl}\text{-L-leucinamide}, \) or a pharmaceutically acceptable salt thereof.

In an embodiment of the process, the excipients comprise a diluent, a binder, and a disintegrant.

In an embodiment of the process, the diluents are selected from the group consisting of lactose anhydrous, lactose monohydrate, mannitol, microcrystalline cellulose, calcium phosphate and starch. In a class of the embodiment, the diluents are lactose monohydrate and microcrystalline cellulose.

In an embodiment of the process, the binder is hydroxypropyl cellulose, polyvinylpyrrolidone or hydroxypropylmethylcellulose. In a class of the embodiment, the binder is hydroxypropyl cellulose.

In an embodiment of the process, the lubricant is magnesium stearate or sodium stearyl fumarate. In a class of the embodiment, the lubricant is magnesium stearate.

In an embodiment of the process, the disintegrant is croscarmellose sodium, starch or sodium starch glycolate. In a class of the embodiment, the disintegrant is croscarmellose sodium.

The instant invention also includes a process for the preparation of a tablet containing a cathepsin K inhibitor, which process comprises:

(a) forming a powder blend of the cathepsin K inhibitor with excipients, using a mixer,
(b) wet granulating the powder blend with a binder to form granules,
(c) drying the granules in a fluid bed dryer,
(d) milling the dried granulate,
(e) lubricating the dried granules, and
(f) compressing the dried granules into a tablet.

In an embodiment of the process, the cathepsin K inhibitor is \( N^1-(1\text{-cyanocyclopropyl})\text{-4-fluoro-iV}^2-\{(1S)-2,2,2\text{-trifluoro-1-}[4'-(methylsulfonyl)\text{-1',1'-biphenyl-4-yl}]\text{ethyl}\text{-L-leucinamide}, \) or a pharmaceutically acceptable salt thereof.

In an embodiment of the process, the excipients comprise a diluent, a binder, and a disintegrant.

In an embodiment of the process, the diluents are selected from the group consisting of lactose anhydrous, lactose monohydrate, mannitol, microcrystalline cellulose, calcium phosphate and starch. In a class of the embodiment, the diluents are lactose monohydrate and microcrystalline cellulose.

In an embodiment of the process, the binder is hydroxypropyl cellulose, polyvinylpyrrolidone or hydroxypropylmethylcellulose. In a class of the embodiment, the binder is hydroxypropyl cellulose.
In an embodiment of the process, the lubricant is magnesium stearate or sodium stearyl fumerate. In a class of the embodiment, the lubricant is magnesium stearate.

In an embodiment of the process, the disintegrant is croscarmellose sodium, starch or sodium starch glycolate. In a class of the embodiment, the disintegrant is croscarmellose sodium.

The instant invention also comprises a pharmaceutical composition comprising by weight, about 0.5 to 40% by weight of a cathepsin K inhibitor, or a pharmaceutically acceptable salt thereof, and from about 60% to 99.5% by weight of excipients selected from diluents and a lubricant.

In an embodiment of the invention, the cathepsin K inhibitor is \( N^1-(1\text{-cyanocyclopropyl \text{-} 4\text{-fluoro-}iV^{2}}-\{(\text{1S})-2,2,2\text{-trifluoro-} 1\text{-}[4\text{'-}(\text{methy}lsulfon}y1>1,1\text{'-biphenyl-4-yl]ethyl}\text{-}L\text{-leucinamide, or a pharmaceutically acceptable salt thereof.}

In an embodiment of the invention, the diluents are selected from the group consisting of lactose anhydrous, lactose monohydrate, mannitol, microcrystalline cellulose, calcium phosphate and starch. In a class of the embodiment, the diluents are lactose monohydrate and microcrystalline cellulose.

In an embodiment of the invention, the lubricant is magnesium stearate or sodium stearyl fumerate. In a class of the embodiment, the lubricant is magnesium stearate.

In an embodiment of the invention, the pharmaceutical composition also contains a binder. In a class of the embodiment, binder is hydroxypropyl cellulose, polyvinylpyrrolidone or hydroxypropylmethylcellulose. In a subclass of the embodiment, the binder is hydroxypropyl cellulose.

In an embodiment of the invention, the pharmaceutical composition consists of: 0.5 to 40% of a cathepsin K inhibitor or salt; 54% to 95.6% of a diluent or diluents; 1-2% of a lubricant. Optionally, the pharmaceutical composition can further include 3-4% dry binder. A class of the embodiment consists of 0.5 to 40% of \( N^2\text{-}[1\text{-cyanocyclopropyl}^\wedge\text{-}fluoro- \text{-}2,2,2\text{-trifluoro-}1\text{-}[4\text{'-}(\text{methy}lsulfon}y1>1,1\text{'-biphenyl-4-yl]ethyl}\text{-}L\text{-leucinamide; 27% to 47.8% of lactose (as a diluent); 27% to 47.8% of microcrystalline cellulose (as a diluent); and 1-2% of magnesium stearate.}

The instant invention includes a process for the preparation of a tablet containing a cathepsin K inhibitor, which process comprises:

(a) mixing together the cathepsin K inhibitor, diluents, and a dry binder,
(b) lubricating the mixture from step (a),
(c) dry granulating the lubricated mixture,
(d) size reducing the granules,
(e) lubricating the granules, and
(f) compressing the tablets on a rotary tablet press.
In an embodiment of the process, the cathepsin K inhibitor, diluent and dry binder are mixed together in a drum blender for 10 minutes. In a class of the embodiment, the drum blender is set at 46 rpm.

In an embodiment of the process, the mixture from step (a) is lubricated in a drum blender for 1 minute. In a class of the embodiment, the drum blender is set at 46 rpm.

In an embodiment of the process, the lubricated mixture from step (b) is dry granulated on a roller compactor. In a class of the embodiment, the roller compactor is set with a roll pressure of 400 MPa, a roll speed of 4.00 rpm and a screw speed of 55.5 rpm.

In an embodiment of the process, the granules from step (c) are size reduced by milling said granules through a screen and a round rasp screen. In a class of the embodiment, the screen measures 1 mm and the round rasp screen measures 1.27 mm.

In an embodiment of the process, the cathepsin K inhibitor is $N^1$-[(\-cyanocyclopropyl)\-4\-fluoro-\-N^2\-\{(1S)-2,2,2-trifluoro-\-1\-[4\-\(\text{methylsulfonyl}\)-1,1\-biphenyl-4-\-yl]ethyl\}-L-leucinamide, or a pharmaceutically acceptable salt thereof.

In an embodiment of the process, the diluents are selected from the group consisting of lactose anhydrous, lactose monohydrate, mannitol, microcrystalline cellulose, calcium phosphate and starch. In a class of the embodiment, the diluents are lactose monohydrate and microcrystalline cellulose.

In an embodiment of the process, the binder is hydroxypropyl cellulose, polyvinylpyrrolidone or hydroxypropylmethylcellulose. In a class of the embodiment, the binder is hydroxypropyl cellulose.

In an embodiment of the process, the lubricant is magnesium stearate or sodium stearyl fumarate. In a class of the embodiment, the lubricant is magnesium stearate.

The instant invention also comprises an intravenous pharmaceutical composition comprising a cathepsin K inhibitor, or a pharmaceutically acceptable salt thereof, water, a modified cyclodextrin and a wetting agent.

In an embodiment of the invention, the cathepsin K inhibitor is $N^1$-[(\-cyanocyclopropyl)\-4\-fluoro-\-N^2\-\{(1S)-2,2,2-trifluoro-\-1\-[4\-\(\text{methylsulfonyl}\)-1,1\-biphenyl-4-\-yl]ethyl\}-L-leucinamide, or a pharmaceutically acceptable salt thereof.

In an embodiment of the invention, the modified cyclodextrin is sulfobutyl ether-7\-β-cyclodextrin (Captisol®) or Hydroxypropyl beta-cyclodextrin. In a class of the embodiment, the modified cyclodextrin is sulfobutyl ether-7\-β-cyclodextrin.

In an embodiment of the invention, the wetting agent is polysorbate 80, polysorbate 20, poloxamer 407, poloxamer 188, Cremaphor EL or a phospholipid. In a class of the embodiment, the wetting agent is polysorbate 80.

The pharmaceutical tablet compositions of the present invention may also contain one or more additional formulation ingredients that may be selected from a wide variety of
excipients known in the pharmaceutical formulation art. According to the desired properties of
the tablet, any number of ingredients may be selected, alone or in combination, based upon their
known uses in preparing tablet compositions. Such ingredients include, but are not limited to,
diluents, binders, compression aids, disintegrants, lubricants, flavors, flavor enhancers,
sweeteners, preservatives, colorants and coatings.

The term "tablet" as used herein is intended to encompass compressed
certified dosage formulations of all shapes and sizes, whether uncoated or coated.
Substances which may be used for coating include hydroxypropylmethylcellulose,
hydroxypropylcellulose, titanium dioxide, talc, sweeteners and colorants.

The pharmaceutical compositions of the present invention are useful in the
therapeutic or prophylactic treatment of disorders associated with cathpesin K functioning. Such
disorders include: osteoporosis, glucocorticoid induced osteoporosis, Paget’s disease,
abnormally disease, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis, periprosthetic
osteolysis, osteogenesis imperfecta, atherosclerosis, obesity, glaucoma, chronic obstructive
pulmonary disease and cancer including metastatic bone disease, hypercalcemia of malignancy,
and multiple myeloma.

The following examples are given for the purpose of illustrating the present
invention and shall not be construed as being limitations on the scope of the invention.

Ranges of conditions for processing:

The wet granulation processes disclosed herein can be performed in (but not
limited to) high shear mixer and fluid bed processor system. Granule is then milled through a
size reduction mill, lubricant is added to the granule contained in a tote, and then mixed.
Granule is then compressed into tablets.

The dry granulation process can be performed in (but not limited to) a roller
compactor. Granule is then milled through a size reduction mill, lubricant is added to the granule
contained in a tote, and then mixed. Granule is then compressed into tablets.

EXAMPLE 1
PREPARATION OF 50 MG TABLETS

<table>
<thead>
<tr>
<th>Component</th>
<th>% wt./wt.</th>
<th>Mg/Tablet</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Batch = 100,000 tablet)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| \(N^1-(1\text{-cyanocyclopropyl})-4\text{-fluoro-}
\N^2-\{(1S)-2,2,2\text{-trifluoro-1-[4'}-
\text{(methylsulfonyl)-1,1'-biphenyl-4-
\text{-yl}]}\text{ethyl}\text{-L-leucinamide} | 12.5 | 50.00 | 5.0 |
| Microcrystalline Cellulose | 40 | 160.00 | 16.0 |
Lactose Monohydrate & 40 & 160.000 & 16.0 \\
Croskarmellose Sodium & 4 & 16.00 & 1.6 \\
Hydroxypropyl cellulose & 3 & 12.00 & 1.2 \\
Magnesium Stearate & 0.5 & 2.00 & 0.2 \\
Total & 100 & 400.00 & 40.0 \\

* removed during the during process

V-[(I-cyanocyclopropyl)-4-fluoro-N2{-[(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethyl}-L-leucinamide, 4% (wt./wt.) croscarmellose sodium, and a 1:1 (wt./wt.) mixture of microcrystalline cellulose and lactose monohydrate are dry blended in a high shear mixer, and then a 3% (wt./wt.) hydroxypropyl cellulose solution is sprayed onto the mixing powders to effect granulation. The wet granulate is dried in a fluid bed dryer, the dried granulate is then milled, and finally lubricated with 0.5% (wt./wt.) magnesium stearate in a blender. Tablets were then compressed on a rotary tablet press.

EXAMPLE 2
PREPARATION OF 5 MG TABLETS

<table>
<thead>
<tr>
<th>Component</th>
<th>% wt./wt.</th>
<th>Mg/Tablet</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1-{(1-cyanocyclopropyl)-4-fluoro-N2{-[(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethyl}-L-leucinamide</td>
<td>5</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>43.75</td>
<td>43.75</td>
<td>4.375</td>
</tr>
<tr>
<td>Lactose Monohydrate</td>
<td>43.75</td>
<td>43.75</td>
<td>4.375</td>
</tr>
<tr>
<td>Croskarmellose Sodium</td>
<td>4</td>
<td>4</td>
<td>0.4</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>3</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>0.5</td>
<td>0.5</td>
<td>0.05</td>
</tr>
<tr>
<td>Purified Water*</td>
<td>[35]</td>
<td>[140.00]</td>
<td>[14.0]</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>10</td>
</tr>
</tbody>
</table>

* removed during the during process

V-[(I-cyanocyclopropyl)-4-fluoro-V- {[1S]-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethyl}-L-leucinamide, 4% (wt./wt.) croscarmellose sodium, and a 1:1 (wt./wt.) mixture of microcrystalline cellulose and lactose monohydrate are dry blended in a high shear mixer, and then a 3% (wt./wt.) hydroxypropyl cellulose solution is sprayed onto the mixing powders to effect granulation. The wet granulate is dried in a fluid bed dryer, the dried granulate is then milled, and finally lubricated with 0.5% (wt./wt.) magnesium stearate in a blender. Tablets were then compressed on a rotary tablet press.
EXAMPLE 3
PREPARATION OF 5 MG TABLETS

<table>
<thead>
<tr>
<th>Component</th>
<th>% wt/wt</th>
<th>Mg/Tablet</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Batch = 100,000 tablet)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JV'-{(1-cyanocyclopropyl)-4-fluoro-N2-{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethyl}-L-leucinamide</td>
<td>5</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>43.75</td>
<td>87.5</td>
<td>8.75</td>
</tr>
<tr>
<td>Lactose Monohydrate</td>
<td>43.75</td>
<td>87.5</td>
<td>8.75</td>
</tr>
<tr>
<td>Croscarmellose Sodium</td>
<td>4</td>
<td>8</td>
<td>0.8</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>3</td>
<td>6</td>
<td>0.6</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>0.5</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Purified Water*</td>
<td>[35]</td>
<td>[140.00]</td>
<td>[14.0]</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>100</td>
<td>200</td>
<td>20</td>
</tr>
</tbody>
</table>

* removed during the during process

JV'-{(1-cyanocyclopropyl)-1>4-fluoro- N2-{(1S)-2,2,2-trifluoro- 1-[4'-(methylsulfonyl)> 1,1'-biphenyl-4-yl]ethyl}-L-leucinamide, 4% (wt./wt.) croscarmellose sodium, and a 1:1 (wt./wt.) mixture of microcrystalline cellulose and lactose monohydrate are dry blended in a high shear mixer, and then a 3% (wt./wt.) hydroxypropyl cellulose solution is sprayed onto the mixing powders to effect granulation. The wet granulate is dried in a fluid bed dryer, the dried granulate is then milled, and finally lubricated with 0.5% (wt./wt.) magnesium stearate in a blender. Tablets were then compressed on a rotary tablet press.

EXAMPLE 4
PREPARATION OF 10 MG TABLETS

<table>
<thead>
<tr>
<th>Component</th>
<th>% wt/wt</th>
<th>Mg/Tablet</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Batch = 100,000 tablet)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JV'-{(1-cyanocyclopropyl)-4-fluoro-N2-{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethyl}-L-leucinamide</td>
<td>10</td>
<td>10.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>42.5</td>
<td>42.50</td>
<td>4.25</td>
</tr>
<tr>
<td>Lactose Monohydrate</td>
<td>42.5</td>
<td>42.50</td>
<td>4.25</td>
</tr>
<tr>
<td>Croscarmellose Sodium</td>
<td>4</td>
<td>4.00</td>
<td>4.00</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>1</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>100</td>
<td>100.00</td>
<td>10.00</td>
</tr>
</tbody>
</table>
N\textsuperscript{1}-(1-cyanocyclopropyl)-4-fluoro- \(N\textsuperscript{2} \)-\{(1S)-2,2,2-trifluoro- 1-[4'-{(methylsulfonyl)}- 1,1'-biphenyl-4-yl]ethyl\}-L-leucinamide, and a 1:1 (wt. /wt.) mixture of lactose anhydrous (type; direct tableting), microcrystalline cellulose (type; Avicel PH102) are mixed together in a drum blender for 10 minutes at 46 rpm. The mixture is then lubricated by addition of 0.5% (wt. /wt.) magnesium stearate and mixing in the same blender for 1 minute at 46 rpm. The mixture was then dry granulated on a roller compactor using the following conditions:

- Roll Pressure = 400 MPa
- Roll Speed = 4.00 rpm
- Screw speed = 55.5 rpm

The compacted ribbons are milled through a 1 mm screen, and then further size reduced in a cone mill equipped with a 1.27 mm round rasp screen. A final lubrication with 0.5% (wt. /wt.) magnesium stearate was performed using the drum blender for 1 minute at 46 rpm. Tablets were then compressed on a rotary tablet press.

**EXAMPLE 5**

**PREPARATION OF 25 MG SOFT GELATIN CAPSULES**

<table>
<thead>
<tr>
<th>Component</th>
<th>% wt./wt.</th>
<th>Mg/Capsule</th>
<th>Weight (kg) (Batch = 100,000 capsules)</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textsuperscript{N}\textsuperscript{1}-(1-cyanocyclopropyl)-4-fluoro- \textsuperscript{N}\textsuperscript{2} -{(1S)-2,2,2-trifluoro- 1-[4'-{(methylsulfonyl)}- 1,1'-biphenyl-4-yl]ethyl}-L-leucinamide</td>
<td>2.5</td>
<td>25.00</td>
<td>2.5</td>
</tr>
<tr>
<td>PEG400</td>
<td>60</td>
<td>600.00</td>
<td>60.0</td>
</tr>
<tr>
<td>Water</td>
<td>10</td>
<td>100.00</td>
<td>100.0</td>
</tr>
<tr>
<td>Butylated Hydroxyanisole (BHA)</td>
<td>0.1</td>
<td>1.00</td>
<td>1.0</td>
</tr>
<tr>
<td>Soft gelatin capsule</td>
<td>27.4</td>
<td>274.00</td>
<td>27.4</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>1000.00</td>
<td>100.0</td>
</tr>
</tbody>
</table>

V-(1-cyanocyclopropyl)-4-fluoro- \(N\textsuperscript{2} \)-\{(1S)-2,2,2-trifluoro- 1-[4'-{(methylsulfonyl)}- 1,1'-biphenyl-4-yl]ethyl\}-L-leucinamide is dissolved in a PEG400/10% \textsubscript{H}_2\textsubscript{O}/0.1% BHA solution and then 1000 mg is filled into soft gelatin capsule. In the capsule filling process, the fill material is injected into the pocket as gelatin ribbon is molded into the capsule shape.
EXAMPLE 6
PREPARATION OF 10 MG HARD GELATIN CAPSULES

<table>
<thead>
<tr>
<th>Component</th>
<th>% wt/wt</th>
<th>Mg/capsule</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Batch = 100,000 capsule)</td>
</tr>
<tr>
<td>$N^1$-(1-cyanocyclopropyl)-4-fluoro-$N^2$-{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl][ethyl]}-L-leucinamide</td>
<td>10</td>
<td>10.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>42.75</td>
<td>42.75</td>
<td>4.275</td>
</tr>
<tr>
<td>Lactose Monohydrate</td>
<td>42.75</td>
<td>42.75</td>
<td>4.275</td>
</tr>
<tr>
<td>Croscarmellose Sodium</td>
<td>4</td>
<td>4.00</td>
<td>0.4</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>0.5</td>
<td>0.5</td>
<td>0.05</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100.00</td>
<td>10</td>
</tr>
<tr>
<td>Hard Gelatin Capsule</td>
<td>n/a</td>
<td>40</td>
<td>4</td>
</tr>
</tbody>
</table>

$N^1$-(1-cyanocyclopropyl)-4-fluoro-$N^2$-{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl][ethyl]}-L-leucinamide, and the 1:1 (wt./wt.) mixture of lactose monohydrate, microcrystalline cellulose are mixed together in a drum blender for 10 minutes at 46 rpm. The mixture is then lubricated by addition of 0.5% (wt./wt.) magnesium stearate and mixing in the same blender for 1 minute at 46 rpm. The oral gelatin capsule formulation process is performed on a dry powder filling capsule machine.

EXAMPLE 7
PREPARATION OF 5 MG HARD GELATIN CAPSULES

<table>
<thead>
<tr>
<th>Component</th>
<th>% wt/wt</th>
<th>Mg/Capsule</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Batch = 100,000 capsule)</td>
</tr>
<tr>
<td>$N^1$-(1-cyanocyclopropyl)-4-fluoro-$N^2$-{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl][ethyl]}-L-leucinamide</td>
<td>0.5</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>PEG4000</td>
<td>89.4</td>
<td>894</td>
<td>89.4</td>
</tr>
<tr>
<td>Butylated Hydroxyanisole (BHA)</td>
<td>0.1</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Water</td>
<td>10</td>
<td>100.00</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>1000.00</td>
<td>100</td>
</tr>
</tbody>
</table>
PEG4000 is liquified at 70°C in a non-hygroscopic environment then V-(I-cyanocyclopropyl)-4-fluoro-N^2-\{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethyl\}-L-leucinamide is added with stirring to the PEG4000 until solubilized. The solution is added to the hopper* of a capsule filling machine, then hard gelatin capsules are filled with 1 g of solution.

* hopper maintained at 75°C

**EXAMPLE 8**

**PREPARATION OF IV FORMULATION**

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount, mg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>N^4-(1-cyanocyclopropyl)-4-fluoro-N^2-{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethyl}-L-leucinamide</td>
<td>0.1</td>
</tr>
<tr>
<td>Captisol</td>
<td>350</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>0.1</td>
</tr>
<tr>
<td>Water for Injection</td>
<td>Qs 1.00 mL</td>
</tr>
</tbody>
</table>

**Vehicle Preparation Procedure:**

Weigh the Captisol® (0.35 g for each ImL of vehicle), then add the Captisol® with three times of rinse to a glass container (volumetric flask) with approximately 90% of the water. Stir the solution with a stirring bar at a speed that creates a vortex. Stir until all solid has dissolved (approximately 60 minutes). Add polysorbate 80 (0.0001 g for each ImL of vehicle), then Qs to the desired final volume with water. Mix well (inverting the flask by 5-6 times), and record the final pH. Filter through to the container by using Millipore GV filter unit (0.22 µm, sterile)

20 **Formulation Preparation Procedure - O.Img/ml of** ^\wedge-(l-cyanocyclopropy\wedge-fluoro-iV^2_{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethyl}-L-leucinamide) in 0.01% polysorbate 80, 35% Captisol®.

Tare the volumetric flask on the balance, add polysorbate 80 (0.1 mg for each ImL of vehicle). Add approximately 90% of the water weight in the formulation to a glass container (volumetric flask). Add 35% Captisol® (0.35 gram per ImL of water), add stirring bar to the solution, stir the solution at a speed that create a vortex, during approximately 30 minutes of stirring, invert the flask couple of times to wash off any particles on the wall of top flask. Weigh V-(I-cyanocyclopropyl)-4-fluoro-V-{(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-
yl]ethyl}-L-leucinamide (0.1 mg for each mL of vehicle), then add V-(1-cyanocyclopropyl)-4-fluoro-2-\{(15)-2,2,2-trifluoro-l-[4'-\(\text{methylsulfonyl}\)l,\'-biphenyl-4-yl]ethyl}-L-leucinamide to a glass container. Sonicate for approximately 5 minutes using a bath sonicator to breakdown the large particles. Continue to stirring at 400 rpm for overnight, invert the flask if any particles were on the wall of top flask. The formulation should be clear; otherwise, continue stirring until the solution is achieved (~24 hours). Qs to volume with water. Filter using Millipore GV filter unit (0.22 µm, sterile). Label the IV formulation and move it to 5°C or -20°C refrigerator immediately.
WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising by weight, about 0.5 to 40% by weight of a cathepsin K inhibitor, or a pharmaceutically acceptable salt thereof, and from about 60% to 99.5% by weight of excipients selected from diluents, a binder, a lubricant, and a disintegrant.

2. The pharmaceutical composition of Claim 1 wherein the cathepsin K inhibitor is \( N^1 \)-[(1-cyanocyclopropyl)-4-fluoro-\( N^2 \)-\{[(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethyl\]-L-leucinamide, or a pharmaceutically acceptable salt thereof.

3. The pharmaceutical composition of Claim 2 wherein the diluents are selected from the group consisting of lactose anhydrous, lactose monohydrate, mannitol, microcrystalline cellulose, calcium phosphate and starch; the binder is hydroxypropyl cellulose, polyvinylpyrrolidone or hydroxypropylmethylcellulose; the lubricant is magnesium stearate or sodium stearyl fumerate; and the disintegrant is croscarmellose sodium, starch or sodium starch glycolate.

4. The pharmaceutical composition of Claim 3 wherein the diluents are lactose monohydrate and microcrystalline cellulose; the binder is hydroxypropyl cellulose; the lubricant is magnesium stearate; and the disintegrant is croscarmellose sodium.

5. A pharmaceutical composition comprising by weight, about 0.5 to 40% by weight of a cathepsin K inhibitor, or a pharmaceutically acceptable salt thereof, and from about 60% to 99.5% by weight of excipients selected from diluents and a lubricant.

6. The pharmaceutical composition of Claim 5 wherein the cathepsin K inhibitor is \( N^1 \)-[(1-cyanocyclopropyl)-4-fluoro-\( N^2 \)-\{[(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethyl\]-L-leucinamide, or a pharmaceutically acceptable salt thereof.

7. The pharmaceutical composition of Claim 6 wherein the diluents are selected from the group consisting of lactose anhydrous, lactose monohydrate, mannitol, microcrystalline cellulose, calcium phosphate and starch; and the lubricant is magnesium stearate or sodium stearyl fumerate.

8. The pharmaceutical composition of Claim 7 wherein the diluents are lactose monohydrate and microcrystalline cellulose; and the lubricant is magnesium stearate.
9. The pharmaceutical composition of Claim 5 which also contains a binder.

10. The pharmaceutical composition of Claim 9 wherein the binder is hydroxypropyl cellulose, polyvinylpyrrolidone or hydroxypropylmethylcellulose.

11. The pharmaceutical composition of Claim 10 wherein the binder is hydroxypropyl cellulose.

12. An intravenous pharmaceutical composition comprising N\(^1\)-(\(\\gamma\)-cyanocyclopropyl)4-fluoro-N\(^2\)-{(15)-2,2,2-trifluoro-L-[4']-(methylsulfonyl)-1,1-biphenyl-4-yl}ethyl]-L-leucinamide, or a pharmaceutically acceptable salt thereof, water, a modified cyclodextrin and a wetting agent.
INTERNATIONAL SEARCH REPORT

A CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07D 209/42 (2008.04)
USPC - 548/492

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)
USPC-548/492

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Google, WEST Google Patent terms-formulation hydroxypropyl cellulose, cathepsin formulation composition, intravenous, cathepsin, composition, formulation, cyclodextan, hydroxypropyl cellulose, croscarmellose sodium, microcrystalline cellulose
SciFinder (structure search)

C DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
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<tr>
<td>Y</td>
<td>EP 0658348 B1 (BRYANT et al.) 19 September 2001 (19 09 2001), para [0004], [0024], [0031]</td>
<td>12</td>
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</tbody>
</table>

D Further documents are listed in the continuation

* "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 claimed

*" &" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

*" P" 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

*" 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 combined with one or more other such documents, such combination being obvious to a person skilled in the art

Date of the actual completion of the international search
19 May 2008 (19 05 2008)

Date of mailing of the international search report
2 June 2008

Authorized officer
Lee W Young

PCT Helpdesk 571-272-4300
PCT/ISA/210 (second sheet) (April 2007)