IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Utility Patent Application (Provisional)

USE OF ZOLEDRONIC ACID AND RELATED COMPOUNDS FOR THE TREATMENT OF PAIN

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BACKGROUND OF THE INVENTION

Complex regional pain syndrome type I (CRPS-I), also known as reflex sympathetic dystrophy (RSD), and complex regional pain syndrome type II (CRPS-II), also known as causalgia, are debilitating pain syndromes. They are characterized by severe pain in a limb accompanied by allodynia, hyperalgesia, edema, changes in skin blood flow and abnormal sudomotor activity.

These disorders are often difficult to treat and there exists a need for additional therapeutic options.

DESCRIPTION OF THE INVENTION

Disclosed are pharmaceutical compositions and methods for the treatment of any type of pain including, but not limited to, postoperative pain, cancer pain, arthritic pain, lumbosacral pain, musculoskeletal pain, neuropathic pain, chronic pain, etc.

Disclosed are pharmaceutical compositions and methods for the treatment of complex regional pain syndrome type I and type II (CRPS-I and CRPS-II).

One embodiment is a pharmaceutical composition comprising pamidronate, neridronate, olpadronate, alendronate, incadronate, ibandronate, risedronate, zoledronate or another bisphosphonate compound for the treatment of pain.

Another embodiment is a pharmaceutical composition comprising pamidronate, neridronate, olpadronate, alendronate, incadronate, ibandronate, risedronate, zoledronate or another bisphosphonate compound for the treatment of CRPS-I and CRPS-II.

The terms pamidronate, neridronate, olpadronate, alendronate, incadronate, ibandronate, risedronate, zoledronate, or another bisphosphonate compound, as used in this application refer to these compounds or their pharmaceutically acceptable salts, and any of their polymorphic forms.

Other names for pamidronate, neridronate, olpadronate, alendronate, incadronate, ibandronate, risedronate, and zoledronate may include but are not limited to pamidronic acid, neridronic acid, olpadronic acid, alendronic acid, incadronic acid, ibandronic acid, risedronic acid, and zoledronic acid, respectively.

Another embodiment is a method for the treatment of treatment of pain comprising administering to an individual pamidronate, neridronate, olpadronate, alendronate, incadronate, ibandronate, risedronate, zoledronate or another bisphosphonate compound.

Yet another embodiment is a method for the treatment of treatment of CRPS-I and CRPS-II comprising administering to an individual pamidronate, neridronate, olpadronate, alendronate, incadronate, ibandronate, risedronate, zoledronate or another bisphosphonate compound.

Any suitable route of administration may be employed for providing an individual with an effective dosage of the pamidronate, neridronate, olpadronate, alendronate, incadronate, ibandronate, risedronate, zoledronate or another bisphosphonate compound. For example, oral, rectal, parenteral, transdermal, sublingual, subcutaneous, intrathecal, intramuscular and the like may be employed as appropriate.

Dosage forms for the pamidronate, neridronate, olpadronate, alendronate, incadronate, ibandronate, risedronate , zoledronate or another bisphosphonate compound in the present embodiments include but are not limited to tablets, coated tablets, cachets, capsules, caplets, troches, dispersions, sustained release formulations, suspensions, solutions, patches and the like.

In addition to the common dosage forms set forth above, the pamidronate, neridronate, olpadronate, alendronate, incadronate, ibandronate, risedronate, zoledronate or another

bisphosphonate compound may also be administered by controlled release or sustained release means and/or delivery devices.

The effective amount of pamidronate, neridronate, olpadronate, alendronate, incadronate, ibandronate, risedronate , zoledronate or another bisphosphonate compound in the treatment of pain, CRPS-I and CRPS-II will vary depending on various factors known to the treating physicians, such as the severity of the condition to be treated, route of administration, formulation and dosage forms, physical characters of the pamidronate, neridronate, olpadronate, alendronate, incadronate, ibandronate, risedronate , zoledronate or another bisphosphonate compound used, and age, weight and response of the individual patients.

In some embodiments the daily oral dose of pamidronate is about 10 mg to about 1,000 mg, about 50 mg to about 500 mg, about 100 mg to about 500 mg, or about 150 mg to about 300 mg. In some embodiments the parenteral dose of pamidronate is about 5 mg to about 500 mg, about 5 mg to about 200 mg, or about 10 mg to about 150 mg.

In some embodiments the daily oral dose of neridronate is about 10 mg to about 1,000 mg, about 50 mg to about 500 mg, about 100 mg to about 500 mg, or about 150 mg to about 300 mg. In some embodiments the parenteral dose of neridronate is about 5 mg to about 500 mg, about 5 mg to about 200 mg, or about 10 mg to about 150 mg.

In some embodiments the daily oral dose of olpadronate is about 0.5 mg to about 400 mg, about 1 mg to about 300 mg, about 5 mg to about 100 mg, or about 2 mg to about 50 mg. In some embodiments the parenteral dose of olpadronate is about 1 mg to about 100 mg, about 1 mg to about 40 mg, or about 2 mg to about 30 mg.

In some embodiments the daily oral dose of alendronate is about 0.5 mg to about 400 mg, about 1 mg to about 200 mg, about 5 mg to about 100 mg, or about 2 mg to about 50 mg. In some embodiments the parenteral dose of alendronate is about 1 mg to about 100 mg, about 1 mg to about 40 mg, or about 2 mg to about 30 mg.

In some embodiments the daily oral dose of incadronate is about 0.5 mg to about 400 mg, about 1 mg to about 300 mg, about 5 mg to about 100 mg, or about 2 mg to about 50 mg. In some

embodiments the parenteral dose of incadronate is about 1 mg to about 100 mg, about 1 mg to about 40 mg, or about 2 mg to about 30 mg.

In some embodiments the daily oral dose of ibandronate is about 0.25 mg to about 100 mg, about 0.5 mg to about 50 mg, about 2.5 mg to about 50 mg, or about 1 mg to about 25 mg. In some embodiments the parenteral dose of ibandronate is about 0.5 mg to about 50 mg, about 0.5 mg to about 20 mg, or about 1 mg to about 15 mg.

In some embodiments the daily oral dose of risedronate is about 0.25 mg to about 100 mg, about 0.5 mg to about 50 mg, about 2.5 mg to about 50 mg, or about 1 mg to about 25 mg. In some embodiments the parenteral dose of risedronate is about 0.25 mg to about 25 mg, about 0.25 mg to about 10 mg, or about 0.5 mg to about 7.5 mg.

In some embodiments the daily oral dose of zoledronate is about 0.005 mg to about 20 mg, about 0.1 mg to about 10 mg, about 0.5 mg to about 10 mg, or about 0.2 mg to about 5 mg. In some embodiments the parenteral dose of zoledronate is about 0.25 mg to about 25 mg, about 0.25 mg to about 10 mg, or about 0.5 mg to about 7.5 mg.

Some embodiments include orally administering zoledronic acid in a form such as the disodium salt. Any suitable amount of zoledronic acid or disodium salt of zoledronic acid may be used, such as about 10 mg to about 500 mg, about 20 mg to about 200 mg, about 50 mg to about 150 mg, about 50 mg, about 100 mg, or about 150 mg. In some embodiments, the oral zoledronic acid is administered daily, weekly, monthly, once a year, or twice a year. The oral zoledronic acid, or disodium salt thereof, may be administered in combination with about 0.1 mg to about 10 mg of zoledronic acid, or a salt thereof, administered intravenously. In some embodiments, about 50 mg, about 100 mg, or about 150 mg of the disodium salt of zoledronic acid is administered orally in combination with 1 mg intravenous zoledronic acid.

Some oral dosage forms comprising zoledronic acid or a salt thereof may have enteric coatings.

In some embodiments, the pamidronate, neridronate, olpadronate, alendronate, incadronate, ibandronate, risedronate , zoledronate or another bisphosphonate compound can be given weekly, monthly, every two or three months, once a year or twice a year.

In some embodiments the weekly oral dose of pamidronate is about 70 mg to about 7,000 mg, about 350 mg to about 3,500 mg, about 700 mg to about 3,500 mg, or about 1,000 mg to about 2,000 mg. In some embodiments the monthly oral dose of pamidronate is about 300 mg to about 30,000 mg, about 1,500 mg to about 15,000 mg, about 3,000 mg to about 15,000 mg, or about 4,000 mg to about 8,000 mg.

In some embodiments the weekly oral dose of neridronate is about 70 mg to about 7,000 mg, about 350 mg to about 3,500 mg, about 700 mg to about 3,500 mg, or about 1,000 mg to about 2,000 mg. In some embodiments the monthly oral dose of neridronate is about 300 mg to about 30,000 mg, about 1,500 mg to about 15,000 mg, about 3,000 mg to about 15,000 mg, or about 4,000 mg to about 8,000 mg.

In some embodiments the weekly oral dose of olpadronate is about 3.5 mg to about 2,800 mg, about 7 mg to about 2,100 mg, about 35 mg to about 700 mg, or about 15 mg to about 350 mg. In some embodiments the monthly oral dose of olpadronate is about 15 mg to about 11,000 mg, about 30 mg to about 8,500 mg, about 150 mg to about 2,800 mg, or about 60 mg to about 1,500 mg.

In some embodiments the weekly oral dose of alendronate is about 3.5 mg to about 2,800 mg, about 7 mg to about 2,100 mg, about 35 mg to about 700 mg, or about 15 mg to about 350 mg. In some embodiments the monthly oral dose of alendronate is about 15 mg to about 11,000 mg, about 30 mg to about 8,500 mg, about 150 mg to about 2,800 mg, or about 60 mg to about 1,500 mg.

In some embodiments the weekly oral dose of incadronate is about 3.5 mg to about 2,800 mg, about 7 mg to about 2,100 mg, about 35 mg to about 700 mg, or about 15 mg to about 350 mg. In some embodiments the monthly oral dose of incadronate is about 15 mg to about 11,000 mg, about 30 mg to about 8,500 mg, about 150 mg to about 2,800 mg, or about 60 mg to about 1,500 mg.

In some embodiments the weekly oral dose of ibandronate is about 1.75 mg to about 700 mg, about 3.5 mg to about 350 mg, about 18 mg to about 350 mg, or about 7 mg to about 175 mg. In some embodiments the monthly oral dose of ibandronate is about 7 mg to about 2,800 mg, about 15 mg to about 1,500 mg, about 70 mg to about 1,500 mg, or about 30 mg to about 700 mg.

In some embodiments the weekly oral dose of risedronate is about 1.75 mg to about 700 mg, about 3.5 mg to about 350 mg, about 18 mg to about 350 mg, or about 7 mg to about 175 mg. In some

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