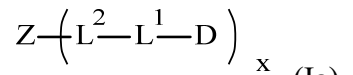
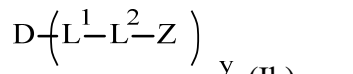
Claims

1. Use of a unit dosage form in the manufacture of a medicament for the treatment of one or more diseases which can be treated with CNP, wherein the unit dosage is to be administered to a patient in need thereof, said unit dosage form comprising a therapeutically effective amount of a CNP conjugate or pharmaceutically acceptable salt thereof, wherein the unit dosage form comprises a unit dose ranging from about 6 µg CNP/kg to at least about 100 µg CNP/kg and wherein the CNP conjugate or pharmaceutically acceptable salt thereof is a compound of formula (Ia) or (Ib):



(Ia),



(Ib),

wherein

-D is a CNP moiety;

-L^1- is a reversible linker moiety;

-L^2- is a single chemical bond or a spacer moiety;

-Z is a polymeric moiety;

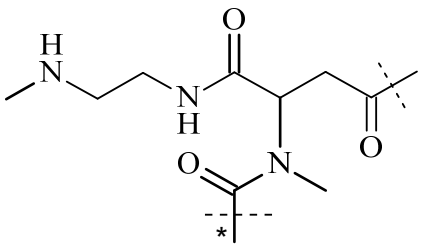
x is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 16; and

y is an integer selected from the group consisting of 1, 2, 3, 4 and 5.

2. The use of claim 1, wherein a patient´s body weight ranges from about 2 kg to about 80 kg.

3. The use of claim 1 or 2, wherein the unit dose is about 100 µg CNP/kg.

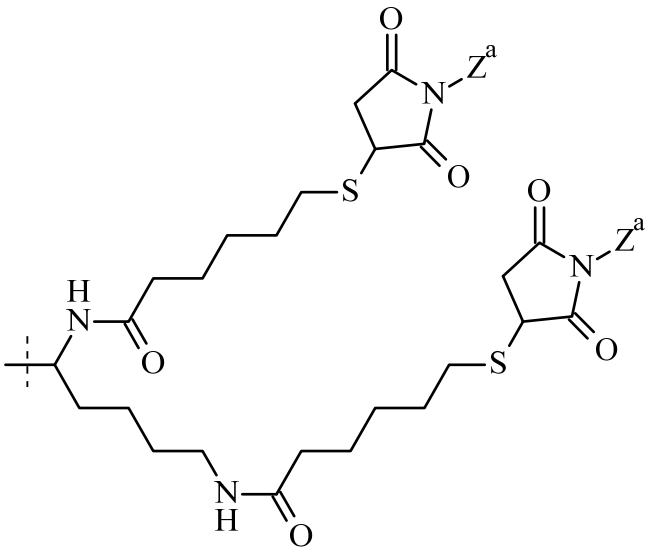
4. The use of any one of claims 1 to 3, wherein the CNP conjugate or pharmaceutically acceptable salt thereof is a compound of formula (IIf):



(IIf), wherein

the unmarked dashed line indicates the attachment to a nitrogen provided by the side chain of the lysine at position 26 of a CNP moiety of SEQ ID NO:24 by forming an amide bond; and

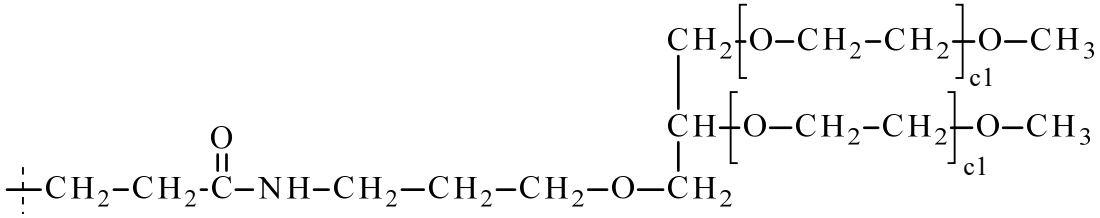
the dashed line marked with the asterisk indicates attachment to -Z having the structure



,

wherein

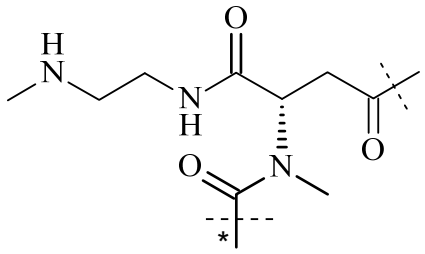
each -Z^a is



wherein

each c1 is an integer independently ranging from 200 to 250.

5. The use of any one of claims 1 to 4, wherein the CNP conjugate or pharmaceutically acceptable salt thereof is a compound of formula (IIf ’):

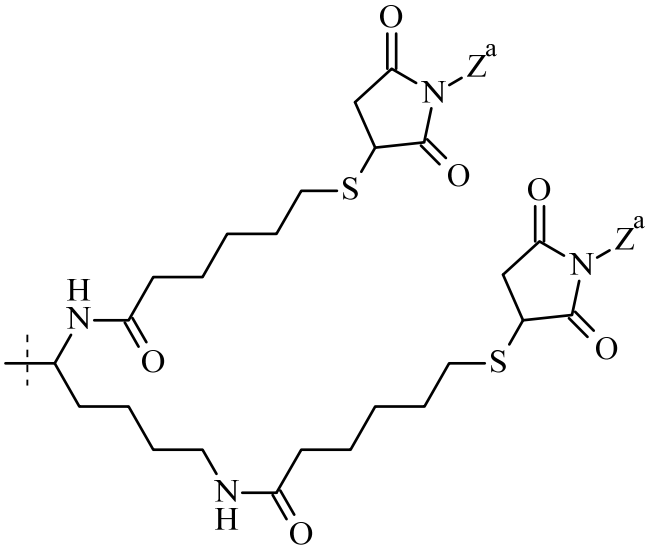


(IIf ’),

wherein

the unmarked dashed line indicates the attachment to a nitrogen provided by the side chain of the lysine at position 26 of the CNP moiety of SEQ ID NO:24 by forming an amide bond; and

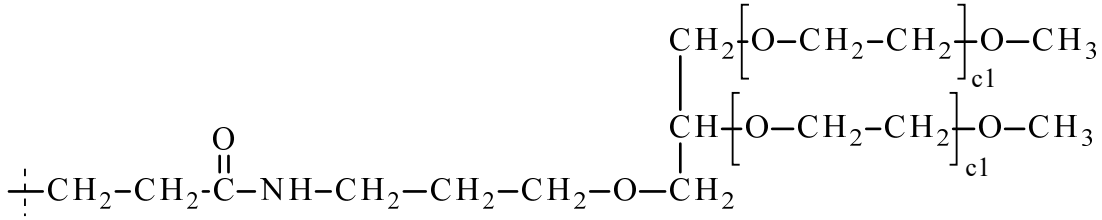
the dashed line marked with the asterisk indicates attachment to -Z having the structure



,

wherein

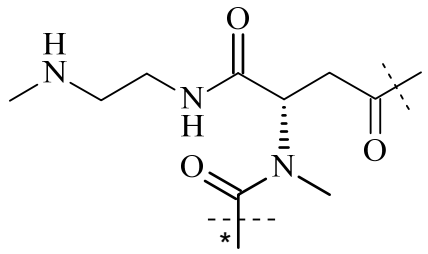
each -Z^a is



wherein

each c1 is an integer independently ranging from 200 to 250.

6. The use of any one of claims 1 to 5, wherein the CNP conjugate or pharmaceutically acceptable salt thereof is a compound of formula (IIf ’):

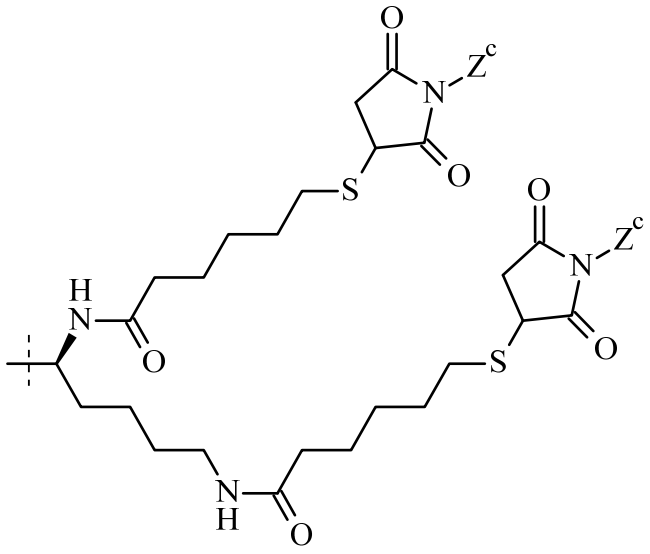


(IIf ’),

wherein

the unmarked dashed line indicates the attachment to a nitrogen provided by the side chain of the lysine at position 26 of the CNP moiety of SEQ ID NO:24 by forming an amide bond; and

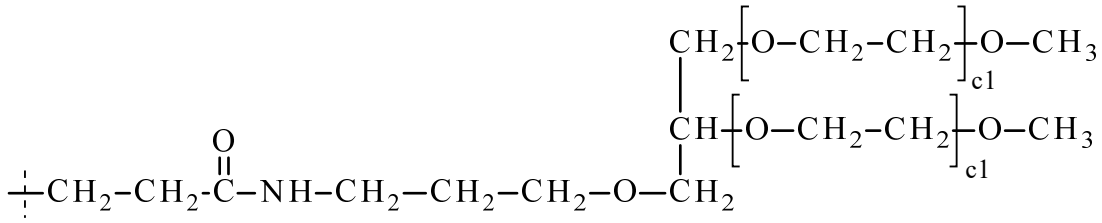
the dashed line marked with the asterisk indicates attachment to -Z having the structure



,

wherein

each -Z^a is



wherein

each c1 is an integer independently ranging from 200 to 250.

7. The use of any one of claims 4 to 6, wherein each c1 is an integer independently ranging from 220 to 245.

8. The use of any one of claims 1 to 7, wherein upon administration of the unit dosage form the incidence of hypotension is less than 10%.

9. The use of any one of claims 1 to 8, wherein upon administration of the unit dosage form the incidence of hypotension is less than 3%.

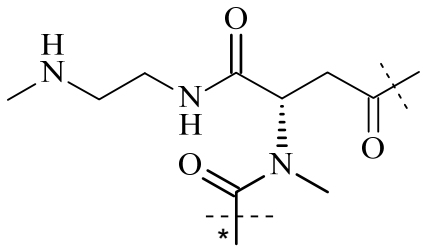
10. The use of any one of claims 1 to 9, wherein the one or more diseases which can be treated with CNP is selected from the group consisting of achondroplasia, hypochondroplasia, short stature, dwarfism, osteochondrodysplasias, thanatophoric dysplasia, osteogenesis imperfecta, achondrogenesis, chondrodysplasia punctata, homozygous achondroplasia, camptomelic dysplasia, congenital lethal hypophosphatasia, perinatal lethal type of osteogenesis imperfecta, short-rib polydactyly syndromes, rhizomelic type of chondrodysplasia punctata, Jansen-type metaphyseal dysplasia, spondyloepiphyseal dysplasia congenita, atelosteogenesis, diastrophic dysplasia, congenital short femur, Langer-type mesomelic dysplasia, Nievergelt-type mesomelic dysplasia, Robinow syndrome, Reinhardt syndrome, acrodysostosis, peripheral dysostosis, Kniest dysplasia, fibrochondrogenesis, Roberts syndrome, acromesomelic dysplasia, micromelia, Morquio syndrome, Kniest syndrome, metatrophic dysplasia, spondyloepimetaphyseal dysplasia, neurofibromatosis, Legius syndrome, LEOPARD syndrome, Noonan syndrome, hereditary gingival fibromatosis, neurofibromatosis type 1, Legius syndrome, cardiofaciocutaneous syndrome, Costello syndrome, SHOX deficiency,

idiopathic short stature, growth hormone deficiency, osteoarthritis, cleidocranial dysostosis, craniosynostosis (e.g., Muenke syndrome, Crouzon syndrome, Apert syndrome, Jackson-Weiss syndrome, Pfeiffer syndrome, or Crouzonodermoskeletal syndrome), dactyly, brachydactyly, camptodactyly, polydactyly, syndactyly, dyssegmental dysplasia, enchondromatosis, fibrous dysplasia, hereditary multiple exostoses, hypophosphatemic rickets, Jaffe-Lichtenstein syndrome, Marfan syndrome, McCune-Albright syndrome, osteopetrosis, osteopoikilosis, hemorrhagic shock, hypertension, restenosis, arteriosclerosis, acute decompensated heart failure, congestive heart failure, cardiac edema, nephredema, hepatic edema, acute renal insufficiency, chronic renal insufficiency, glaucoma, elevated intraocular pressure, multiple myeloma, myeloproliferative syndrome, leukemia, plasma cell leukemia, lymphoma, glioblastoma, prostate cancer, bladder cancer, mammary cancer, growth retardation, skull deformities, orthodontic defects, cervical cord compression, spinal stenosis, hydrocephalus, hearing loss due to chronic otitis, cardiovascular disease, neurological disease and obesity.

11. The use of any one of claims 1 to 10, wherein the disease the one or more diseases which can be treated with CNP is selected from the group consisting of hypophosphatasia, hypochondroplasia, Muenke syndrome, hypertension, osteogenesis imperfecta and achondroplasia.

12. The use of any one of claims 1 to 11, wherein the disease the one or more diseases which can be treated with CNP is achondroplasia.

13. Use of a CNP conjugate or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of achondroplasia in a human patient, wherein the CNP conjugate or pharmaceutically acceptable salt thereof is to be administered to a patient in need thereof at a unit dose of 100 µg CNP/kg, wherein the CNP conjugate is a compound of formula (IIf ’):

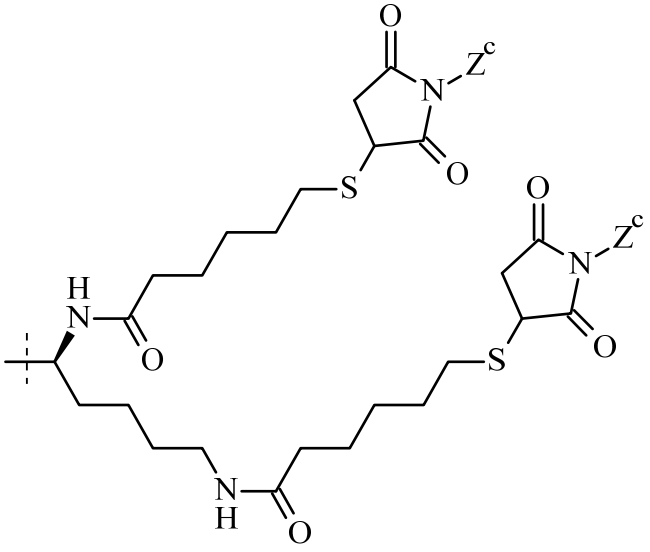


(IIf'),

wherein

the unmarked dashed line indicates the attachment to a nitrogen provided by the side chain of the lysine at position 26 of the CNP moiety of SEQ ID NO:24 by forming an amide bond;

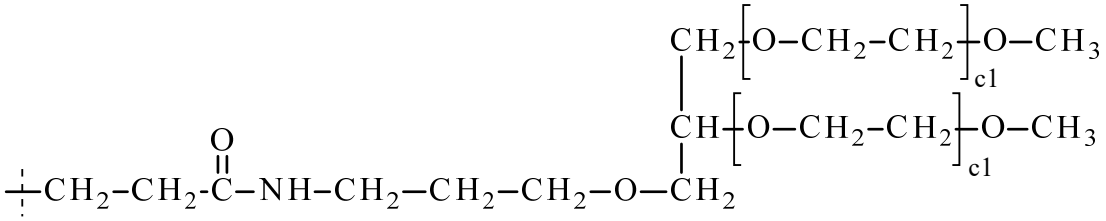
the dashed line marked with the asterisk indicates attachment to -Z having the structure



,

wherein

each -Z^c is

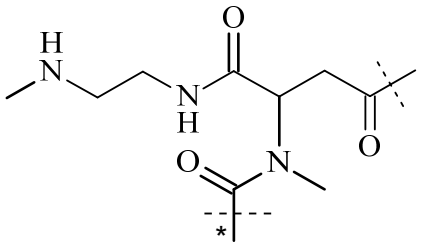


and wherein

each c1 is an integer independently ranging from 200 to 250,

wherein the unit dose is to be administered weekly.

14. Use of a CNP conjugate or pharmaceutically acceptable salt thereof in the manufacture of a medicament for increasing growth velocity in a human patient, wherein the CNP conjugate or pharmaceutically acceptable salt thereof is to be administered to a patient in need thereof, wherein the CNP conjugate or pharmaceutically acceptable salt thereof is of (a) formula (IIf):

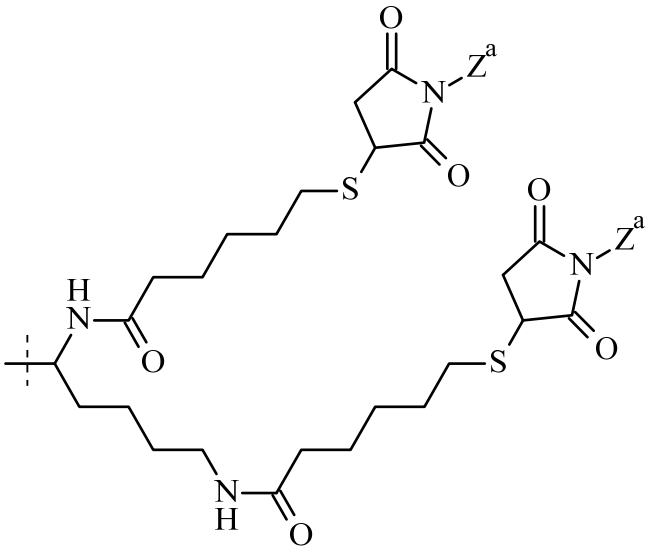


(IIf),

wherein

the unmarked dashed line indicates the attachment to a nitrogen provided by the side chain of the lysine at position 26 of the CNP moiety of SEQ ID NO:24 by forming an amide bond;

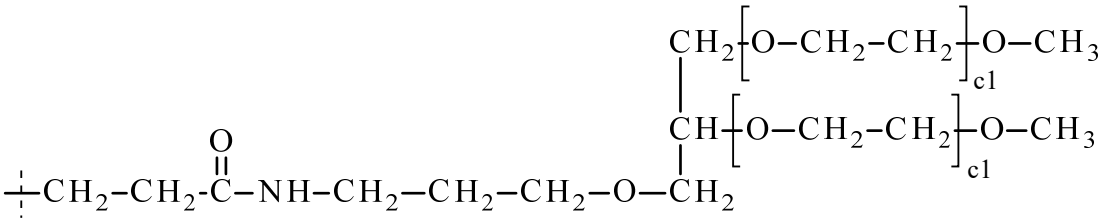
the dashed line marked with the asterisk indicates attachment to -Z having the structure



,

wherein

each -Z^a is

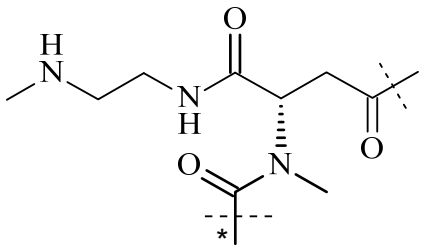


and wherein

each c1 is an integer independently ranging from 200 to 250;

or

(b) formula (IIf ’):

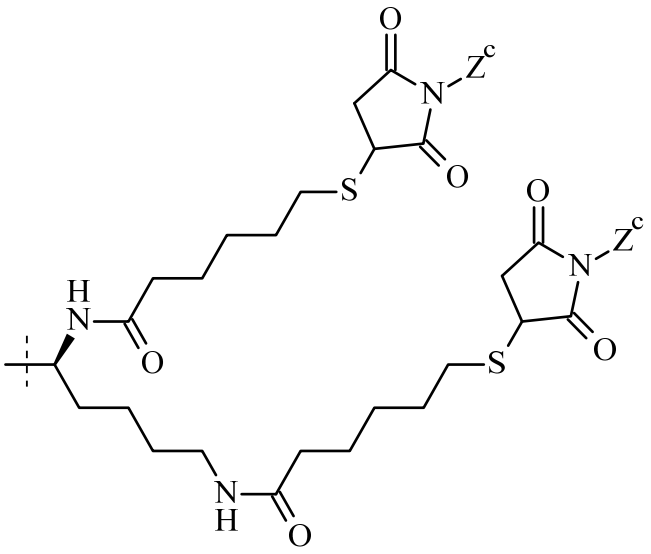


(IIf ’),

wherein

the unmarked dashed line indicates the attachment to a nitrogen provided by the side chain of the lysine at position 26 of the CNP moiety of SEQ ID NO:24 by forming an amide bond;

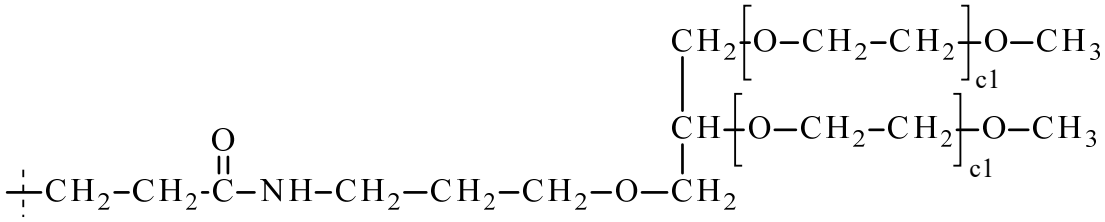
the dashed line marked with the asterisk indicates attachment to -Z having the structure



,

wherein

each -Z^c is



and wherein

each c1 is an integer independently ranging from 200 to 250;

at a unit dose of 100 µg CNP/kg, wherein the unit dose is to be administered weekly.

15. The use of claim 13 or 14, wherein each c1 is about 225.

16. Use of a CNP conjugate or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a skeletal dysplasia, such as achondroplasia, wherein a unit dosage form comprising a CNP conjugate or pharmaceutically acceptable salt thereof of formula (IIf) or (IIf ') is to be administered to a patient in need thereof, wherein each of (IIf) and (IIf ') are as defined in claim 14, at a unit dose of 100 µg CNP/kg, wherein said unit dosage form is to be administered weekly to a human patient with open epiphysis and said treatment reduces the incidence of achondroplasia-related adverse events in the human patient.

17. The use of claim 16, wherein the achondroplasia-related adverse events are selected from the group consisting of sleep apnea syndrome, ear infection, foramen magnum stenosis and kyphosis.