

(19)

LATVIJAS REPUBLIKAS  
PATENTU VALDE

(11) LV 12720 B

(51) Int.Cl. <sup>7</sup> C07F9/38Latvijas patents uz izgudrojumu  
1995.g. 30.marta Latvijas Republikas likums

(12)

Īsziņas

(21) Pieteikuma numurs: P-01-26

(22) Pieteikuma datums: 05.04.2001

(41) Pieteikuma publikācijas datums: 20.09.2001

(45) Patenta publikācijas datums: 20.02.2002

(30) Prioritāte:

98,313	27.08.1998	US
129,743	16.04.1999	US
144,461	19.07.1999	US

(86) PCT pieteikums:

PCT/US99/19838,	27.08.1999
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(87) PCT publikācija:

WO 00/12517,	09.03.2000
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(73) Īpašnieks(i):  
TEVA PHARMACEUTICAL INDUSTRIES LTD.;  
Basel Street 5, P.O.Box 3190, 49131 Patach  
Tiqva, IL

(72) Izgudrotājs(i):  
Nina FINKELSTEIN (IL),  
Ramy LIDOR-HADAS (IL),  
Judith ARONHIME (IL)

(74) Pilnvarotais vai pārstāvis:  
Vladimirs ANOHINS,  
Aģentūra "TRIA ROBIT",  
Aizkraukles iela 23, Rīga LV-1006, LV

(54) Virsraksts: **Nātrija alendronāta jaunas hidratā formas, to iegūšanas paņēmieni un farmaceitiskas kompozīcijas**

(57) Kopsavilkums: Aprakstītas nātrija alendronāta jaunas hidratu formas ar ūdens saturu no 1% līdz 12%, un šo formu iegūšanas paņēmieni. Aprakstītas arī nātrija alendronāta jaunas kristāliskās formas B, D, E, F, G un H, un šo formu iegūšanas paņēmieni. Šīs jaunās formas izmanto farmaceitiskās kompozīcijās kaulu rezorbcijas ārstēšanai kaulu slimību gadījumos.

## IZGUDROJUMA FORMULA

1. 4-Amino-1-oksibutilidēn-1,1-bisfosfonskābes mononātrija sāls savienojums ar ūdens saturu no 1,3% līdz 11,7%.
2. Savienojuma saskaņā ar 1. punktu hidratā forma, šo hidratā formu izvēlas no grupas, kas sastāv no  $\frac{1}{4}$  hidratā,  $\frac{1}{3}$  hidratā, pushidratā,  $\frac{2}{3}$  hidratā,  $\frac{3}{4}$  hidratā, monohidratā,  $\frac{5}{4}$  hidratā,  $\frac{4}{3}$  hidratā,  $\frac{3}{2}$  hidratā un dihidratā.
3. Kristālais mononātrija alendronāta monohidrāts.
4. Kristāliskā mononātrija alendronāta monohidrāta saskaņā ar 3. punktu paraugs ar ūdens saturu 6,2% (masas).
5. Kristālais mononātrija alendronāta monohidrāts, kurš ir stabils pret dehidratāciju līdz pat 150°C temperatūrai.
6. Kristālais mononātrija alendronāta monohidrāts saskaņā ar 5. punktu, kurš papildus raksturojas ar maksimumiem uz pulvera rentgenogrammas pie sekojošām  $2\theta$  vērtībām:  $12,7 \pm 0,2$ ;  $16,2 \pm 0,2$ ;  $17,3 \pm 0,2$ ;  $17,6 \pm 0,2$ ;  $24,8 \pm 0,2$  un  $25,5 \pm 0,2$ .
7. Kristāliskā mononātrija alendronāta monohidrāta saskaņā ar vienu no 3.-6. punktiem iegūšanas paņēmiens, kurā ietilpst stadijas:
  - a) 4-amino-1-oksibutilidēn-1,1-bisfosfonskābes viena ekvivalenta suspendēšana zemākajā spirtā;
  - b) nātrija bāzes viena ekvivalenta un ūdens no 5 līdz 200 ekvivalentiem šķīduma zemākajā spirtā pievienošana 4-amino-1-oksibutilidēn-1,1-bisfosfonskābes suspensijai; un
  - c) kristāliskā mononātrija alendronāta monohidrāta izdalīšana.
8. Paņēmiens saskaņā ar 7. punktu, kas atšķiras ar to, ka 4-amino-1-oksibutilidēn-1,1-bisfosfonskābe ir monohidrāta formā.
9. Paņēmiens saskaņā ar 7. punktu, kas atšķiras ar to, ka zemāko spirtu izvēlas no grupas, kas sastāv no metanola, etanola un izopropanola.

10. Paņēmiens saskaņā ar 7. punktu, kas atšķiras ar to, ka nātrija bāzi izvēlas no grupas, kas sastāv no nātrija hidroksīda, nātrija metilāta un nātrija etilāta.
11. Paņēmiens saskaņā ar 7. punktu, kas atšķiras ar to, ka 4-amino-1-oksibutilidēn-1,1-bisfosfonkābe ir bezūdens formā.
12. Savienojuma saskaņā ar vienu no 3.-6. punktiem iegūšanas paņēmiens, kurā ietilpst stadijas:
- a) mononātrija 4-amino-1-oksibutilidēn-1,1-bisfosfonāta sāls viena ekvivalenta apstrāde zemākajā spirtā ar 20-40 ūdens ekvivalentiem; un
  - b) šī savienojuma izdalīšana.
13. Paņēmiens saskaņā ar 12. punktu, kas atšķiras ar to, ka stadijas (a) zemākais spirts ir etanols.
14. Savienojuma saskaņā ar vienu no 3.-6. punktiem iegūšanas paņēmiens, kurā ietilpst stadijas:
- a) dinātrija 4-amino-1-oksibutilidēn-1,1-bisfosfonāta sāls viena ekvivalenta apstrāde zemākajā spirtā ar 20-40 ūdens ekvivalentiem un alendronskābes vienu ekvivalentu; un
  - b) šī savienojuma izdalīšana.
15. Paņēmiens saskaņā ar 14. punktu, kas atšķiras ar to, ka stadijas (a) zemākais spirts ir etanols.
16. Savienojuma saskaņā ar vienu no 3.-6. punktiem iegūšanas paņēmiens, kurā ietilpst stadijas:
- a) trinātrija 4-amino-1-oksibutilidēn-1,1-bisfosfonāta sāls viena ekvivalenta apstrāde zemākajā spirtā ar 20-40 ūdens ekvivalentiem un alendronskābes diviem ekvivalentiem; un
  - b) šī savienojuma izdalīšana.
17. Paņēmiens saskaņā ar 16. punktu, kas atšķiras ar to, ka stadijas (a) zemākais spirts ir etanols.

18. Savienojuma saskaņā ar vienu no 3.-6. punktiem iegūšanas paņēmiens, kurā ietilpst stadijas:
- a) tetranātrijs 4-amino-1-oksibutilidēn-1,1-bisfosfonāta sāls viena ekvivalenta apstrāde zemākajā spirtā ar 20-40 ūdens ekvivalentiem un alendronskābes trim ekvivalentiem; un
  - b) šī savienojuma izdalīšana.
19. Paņēmiens saskaņā ar 18. punktu, kas atšķiras ar to, ka stadijas (a) zemākais spirts ir etanols.
20. Paņēmiens saskaņā ar 12. punktu, kas atšķiras ar to, ka nātrijs 4-amino-1-oksibutilidēn-1,1-bisfosfonāta sāls ir mononātrijs sāls trihidrāts.
21. Kristālais mononātrijs alendronāta monohidrāts, kurš raksturojas ar maksimumiem uz pulvera rentgenogrammas pie sekojošām  $2\theta$  vērtībām:  $9,3\pm 0,2$ ;  $12,4\pm 0,2$ ;  $13,5\pm 0,2$ ;  $26,3\pm 0,2$ ; un  $30,0\pm 0,2$ .
22. Savienojuma saskaņā ar 21. punktu iegūšanas paņēmiens, kurā ietilpst stadijas:
- a) mononātrijs 4-amino-1-oksibutilidēn-1,1-bisfosfonāta trihidrāta apstrāde ar atūdeņojoša (žāvējoša) aģenta efektīvu daudzumu; un
  - b) šī savienojuma izdalīšana saskaņā ar 21. punktu.
23. Paņēmiens saskaņā ar 22. punktu, kas atšķiras ar to, ka stadijas (a) reakciju veic etanolā.
24. Mononātrijs alendronāta trihidrāts.
25. 4-Amino-1-oksibutilidēn-1,1-bisfosfonskābes mononātrijs sāls savienojums ar ūdens saturu no 2,8% līdz 3,9%.
26. Savienojums saskaņā ar 25. punktu ar ūdens saturu 3,2%.
27. Savienojums saskaņā ar 25. punktu, kurš raksturojas ar maksimumiem uz pulvera rentgenogrammas pie  $2\theta$  sekojošām vērtībām:  $7,0\pm 0,2$ ;  $9,3\pm 0,2$  un  $14,0\pm 0,2$ .

28. Savienojuma saskaņā ar 24. vai 25. punktu iegūšanas paņēmiens, kurā ietilpst stadijas:

- a) 4-amino-1-oksibutilidēn-1,1-bisfosfonskābes apstrāde zemākajā spirtā ar nātrija bāzes vienu ekvivalentu un 9-15 ūdens ekvivalentiem; un
- b) šī savienojuma saskaņā ar 24. vai 25. punktu izdalīšana.

29. Paņēmiens saskaņā ar 28. punktu, kas atšķiras ar to, ka 4-amino-1-oksibutilidēn-1,1-bisfosfonskābe ir monohidrāta formā.

30. Paņēmiens saskaņā ar 28. punktu, kas atšķiras ar to, ka zemāko spirtu izvēlas no grupas, kas sastāv no metanola, etanola un izopropanola.

31. Paņēmiens saskaņā ar 28. punktu, kas atšķiras ar to, ka nātrija bāzi izvēlas no grupas, kas sastāv no nātrija hidroksīda, nātrija metilāta un nātrija etilāta.

32. Paņēmiens saskaņā ar 28. punktu, kas atšķiras ar to, ka 4-amino-1-oksibutilidēn-1,1-bisfosfonskābe ir bezūdens formā.

33. 4-Amino-1-oksibutilidēn-1,1-bisfosfonskābes mononātrija sāls savienojums ar ūdens saturu no 2,5% līdz 3,5%.

34. Savienojums saskaņā ar 33. punktu, kurš raksturojas ar maksimumiem uz pulvera rentgenogrammas pie  $2\Theta$  sekojošām vērtībām:  $9,2\pm 0,2$ ;  $14,2\pm 0,2$ ;  $15,0\pm 0,2$ ;  $17,1\pm 0,2$ ;  $20,7\pm 0,2$ ;  $22,0\pm 0,2$  un  $22,4\pm 0,2$ .

35. Savienojuma saskaņā ar 2. vai 33. punktu iegūšanas paņēmiens, kurā ietilpst stadijas:

- a) 4-amino-1-oksibutilidēn-1,1-bisfosfonskābes apstrāde zemākajā spirtā ar nātrija bāzes vienu ekvivalentu un 17-22 ūdens ekvivalentiem; un
- b) šī savienojuma saskaņā ar 2. vai 33. punktu izdalīšana.

36. Paņēmiens saskaņā ar 35. punktu, kas atšķiras ar to, ka 4-amino-1-oksibutilidēn-1,1-bisfosfonskābe ir monohidrāta formā.

37. Paņēmiens saskaņā ar 35. punktu, kas atšķiras ar to, ka zemāko spirtu izvēlas no grupas, kas sastāv no metanola, etanola un izopropanola.

38. Paņēmiens saskaņā ar 35. punktu, kas atšķiras ar to, ka nātrija bāzi izvēlas no grupas, kas sastāv no nātrija hidroksīda, nātrija metilāta un nātrija etilāta.
39. 4-Amino-1-oksibutilidēn-1,1-bisfosfonskābes mononātrija sāls savienojums ar ūdens saturu no 6,4% līdz 9,0%.
40. Savienojums saskaņā ar 39. punktu, kurš raksturojas ar maksimumiem uz pulvera rentgenogrammas pie  $2\theta$  sekojošām vērtībām:  $12,2\pm 0,2$ ;  $13,3\pm 0,2$ ;  $14,8\pm 0,2$ ;  $15,8\pm 0,2$ ;  $16,3\pm 0,2$  un  $17,2\pm 0,2$ .
41. Savienojuma saskaņā ar 2. vai 39. punktu iegūšanas paņēmiens, kurā ietilpst stadijas:
- 4-amino-1-oksibutilidēn-1,1-bisfosfonskābes apstrāde zemākajā spirtā ar nātrija bāzes vienu ekvivalentu un 0-4 ūdens ekvivalentiem; un
  - ši savienojuma saskaņā ar 2. vai 39. punktu izdalīšana.
42. Paņēmiens saskaņā ar 41. punktu, kas atšķiras ar to, ka 4-amino-1-oksibutilidēn-1,1-bisfosfonskābe ir monohidrāta formā.
43. Paņēmiens saskaņā ar 41. punktu, kas atšķiras ar to, ka zemāko spirtu izvēlas no grupas, kas sastāv no metanola, etanola un izopropanola.
44. Paņēmiens saskaņā ar 41. punktu, kas atšķiras ar to, ka nātrija bāzi izvēlas no grupas, kas sastāv no nātrija hidroksīda, nātrija metilāta un nātrija etilāta.
45. 4-Amino-1-oksibutilidēn-1,1-bisfosfonskābes mononātrija sāls savienojums ar ūdens saturu no 3,2% līdz 5,8%.
46. Savienojums saskaņā ar 45. punktu, kurš raksturojas ar maksimumiem uz pulvera rentgenogrammas pie  $2\theta$  sekojošām vērtībām:  $13,1\pm 0,2$ ;  $15,2\pm 0,2$ ;  $16,3\pm 0,2$ ;  $22,3\pm 0,2$ ;  $22,5\pm 0,2$ ;  $23,4\pm 0,2$  un  $23,7\pm 0,2$ .
47. Savienojuma saskaņā ar 2. vai 45. punktu iegūšanas paņēmiens, kurā ietilpst stadijas:

- a) bezūdens 4-amino-1-oksibutilidēn-1,1-bisfosfonskābes apstrāde zemākajā spirtā ar nātrija bāzes vienu ekvivalentu un 0-4 ūdens ekvivalentiem; un
  - b) šī savienojuma saskaņā ar 2. vai 45. punktu izdalīšana.
48. Paņēmiens saskaņā ar 47. punktu, kas atšķiras ar to, ka 4-amino-1-oksibutilidēn-1,1-bisfosfonskābe ir bezūdens formā.
49. Paņēmiens saskaņā ar 48. punktu, kas atšķiras ar to, ka zemāko spirtu izvēlas no grupas, kas sastāv no metanola, etanola un izopropanola.
50. Paņēmiens saskaņā ar 48. punktu, kas atšķiras ar to, ka nātrija bāzi izvēlas no grupas, kas sastāv no nātrija hidroksīda, nātrija metilāta un nātrija etilāta.
51. 4-Amino-1-oksibutilidēn-1,1-bisfosfonskābes mononātrija sāls savienojums ar ūdens saturu no 1,3% līdz 3,1%.
52. Savienojums saskaņā ar 51. punktu, kurš raksturojas ar maksimumiem uz pulvera rentgenogrammas pie  $2\theta$  sekojošām vērtībām:  $13,0 \pm 0,2$ ;  $13,4 \pm 0,2$ ;  $14,2 \pm 0,2$ ;  $19,1 \pm 0,2$ ;  $19,4 \pm 0,2$ .
53. Savienojuma saskaņā ar 2. vai 51. punktu iegūšanas paņēmiens, kurā ietilpst stadijas:
- a) 4-amino-1-oksibutilidēn-1,1-bisfosfonskābes apstrāde zemākajā spirtā ar nātrija bāzes vienu ekvivalentu un 3-20 ūdens ekvivalentiem; un
  - b) šī savienojuma saskaņā ar 2. vai 51. punktu izdalīšana.
54. Paņēmiens saskaņā ar 53. punktu, kas atšķiras ar to, ka 4-amino-1-oksibutilidēn-1,1-bisfosfonskābe ir monohidrāta formā.
55. Paņēmiens saskaņā ar 53. punktu, kas atšķiras ar to, ka zemāko spirtu izvēlas no grupas, kas sastāv no metanola, etanola un izopropanola.
56. Paņēmiens saskaņā ar 53. punktu, kas atšķiras ar to, ka nātrija bāzi izvēlas no grupas, kas sastāv no nātrija hidroksīda, nātrija metilāta un nātrija etilāta.

57. Paņēmiens saskaņā ar 53. punktu, kas atšķiras ar to, ka 4-amino-1-oksibutilidēn-1,1-bisfosfonskābe ir bezūdens formā.
58. Mononātrijs alendronāta dihidrāts.
59. 4-Amino-1-oksibutilidēn-1,1-bisfosfonskābes mononātrijs sāls savienojums ar ūdens saturu 11,7%.
60. Savienojums saskaņā ar 59. punktu, kurš raksturojas ar maksimumiem uz pulvera rentgenogrammas pie 2 $\Theta$  sekojošām vērtībām: 9,3 $\pm$ 0,2; 12,4 $\pm$ 0,2; 13,5 $\pm$ 0,2; 26,3 $\pm$ 0,2 un 30,2 $\pm$ 0,2.
61. Savienojuma saskaņā ar 58. vai 59. punktu iegūšanas paņēmiens, kurā ietilpst stadijas:
- 4-amino-1-oksibutilidēn-1,1-bisfosfonskābes mononātrijs sāls trihidrāta apstrāde ar attīdējoša (žāvējoša) aģenta efektīvu daudzumu; un
  - 4-amino-1-oksibutilidēn-1,1-bisfosfonskābes mononātrijs sāls dihidrāta izdalīšana.
62. Farmaceutiska kompozīcija, kurā ietilpst savienojuma saskaņā ar vienu no 1., 3., 25., 33., 39., 45. un 51. punktiem farmaceutiski efektīvs daudzums.
63. Farmaceutiska kompozīcija saskaņā ar 62. punktu, kuru lieto osteoporozes ārstēšanai un/vai profilaksei subjektiem.
64. Savienojuma saskaņā ar 1. punktu iegūšanas paņēmiens, kurā ietilpst stadijas:
- 4-amino-1-oksibutilidēn-1,1-bisfosfonskābes viena ekvivalenta reakcija ar nātrijs bāzes vienu ekvivalentu organiskajā šķīdinātājā, kas satur ūdeni; šo šķīdinātāju izvēlas no grupas, kas sastāv no acetona, dimetilsulfoksīda, dimetilformamīda, acetonitrila, spirtiem, polispiertiem, polispirtu esteriem, piridīna, sulfolāna, N-metilpirolidinona un dioksāna; un
  - šī savienojuma saskaņā ar 1. punktu izdalīšana.
65. Kristāliskā mononātrijs alendronāta monohidrāta saskaņā ar 3. punktu iegūšanas paņēmiens, kurā ietilpst stadijas:
- 4-amino-1-oksibutilidēn-1,1-bisfosfonskābes viena ekvivalenta suspensēšana ar nātrijs bāzes vienu ekvivalentu šķīdinātāju maisījumā; šī organisku šķīdinātāju izvēlas no grupas,



kas sastāv no acetona, DMSO, DMF, acetonitrila, spirtiem, polispirtiem, polispirtu esteriem, piridīna, sulfolāna, N-metilpirolidinona un dioksāna un ūdens; un

b) Kristāliskā mononātrija alendronāta monohidrāta izdalīšana no šķīdinātāju maisījuma.

66. Savienojuma saskaņā ar 25. punktu iegūšanas paņēmieni, kurā ietilpst stadijas:

a) 4-amino-1-oksibutilidēn-1,1-bisfosfonskābes viena ekvivalenta reakcija ar nātrija bāzes vienu ekvivalentu organiskajā šķīdinātājā, kas satur ūdeni; šo šķīdinātāju izvēlas no grupas, kas sastāv no acetona, dimetilsulfoksīda, dimetilformamīda, acetonitrila, spirtiem, polispirtiem, polispirtu esteriem, piridīna, sulfolāna, N-metilpirolidinona un dioksāna; un

b) šī savienojuma saskaņā ar 25. punktu izdalīšana.

67. Savienojuma saskaņā ar 33. punktu iegūšanas paņēmieni, kurā ietilpst stadijas:

a) 4-amino-1-oksibutilidēn-1,1-bisfosfonskābes viena ekvivalenta reakcija ar nātrija bāzes vienu ekvivalentu organiskajā šķīdinātājā, kas satur ūdeni; šo šķīdinātāju izvēlas no grupas, kas sastāv no acetona, dimetilsulfoksīda, dimetilformamīda, acetonitrila, spirtiem, polispirtiem, polispirtu esteriem, piridīna, sulfolāna, N-metilpirolidinona un dioksāna; un

b) šī savienojuma saskaņā ar 33. punktu izdalīšana.

68. Savienojuma saskaņā ar 39. punktu iegūšanas paņēmieni, kurā ietilpst stadijas:

a) 4-amino-1-oksibutilidēn-1,1-bisfosfonskābes viena ekvivalenta reakcija ar nātrija bāzes vienu ekvivalentu organiskajā šķīdinātājā, kas satur ūdeni; šo šķīdinātāju izvēlas no grupas, kas sastāv no acetona, dimetilsulfoksīda, dimetilformamīda, acetonitrila, spirtiem, polispirtiem, polispirtu esteriem, piridīna, sulfolāna, N-metilpirolidinona un dioksāna; un

b) šī savienojuma saskaņā ar 39. punktu izdalīšana.

69. Savienojuma saskaņā ar 45. punktu iegūšanas paņēmieni, kurā ietilpst stadijas:

a) 4-amino-1-oksibutilidēn-1,1-bisfosfonskābes viena ekvivalenta reakcija ar nātrija bāzes vienu ekvivalentu organiskajā šķīdinātājā, kas satur ūdeni; šo šķīdinātāju izvēlas no grupas, kas sastāv no acetona, dimetilsulfoksīda, dimetilformamīda, acetonitrila, spirtiem, polispirtiem, polispirtu esteriem, piridīna, sulfolāna, N-metilpirolidinona un dioksāna; un

b) šī savienojuma saskaņā ar 45. punktu izdalīšana.

70. Savienojuma saskaņā ar 51. punktu iegūšanas paņēmieni, kurā ietilpst stadijas:

- a) 4-amino-1-oksibutilidēn-1,1-bisfosfonskābes viena ekvivalenta reakcija ar nātrija bāzes vienu ekvivalentu organiskajā šķīdinātājā, kas satur ūdeni; šo šķīdinātāju izvēlas no grupas, kas sastāv no acetona, dimetilsulfoksīda, dimetilformamīda, acetonitrila, spirtiem, polispirtiem, polispirtu esteriem, piridīna, sulfolāna, N-metilpirolidinona un dioksāna; un
- b) šī savienojuma saskaņā ar 51. punktu izdalīšana.

71. Savienojuma saskaņā ar 3. punktu iegūšanas paņēmieni, kurā ietilpst stadijas:

- a) 4-amino-1-oksibutilidēn-1,1-bisfosfonskābes viena ekvivalenta reakcija ar nātrija bāzes vienu ekvivalentu organiskajā šķīdinātājā, kas satur ūdeni; šo šķīdinātāju izvēlas no grupas, kas sastāv no acetona, dimetilsulfoksīda, dimetilformamīda, acetonitrila, spirtiem, polispirtiem, polispirtu esteriem, piridīna, sulfolāna, N-metilpirolidinona un dioksāna; un
- b) šī savienojuma saskaņā ar 3. punktu izdalīšana.

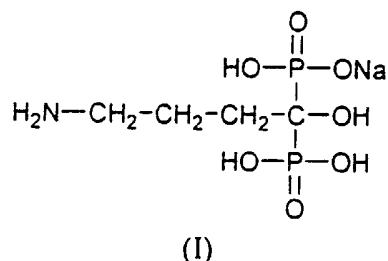
**NOVEL HYDRATE FORMS OF ALENDRONATE  
SODIUM, PROCESSES FOR MANUFACTURE THEREOF, AND  
PHARMACEUTICAL COMPOSITIONS THEREOF**

**FIELD OF THE INVENTION**

This invention relates to new hydrate and crystalline forms of alendronate sodium, processes for the manufacture thereof, and pharmaceutical compositions thereof.

**BACKGROUND OF THE INVENTION**

Alendronate sodium, the sodium salt of alendronic acid, also known as 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium, has the formula I:



It is an agent for combating bone resorption in bone diseases including osteoporosis and Paget's disease.

Various methods for preparing alendronic acid are known in the art and have been disclosed in M.I. Kabachnik et al., Synthesis and Acid - Base and Complexing Properties of Amino-Substituted  $\alpha$ -Hydroxyalkylidene-diphosphonic Acids, Izv. Akad. Nauk USSR, Ser. Khim, 2,433 (1978) and in U.S. Patent Nos. 4,407,761, 4,621,077, 4,705,651, 5,039,819 and 5,159,108.

U.S. Patent No. 4,922,007 describes the preparation of a trihydrate of alendronate sodium by reaction of 4-aminobutyric acid with phosphorous acid and phosphorous trichloride in the presence of methanesulfonic acid followed by the addition of sodium hydroxide.

The present invention provides new hydrate forms of alendronate sodium, having water content of 1.3 to 11.7 percent, and processes for their manufacture. Moreover, the present invention provides new crystalline forms of alendronate sodium,

designated forms B, D, E, F, G and H, and processes for the manufacture thereof.

## OBJECTS AND SUMMARY OF THE INVENTION

5 The present invention provides novel hydrate forms of alendronate sodium having water content of between 1.3 and 11.7 percent water. Typically, but without limitation, the present invention relates to the following novel hydrate forms of alendronate monosodium: 1/4 hydrate, 1/3 hydrate, hemihydrate, 2/3 hydrate, 3/4 hydrate, monohydrate, 5/4 hydrate, 4/3 hydrate, 3/2 hydrate, 5/3 hydrate, 7/4 hydrate and dihydrate.

10 The present invention provides a new crystalline Form B of alendronate sodium, having a powder x-ray diffractogram substantially as depicted in Fig. 1a, with characteristic peaks at  $12.2 \pm 0.2$ ,  $13.3 \pm 0.2$ ,  $14.8 \pm 0.2$ ,  $15.8 \pm 0.2$ ,  $16.3 \pm 0.2$ ,  $16.6 \pm 0.2$ ,  $17.2 \pm 0.2$ ,  $19.4 \pm 0.2$ ,  $21.3 \pm 0.2$ ,  $22.6 \pm 0.2$ ,  $23.2 \pm 0.2$ ,  $24.0 \pm 0.2$ ,  $25.2 \pm 0.2$ ,  $25.8 \pm 0.2$ ,  $27.4 \pm 0.2$ ,  $29.4 \pm 0.2$ , and  $36.0 \pm 0.2$  degrees 2 theta. Alendronate sodium Form B has significant IR bands as depicted in Fig. 1c at  $654 \text{ cm}^{-1}$ ,  $955 \text{ cm}^{-1}$ ,  $1074 \text{ cm}^{-1}$ ,  $1261 \text{ cm}^{-1}$ ,  $1309 \text{ cm}^{-1}$ , and  $1614 \text{ cm}^{-1}$ . The TGA curve, Fig. 1b, shows a clear two-step loss on drying of 7.2%, which implies that the crystal form B contains a stoichiometric quantity of water close to that of the monohydrate (expected loss on drying value: 6.2%).

20 Another embodiment of the invention is a new crystalline Form D of alendronate sodium, having a powder X-ray diffractogram substantially as depicted in Fig. 4a, with characteristic peaks at  $13.1 \pm 0.2$ ,  $15.2 \pm 0.2$ ,  $16.3 \pm 0.2$ ,  $18.4 \pm 0.2$ ,  $20.8 \pm 0.2$ ,  $22.3 \pm 0.2$ ,  $22.5 \pm 0.2$ ,  $23.4 \pm 0.2$ ,  $23.7 \pm 0.2$ ,  $31.4 \pm 0.2$ , and  $35.7 \pm 0.2$  degrees 2 theta. Form D as depicted in Fig. 4c has significant IR bands at  $662 \text{ cm}^{-1}$ ,  $919 \text{ cm}^{-1}$ ,  $934 \text{ cm}^{-1}$ ,  $954 \text{ cm}^{-1}$ ,  $1054 \text{ cm}^{-1}$ ,  $1072 \text{ cm}^{-1}$ ,  $1297 \text{ cm}^{-1}$  and  $1318 \text{ cm}^{-1}$ . The TGA curve, as depicted in Fig. 4b, shows a gradual loss on drying of 4.1 % up to  $180^\circ\text{C}$ .

25 An additional embodiment is a new crystalline Form E of alendronate sodium, having a powder X-ray diffractogram substantially as depicted in FIG. 5a, with characteristic peaks at  $7.0 \pm 0.2$ ,  $9.3 \pm 0.2$ ,  $11.8 \pm 0.2$ ,  $13.3 \pm 0.2$ ,  $14.0 \pm 0.2$ ,  $15.3 \pm 0.2$ ,  $16.2 \pm 0.2$ ,  $17.4 \pm 0.2$ , and  $19.4 \pm 0.2$  degrees 2 theta. Form E has significant IR bands as depicted in Fig. 5c at  $660 \text{ cm}^{-1}$ ,  $897 \text{ cm}^{-1}$ ,  $924 \text{ cm}^{-1}$ ,  $953 \text{ cm}^{-1}$ ,  $970 \text{ cm}^{-1}$ ,  $1017 \text{ cm}^{-1}$ ,  $1040$

$\text{cm}^{-1}$ ,  $1093 \text{ cm}^{-1}$ ,  $149 \text{ cm}^{-1}$ ,  $1177 \text{ cm}^{-1}$ ,  $1252 \text{ cm}^{-1}$ ,  $1293 \text{ cm}^{-1}$ ,  $1337 \text{ cm}^{-1}$ ,  $1535 \text{ cm}^{-1}$ ,  $1606 \text{ cm}^{-1}$ , and  $1639 \text{ cm}^{-1}$ . The TGA curve, as depicted in Fig. 5b shows a gradual loss on drying of 4.1 % up to  $150^{\circ}\text{C}$ .

A still further embodiment of the invention is a new crystalline Form F of alendronate sodium, having a powder X-ray diffractogram substantially as depicted in FIG. 6a, with characteristic peaks at  $9.3 \pm 0.2$ ,  $11.7 \pm 0.2$ ,  $13.0 \pm 0.2$ ,  $13.4 \pm 0.2$ ,  $14.2 \pm 0.2$ ,  $15.3 \pm 0.2$ ,  $16.2 \pm 0.2$ ,  $17.4 \pm 0.2$ ,  $19.1 \pm 0.2$ ,  $19.4 \pm 0.2$  and  $25.5 \pm 0.2$  degrees 2 theta. Form F has significant IR bands as depicted in Fig. 6c at  $660 \text{ cm}^{-1}$ ,  $893 \text{ cm}^{-1}$ ,  $930 \text{ cm}^{-1}$ ,  $9953 \text{ cm}^{-1}$ ,  $970 \text{ cm}^{-1}$ ,  $982 \text{ cm}^{-1}$ ,  $1010 \text{ cm}^{-1}$ ,  $1033 \text{ cm}^{-1}$ ,  $1052 \text{ cm}^{-1}$ ,  $1060 \text{ cm}^{-1}$ ,  $1069 \text{ cm}^{-1}$ ,  $1109 \text{ cm}^{-1}$  and  $1169 \text{ cm}^{-1}$ ,  $1251 \text{ cm}^{-1}$ ,  $1338 \text{ cm}^{-1}$ ,  $1498 \text{ cm}^{-1}$ ,  $1544 \text{ cm}^{-1}$ ,  $1603 \text{ cm}^{-1}$ ,  $1637 \text{ cm}^{-1}$ ,  $1664 \text{ cm}^{-1}$ . The TGA Fig. 5b curve shows a gradual loss on drying of 4.1 % up to  $150^{\circ}\text{C}$ .

A further embodiment is a new crystalline Form G of alendronate sodium, having a powder X-ray diffractogram substantially as depicted in FIG. 7a, with characteristic peaks at  $9.5 \pm 0.2$ ,  $10.1 \pm 0.2$ ,  $12.7 \pm 0.2$ ,  $16.2 \pm 0.2$ ,  $17.3 \pm 0.2$ ,  $17.6 \pm 0.2$ ,  $19.1 \pm 0.2$ ,  $20.4 \pm 0.2$ ,  $20.9 \pm 0.2$ ,  $22.1 \pm 0.2$ ,  $24.8 \pm 0.2$ ,  $25.5 \pm 0.2$ ,  $28.0 \pm 0.2$ ,  $29.0 \pm 0.2$ ,  $29.6 \pm 0.2$ ,  $30.4 \pm 0.2$ ,  $32.4 \pm 0.2$ , and  $32.8 \pm 0.2$  degrees 2 theta. Form G has significant IR bands as depicted in Fig. 7c at  $665 \text{ cm}^{-1}$ ,  $751 \text{ cm}^{-1}$ ,  $856 \text{ cm}^{-1}$ ,  $895 \text{ cm}^{-1}$ ,  $913 \text{ cm}^{-1}$ ,  $939 \text{ cm}^{-1}$ ,  $1011 \text{ cm}^{-1}$ ,  $1021 \text{ cm}^{-1}$ ,  $1050 \text{ cm}^{-1}$ ,  $1091 \text{ cm}^{-1}$ ,  $1155 \text{ cm}^{-1}$ ,  $1273 \text{ cm}^{-1}$ ,  $1305 \text{ cm}^{-1}$ ,  $1337 \text{ cm}^{-1}$ ,  $1510 \text{ cm}^{-1}$ , and  $1639 \text{ cm}^{-1}$ . The TGA curve, Fig. 7b, shows a loss on drying of 6.5% which indicates that the crystal form G contains a stoichiometric quantity of water corresponding to that of the monohydrate (expected loss on drying value: 6.2%). This TGA step is sharp and occurs at  $195^{\circ}\text{C}$ . The relatively high temperature of dehydration implies that the water is bound tightly to the alendronate molecule. The dehydration step is immediately followed by another step due to decomposition. Due to the decomposition process that occurs adjacent to the dehydration, the conventional loss of drying method is not feasible, and for loss on drying determination the TGA is used.

Yet another embodiment is a new crystalline Form H of alendronate sodium, having a powder X-ray diffractogram substantially as depicted in FIG. 8a, with characteristic peaks at  $9.2 \pm 0.2$ ,  $13.0 \pm 0.2$ ,  $14.2 \pm 0.2$ ,  $15.0 \pm 0.2$ ,  $17.1 \pm 0.2$ ,  $20.7 \pm 0.2$ ,  $22.0 \pm 0.2$ ,  $22.4 \pm 0.2$ , degrees two theta. Form H has significant IR bands, as depicted in Fig. 8c, of  $664 \text{ cm}^{-1}$ ,  $688 \text{ cm}^{-1}$ ,  $722 \text{ cm}^{-1}$ ,  $751 \text{ cm}^{-1}$ ,  $863 \text{ cm}^{-1}$ ,  $893 \text{ cm}^{-1}$ ,  $918 \text{ cm}^{-1}$ ,  $936 \text{ cm}^{-1}$ ,

984 cm<sup>-1</sup>, 1010 cm<sup>-1</sup>, 1036 cm<sup>-1</sup>, 1052 cm<sup>-1</sup>, 1092 cm<sup>-1</sup>, 1157 cm<sup>-1</sup>, 1273 cm<sup>-1</sup>, 1303 cm<sup>-1</sup>, and 1338 cm<sup>-1</sup>, 1499 cm<sup>-1</sup>, 1598 cm<sup>-1</sup>, 1636 cm<sup>-1</sup>, and 1664 cm<sup>-1</sup>. The TGA curve Fig. 8b shows a sharp loss on drying of 3.7% at 170°C.

5 All of sodium alendronate crystalline forms B, D, E, F, G and H contain water in the amount of 2.2 to 9.0% by weight.

The invention further provides a new hydrate form of alendronate sodium having a water content of 1.3 % to 3.1 %.

A further embodiment is a new hydrate form of alendronate sodium having a water content of 2.5% to 3.5%.

10 A further embodiment is a new hydrate form of alendronate sodium having a water content of 2.8% to 3.9%.

An additional embodiment is a new hydrate form of alendronate sodium having a water content of 3.2% to 5.8%.

15 Another embodiment is a new hydrate form of alendronate sodium having a water content of 5.1 % to 7. 0%.

A still further embodiment is a new hydrate form of alendronate sodium having a water content of 6.4% to 9.0%.

The invention also provides a new crystalline Form B of alendronate sodium, having a water content of 6.4% to 9.0%.

20 The invention further provides a new crystalline Form D of alendronate sodium, having a water content of 3.2% to 5.8%.

The invention further provides a new crystalline Form F of alendronate sodium, having a water content of 1.3 % to 3.1 %.

25 The invention further provides a new crystalline Form G of alendronate sodium, having a water content of 5.1 % to 7.0%.

The invention further provides a new crystalline Form E of alendronate sodium, having a water content of 2.8% to 3.9%.

The invention further provides a new crystalline Form H of alendronate sodium, having a water content of 2.5% to 3.5%.

30 The invention provides a new monohydrate and a new dihydrate of alendronate sodium, having an X-ray diffractogram substantially as depicted in FIG. 2a

and 3a, accordingly, with characteristic peaks at  $9.3 \pm 0.2$ ,  $12.4 \pm 0.2$ ,  $13.5 \pm 0.2$ ,  $17.1 \pm 0.2$ ,  $18.5 \pm 0.2$ ,  $19.7 \pm 0.2$ ,  $20.3 \pm 0.2$ ,  $21.0 \pm 0.2$ ,  $21.8 \pm 0.2$ ,  $23.4 \pm 0.2$ ,  $24.3 \pm 0.2$ ,  $24.9 \pm 0.2$ ,  $26.3 \pm 0.2$ ,  $30.0 \pm 0.2$ , and  $34.4 \pm 0.2$  degrees 2 theta. Form C as depicted in Figs. 2c and 3c has significant IR bands at  $660 \text{ cm}^{-1}$ ,  $745 \text{ cm}^{-1}$ ,  $865 \text{ cm}^{-1}$ ,  $913 \text{ cm}^{-1}$ ,  $952 \text{ cm}^{-1}$ ,  $966 \text{ cm}^{-1}$ ,  $1017 \text{ cm}^{-1}$ ,  $1046 \text{ cm}^{-1}$ ,  $1128 \text{ cm}^{-1}$ ,  $1174 \text{ cm}^{-1}$ ,  $1235 \text{ cm}^{-1}$ ,  $1340 \text{ cm}^{-1}$ ,  $1402 \text{ cm}^{-1}$ ,  $1544 \text{ cm}^{-1}$ ,  $1606 \text{ cm}^{-1}$ , and  $1644 \text{ cm}^{-1}$ . The TGA curve of the monohydrate Form C (Fig. 2b) shows a loss on drying of 5.6% which implies that the crystal Form C contains a stoichiometric quantity of water close to that of the monohydrate (expected loss on drying value: 6.2%). The TGA curve of the dihydrate Form C (Fig. 3b) shows a sharp loss on drying of 12.0% which implies that the crystal Form C contains a stoichiometric quantity of water corresponding to dihydrate (expected loss on drying value: 11.7%).

The present invention also relates to the method of preparing the compound 4-amino-1-hydroxybutylidene-1, 1-bisphosphonic acid monosodium salt having water content of 1.3% to 11.7% by reacting alendronic acid with one equivalent of sodium base in an aqueous organic solvent selected from the group consisting of: acetone, DMSO, DMF, acetonitrile, alcohols, polyalcohols and/or their ethers, pyridine, sulfolane, N-methyl pyrrolidinone and dioxane.

The invention further provides a method for making Form D of alendronate sodium, comprising treating alendronic acid anhydrous in a lower alkanol with 1 equivalent of sodium base and 0 to 4 equivalents of water, followed by isolating the crystalline alendronate sodium Form D.

The invention further provides a method for making Form E of alendronate sodium, comprising treating alendronic acid, which is in anhydrous or monohydrate form, in a lower alkanol with 1 equivalent of sodium base and 9 to 15 equivalents of water, followed by isolating the crystalline alendronate sodium Form E.

The invention further provides a method for making Form F of alendronate sodium, comprising treating alendronic acid, in a lower alkanol with 1 equivalent of sodium base and 5 to 8 equivalents of water for anhydrous form and 3 to 20 equivalents of water for monohydrate form, followed by isolating the crystalline alendronate sodium Form F.

The invention further provides a method for making alendronate sodium

monohydrate, comprising treating alendronic acid, in a lower alkanol with 1 equivalent of sodium base and water under the conditions described hereinafter, followed by isolating the alendronate sodium monohydrate

The invention further provides a method for making Form G of alendronate sodium, comprising treating alendronic acid, in a lower alkanol with 1 equivalent of sodium base and water under the conditions described hereinafter, followed by isolating the crystalline alendronate sodium Form G.

Typical but not limiting conditions for preparing alendronate sodium Form G are as described in the following table:

Starting Alendronic Acid Hydrate Form	Solvent	Preferred Range of Water Equivalent	Range of Water Equivalent
Monohydrate	Methanol	20-200	40-175
Monohydrate	Ethanol	15-100	20-80
Monohydrate	Isopropanol	5-40	10-20
Anhydrous	Methanol	50-125	80-100
Anhydrous	Ethanol	15-40	25-35

The invention further provides a method for making Form G of alendronate sodium comprising treating any one or more of the crystal forms of alendronate sodium selected from the group which consists of Form B, Form C, Form D, Form E, Form F and Form H, in a lower alkanol, preferably ethanol, with 20-40 equivalents of water under the conditions described hereinafter followed by isolating the crystalline alendronate sodium Form G.

The invention further provides a method for making Form G of alendronate sodium comprising treating alendronate monosodium trihydrate in a lower alkanol, preferably ethanol, with 25-35 equivalents of water under the condition described hereinafter, followed by isolating the crystalline alendronate sodium Form G.

The invention further provides a method for making Form G of alendronate sodium comprising treating any one or more forms of alendronate sodium salts preferably selected from the group consisting of monosodium, disodium, trisodium and tetrasodium



salts, in a lower alkanol preferably ethanol with 20-40 equivalents of water under the conditions described hereinafter, followed by isolating the crystalline alendronate sodium Form G. In the event that the starting sodium salt is higher than monosodium (e.g. disodium, trisodium or tetrasodium) it is necessary to add an acid, preferably alendronic acid, in order to maintain the pH at about 4.4.

The invention further provides a method for making Form H of alendronate sodium, comprising treating alendronic acid, which is the anhydrous or monohydrate form, in a lower alkanol with one equivalent of sodium base and 25 to 35 equivalents of water, under the conditions described hereinafter, followed by isolating the crystalline alendronate sodium Form H.

The invention further provides a method for making Form B of alendronate sodium, comprising treating alendronic acid monohydrate in a lower alkanol with one equivalent of sodium base and 0 to 4 equivalents of water, followed by obtaining the crystalline alendronate sodium Form B.

The invention further provides a method for making alendronate sodium dihydrate comprising treating crystalline alendronate sodium trihydrate with an effective amount of drying agent followed by isolating the crystalline alendronate sodium dihydrate.

The invention further provides a method for making alendronate sodium monohydrate comprising treating crystalline alendronate sodium trihydrate with a sufficient amount of drying agent followed by isolating the crystalline alendronate sodium monohydrate.

The invention further provides a method for making alendronate sodium monohydrate comprising treating crystalline alendronate sodium dihydrate with a sufficient amount of drying agent followed by isolating the crystalline alendronate sodium monohydrate.

The invention further relates to a pharmaceutical composition which comprises alendronate sodium, having water content of 1.3 to 11.7 percent in a therapeutically effective amount, and a pharmaceutically acceptable carrier.

The invention further relates to a pharmaceutical composition which comprises alendronate sodium in Form B, D, E, F, G and/or H in a therapeutically

effective amount, and a pharmaceutically acceptable carrier.

#### **BRIEF DESCRIPTION OF THE DRAWINGS**

5           FIGS. 1a, 1b, and 1c show, respectively, the powder X-ray diffraction spectrum, the thermogravimetric (TGA) curve and the infrared spectrum of alendronate sodium Form B.

          FIGS. 2a, 2b, and 2c show, respectively, the powder X-ray diffraction spectrum, the thermogravimetric (TGA) curve and the infrared spectrum of alendronate sodium monohydrate Form C.

10           FIGS. 3a, 3b, and 3c show, respectively, the powder X-ray diffraction spectrum, the thermogravimetric (TGA) curve and the infrared spectrum of alendronate sodium dihydrate Form C.

          FIGS. 4a, 4b, and 4c show, respectively, the powder X-ray diffraction spectrum, the thermogravimetric (TGA) curve and the infrared spectrum of alendronate sodium Form D.

15           FIGS. 5a, 5b, and 5c show, respectively, the powder X-ray diffraction spectrum, the (thermogravimetric (TGA) curve) and the infrared spectrum of alendronate sodium Form E.

          FIGS. 6a, 6b, and 6c show, respectively, the powder X-ray diffraction spectrum, the thermogravimetric (TGA) curve and the infrared spectrum of alendronate sodium Form F.

          FIGS. 7a, 7b, and 7c show, respectively, the powder X-ray diffraction spectrum, the thermogravimetric (TGA) curve and the infrared spectrum of alendronate sodium Form G.

25           Figures 8a, 8b and 8c show respectively the powder X-ray diffraction spectrum, the thermogravimetric (TGA) curve and the infrared spectrum of alendronate sodium of Form H.

### DETAILED DESCRIPTION OF THE INVENTION

The invention discloses new hydrate forms of alendronate sodium having water contents of 1.3 percent to 11.7 percent.

5 The present invention also discloses new crystalline forms of alendronate sodium which have been designated Forms B, D, E, F, G and H.

The term "water content" refers to the content of water based upon the Loss on Drying method as described in Pharmacopeial Forum, Vol. 24, No. 1, page 5438 (Jan - Feb 1998). The calculation of water content is based upon the percent of weight that is lost by drying. For Forms G and H the term "water content" refers to the content of water  
10 based upon a TGA measurement and a step analysis in the temperature range of about 25°C - 215°C for Form G, and 25°C - 200°C for Form H.

The term "lower alkanol" refers to alkanols having 1 to 4 carbon atoms. Preferred lower alkanols include ethanol, methanol and isopropanol.

15 The term "equivalents of water" means molar equivalents of water.

The term "equivalents of sodium base" means molar equivalents of sodium base.

Those skilled in the art will appreciate that the term "monohydrate" when used in reference to alendronic acid describes a crystalline material having a water content of 6.7%. Those skilled in the art will also understand that the term "anhydrous" when used  
20 in reference to alendronic acid describes alendronic acid that is substantially free of water.

One of skill in the art will appreciate that the term "monohydrate" when used in reference to the monosodium salt of alendronic acid describes a crystalline material having a water content of approximately 6.2%.

25 One skilled in the art will also appreciate that the term "dihydrate" when used in reference to the monosodium salt of alendronic acid describes a crystalline material having a water content of approximately 11.7%.

One skilled in the art will also appreciate that the term "1/4 hydrate" when used in reference to the monosodium salt of alendronic acid describes a crystalline material having a water content of approximately 1.6%.

30 One skilled in the art will also appreciate that the term "1/3 hydrate" when used in reference to the monosodium salt of alendronic acid describes a crystalline

material having a water content of approximately 2.1 %.

One skilled in the art will also appreciate that the term "hemihydrate" when used in reference to the monosodium salt of alendronic acid describes a crystalline material having a water content of approximately 3.2%.

5 One skilled in the art will also appreciate that the term "2/3 hydrate" when used in reference to the monosodium salt of alendronic acid describes a crystalline material having a water content of approximately 4.2%.

10 One skilled in the art will also appreciate that the term "3/4 hydrate" when used in reference to the monosodium salt of alendronic acid describes a crystalline material having a water content of approximately 4.7%.

One skilled in the art will also appreciate that the term "5/4 hydrate" when used in reference to the monosodium salt of alendronic acid describes a crystalline material having a water content of approximately 7.6%.

15 One skilled in the art will also appreciate that the term "4/3 hydrate" when used in reference to the monosodium salt of alendronic acid describes a crystalline material having a water content of approximately 8.1 %.

One skilled in the art will also appreciate that the term "3/2 hydrate" when used in reference to the monosodium salt of alendronic acid describes a crystalline material having a water content of approximately 9.1 %.

20 Finally, those skilled in the art will appreciate that the term "trihydrate" when used in reference to the monosodium salt of alendronic acid refers to a crystalline material having a water content of approximately 16.6%.

The term "sodium base" refers to sodium hydroxide and the sodium alkoxide of a lower alkanol.

25 Alendronic acid can be prepared by methods that are well known in the art. MI Kabachnik et al., Izv. Akad. Nauk USSR, Ser. Khim, 2, 433 (1978) discloses a reaction for making alendronic acid;

30 Alendronic acid can also be prepared by the process disclosed in U.S. Patent No. 4,621,077. It will be appreciated that when alendronic acid is recrystallized from water, as in the above process, the monohydrate is formed.

Alendronate sodium trihydrate can be prepared by the process disclosed in

U.S. Patent No. 4,922,007.

The contents of all references cited are incorporated by reference.

Alendronic acid monohydrate can be converted to alendronic acid anhydrous by heating in a vacuum oven at 110-220°C at a vacuum of less than 5 mm Hg for 24 hours.

5 In accordance with the process aspect of the present invention, alendronic acid anhydrous as prepared by any of the known methods is added to a lower alkanol, preferably ethanol, together with a sodium base, preferably sodium hydroxide, and an amount of water that depends upon the desired crystal form of alendronate sodium. The  
10 molar ratio of sodium base to alendronic acid is 1:1. Those skilled in the art will appreciate that a higher ratio of NaOH would yield the undesirable disodium and trisodium salts. The reaction mixture is boiled under reflux while being stirred vigorously for approximately 15 hours, until the pH of the liquid phase remains constant (approx. pH 7). Crystalline alendronate sodium is then isolated, preferably by filtration after cooling to  
15 ambient temperature, washing with absolute ethanol, optionally washing with absolute ethyl ether and drying overnight in a vacuum oven at ambient temperature and at a pressure of 10 mm to 15 mm of mercury. For the purposes of this specification, ambient temperature is from about 20°C to about 25°C.

In accordance with the aspects of this invention wherein alendronic acid  
20 monohydrate is converted to alendronate sodium, alendronic acid monohydrate as prepared by any of the known methods is added to an alkanol, preferably ethanol, together with a sodium base, preferably sodium hydroxide, and a desired amount of water. The amount of water depends upon the crystal form that is desired. The molar ratio of sodium base to alendronic acid is 1:1. The reaction mixture is boiled under reflux while stirring  
25 vigorously for approximately 15 hours, until the pH of the liquid phase remains constant (approx. pH 7). Crystalline alendronate sodium is then isolated, preferably by filtration after cooling to ambient temperature followed by washing with absolute ethanol, washing with absolute ether and drying overnight in a vacuum oven at ambient temperature and at a pressure of 10 mm to 15 mm of mercury.

30 In accordance with the aspects of this invention wherein alendronate sodium trihydrate (Form C) is converted to alendronate sodium dihydrate (Form C),

alendronate sodium trihydrate as prepared by methods known in the art is added to an alkanol which is substantially free of water, preferably absolute ethanol. This mixture is treated with a drying agent, preferably by refluxing the mixture in a reflux condenser wherein the condensate formed passes through 3Å molecular sieves. The weight:weight ratio of molecular sieves to alendronate sodium trihydrate is preferably about 2:1 and most preferably 12:5. Refluxing of the mixture is preferably done for 24 hours with stirring. Alendronate sodium dihydrate is then isolated, preferably by filtration after cooling to ambient temperature, washing with absolute ether and drying overnight in a vacuum oven at ambient temperature and at a pressure of 10 mm to 15 mm of mercury.

In accordance with the aspects of this invention wherein alendronate sodium trihydrate (Form C) is converted to alendronate sodium monohydrate (Form C), alendronate sodium trihydrate as prepared by any of the methods known in the art is added to an alkanol which is substantially free of water, preferably absolute ethanol. This mixture is treated with a drying agent, preferably by refluxing the mixture in a reflux condenser wherein the condensate formed passed through 3Å molecular sieves. If and when a first portion of molecular sieves is exhausted, a second portion of fresh molecular sieves is used. The weight:weight ratio of molecular sieves to alendronate sodium trihydrate is preferably about 2:1 and most preferably 12:5. Refluxing of the mixture is preferably done for 24 hours with stirring. The mixture is allowed to cool to ambient temperature before recharging with an equivalent amount of molecular sieves. Alendronate sodium monohydrate is then isolated, preferably by cooling to ambient temperature, filtration, washing with absolute ether and drying overnight in a vacuum oven at ambient temperature and a pressure of 10 mm and 15 mm of mercury.

In accordance with the present invention, the new crystalline forms of alendronate sodium and the new hydrate forms of alendronate sodium may be prepared as pharmaceutical compositions which are particularly useful for the treatment of bone resorption in bone diseases including osteoporosis and Paget's disease. Such compositions may comprise one of the new crystalline and hydrate forms of alendronate sodium with pharmaceutically acceptable carriers and/or excipients.

For example, these compositions may be prepared as medicaments to be administered orally, parenterally, rectally, transdermally, buccally, or nasally. Suitable

forms for oral administration include tablets, compressed or coated pills, dragees, sachets, hard or gelatin capsules, sub-lingual tablets, syrups and suspensions; for parenteral administration the invention provides ampoules or vials that include an aqueous or non-aqueous solution or emulsion; for rectal administration there are provided suppositories with hydrophilic or hydrophobic vehicles; and for topical application as ointments or aerosol formulations known in the art; transdermal delivery there are provided suitable delivery systems as known in the art; and for nasal delivery there are provided suitable aerosol delivery systems known in the art.

The powder X-ray diffraction patterns were obtained by methods known in the art using a Philips X-Ray powder diffractometer, Goniometer model 1050/70 at a scanning speed of 2° per minute.

The thermogravimetric curves were obtained by methods known in the art using a Mettler TGA TG50. The weight of the samples was about 10 mg. The temperature range was from 25°C to at least 200°C, at the rate of 10°C/min. Samples were purged with nitrogen gas at a flow rate of 40 ml/min. Standard 150 ml aluminum crucibles were used.

The infrared spectra were obtained by methods known in the art using a Perkin Elmer FT-IR Paragon 1000 spectrometer. Samples were analyzed in Nujol mulls. Spectra were obtained at 4 cm<sup>-1</sup> resolution and 16 scans each.

The atomic absorption analysis was obtained by methods known in the art using a Perkin Elmer 5000 Flame Atomic Absorption instrument. Sodium content was determined against standard solutions obtained from Merck and Aldrich.

### EXAMPLES

This invention will be better understood from the experimental details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the claims that follow thereafter.

#### **Example 1**

##### **Preparation of Alendronic Acid Monohydrate**

Alendronic acid was crystallized from water to make alendronic acid

monohydrate. The resulting alendronic acid monohydrate was dried at 50°C at 10 mm Hg pressure for 15 hours to give dry alendronic acid monohydrate containing 6.9% water.

### Example 2

#### Preparation of Anhydrous Alendronic Acid

The alendronic acid monohydrate from Example 1 was further dried at 110-120°C in 1 mm Hg for 4 hours to give anhydrous alendronic acid. The water content was 0.3% by weight.

### Example 3

#### Preparation of Alendronate Sodium from Anhydrous Alendronic Acid

A 250 ml flask was fitted with a mechanical stirrer, a thermometer, and a reflux condenser. The flask was charged with 41.1 ml of a solution of sodium hydroxide in ethanol (0.49N, 20.1 mmol), 8.9 ml of ethanol, water (0 to 40 mol. eq., according to the crystal form desired), and 5g (20.1 mmol) of anhydrous alendronic acid. The reaction mixture was boiled with vigorous stirring for about 15 hours until the pH of the liquid phase remained constant (approx. pH 7). After cooling of the reaction mixture to ambient temperature, the solid material was filtered, washed with absolute ethanol, and dried overnight in a vacuum oven (10-15mmHg, ambient temperature) to give 96-99% sodium alendronate having the following crystal forms: crystal Form D, when 0-4 (preferably 0-2) mol. eq. water were used; crystal Form F, when 5-8 (preferably 6-7) mol. eq. water were used; crystal Form E, when 9-15 (preferably 12) mol. eq. water were used; and crystal Form G, when 15-40 (preferably 25-35) mol. eq. water were used. The monosodium salt was confirmed by atomic absorption and by measuring the pH of a 0.5% aqueous solution of the salt (approx. pH 4.4).

### Example 4

#### Preparation of Alendronate Sodium from Alendronic Acid Monohydrate

A 250 ml flask was fitted with a mechanical stirrer, a thermometer, and a reflux condenser. The flask was charged with 38.2 ml of a solution of sodium hydroxide in ethanol (0.49 N, 18.7 mmol), 4.8 ml of ethanol, water (0 to 100 mol. eq., according to the crystal form desired), and 5 g (18.7 mmol) of alendronic acid monohydrate. The



reaction mixture was boiled with vigorous stirring for about 15 hours until stability of pH of the liquid phase was reached (approx. pH 7). After cooling of the reaction mixture to ambient temperature the precipitate was filtered, washed with absolute ethanol, and dried overnight in a vacuum oven (10-15mm Hg, ambient temperature) to give 96-99% sodium alendronate having the following crystalline forms: crystalline Form B, when 0-4 (preferably 0-2) mol. eq. water were used; crystalline Form F, when 3-5 mol. eq. water were used; crystalline Form E, when 11-13 (preferably 12) mol. eq. water were used; and crystalline Form G, when 15-100 (preferably 20-80) mol. eq. water were used.

The monosodium salt was confirmed by atomic absorption and by measuring the pH of a 0.5% aqueous solution of the salt (approx. pH 4.4).

The water content is determined using the TGA technique, heating the sample to 230°C and calculating the sharp LOD (loss on drying) step, which occurs above 150°C.

#### Example 5

##### Preparation of Sodium Alendronate Dihydrate

A one liter flask was fitted with a magnetic bar stirrer, Soxhlet extraction funnel (operating volume 150 ml) charged with 3 Å molecular sieves (60 g), and reflux condenser connected to a drying tube with 3 Å molecular sieves. The flask was charged with sodium alendronate trihydrate (25 g) and absolute ethanol (450 ml, vol.% of water < 0.1%). The mixture was boiled with stirring for 24 hours. After cooling to ambient temperature the solid material was filtered, washed with absolute ethyl ether, and dried overnight in a vacuum oven (10-15 mm Hg, ambient temperature) to give sodium alendronate dihydrate.

#### Example 6

##### Preparation of Sodium Alendronate Monohydrate

A one liter flask was fitted with a magnetic bar stirrer, Soxhlet extraction funnel (operating volume 150 ml) charged with 3 Å molecular sieves (60 g), and reflux condenser connected to a drying tube with 3 Å molecular sieves. The flask was charged with sodium alendronate trihydrate (25 g) and absolute ethanol (450 ml, vol.% of water <

0.1%). The mixture was boiled with stirring for 24 hours. After cooling to ambient temperature, the used molecular sieves were replaced by a new portion of 3Å molecular sieves (60 g) and the reflux was continued for additional 24 hours. After cooling to ambient temperature the solid material was filtered, washed with absolute ethyl ether, and dried overnight in a vacuum oven (10-15 mm Hg, ambient temperature) to give sodium alendronate monohydrate.

#### Example 7

##### Preparation of Alendronate Sodium Form G from Alendronic Acid Monohydrate

Preparation of aqueous ethanolic sodium hydroxide:

Absolute ethanol (250 ml) and water (59 ml, 35x0.094mol) were mixed. Sodium hydroxide (3.8 g, assay 99%, 0.094 mol) was dissolved in 45 ml of this aqueous ethanol. The remaining aqueous ethanol was used to prepare a suspension of alendronic acid monohydrate.

A one liter flask was fitted with a mechanical stirrer, a thermometer, and a reflux condenser. The flask was charged with alendronic acid monohydrate (25 g, 0.094 mol) and aqueous ethanol. The mixture was heated to boiling with stirring. The aqueous ethanolic sodium hydroxide was added dropwise to the suspension of alendronic acid monohydrate in aqueous ethanol for 3 hours at reflux with vigorously stirring. Then the mixture was stirred at reflux for additional 15 hours. The mixture was cooled to room temperature with stirring. The solid was filtered, washed with absolute ethanol, then with absolute ethyl ether, and dried overnight in a vacuum oven (10-15 mm Hg, ambient temperature) to give 26.2 g of alendronate sodium, having crystalline Form G.

#### Example 8

##### Preparation of Alendronate Sodium Form G from Alendronic Acid Monohydrate

Preparation of aqueous ethanolic sodium hydroxide:

Absolute ethanol (250 ml) and water (59 ml, 35x0.094 mol) were mixed. Sodium hydroxide (3.8 g, assay 99%, 0.094 mol) was dissolved in 45 ml of this aqueous ethanol. The remaining aqueous ethanol was used to prepare a suspension of alendronic

acid monohydrate.

A one liter flask was fitted with a mechanical stirrer, a thermometer, and a reflux condenser. The flask was charged with alendronic acid monohydrate (25 g, 0.094 mol) and aqueous ethanol. The mixture was heated to boiling with stirring. The aqueous  
5 ethanolic sodium hydroxide was added dropwise to the suspension of alendronic acid monohydrate in aqueous ethanol for 3 hours at reflux with vigorously stirring. Then the mixture was stirred at reflux for additional 15 hours. The mixture was cooled to room temperature with stirring. The solid was filtered, washed with absolute ethanol, and dried overnight in a vacuum oven (10-15 mm Hg, ambient temperature) to give 26.2 g of  
10 alendronate sodium, having crystalline Form G.

### Example 9

#### 15 Preparation of Alendronate Sodium Form G from Alendronic Acid Monohydrate

Preparation of aqueous ethanolic sodium hydroxide:

Absolute ethanol (250 ml) and water (59 ml, 35x0.094 mol) were mixed. Sodium hydroxide (3.8 g, assay 99%, 0.094 mol) was dissolved in 45 ml of this aqueous  
20 ethanol. The remaining aqueous ethanol was used to prepare a suspension of alendronic acid monohydrate.

A one liter flask was fitted with a mechanical stirrer, a thermometer, and a reflux condenser. The flask was charged with alendronic acid monohydrate (25 g, 0.094 mol) and aqueous ethanol. The mixture was heated to boiling with stirring. The aqueous  
25 ethanolic sodium hydroxide was added dropwise to the suspension of alendronic acid monohydrate in aqueous ethanol for 3 hours at reflux with vigorously stirring. Then the mixture was stirred at reflux for additional 15 hours. The mixture was cooled to room temperature with stirring. The solid was filtered, washed with absolute ethanol, and dried overnight in a vacuum oven (10-15 mm Hg, 40-50°C) to give 26.2g of alendronate  
30 sodium, having crystalline Form G.

### Example 10

### **Preparation of Alendronate Sodium Form G from Alendronic Acid Monohydrate**

Preparation of aqueous ethanolic sodium hydroxide:

Absolute ethanol (250 ml) and water (59 ml, 35x0.094 mol) were mixed.

5 Sodium hydroxide (3.8 g, assay 99%, 0.094 mol) was dissolved in 45 ml of this aqueous ethanol. The remaining aqueous ethanol was used to prepare a suspension of alendronic acid monohydrate.

A one liter flask was fitted with a mechanical stirrer, a thermometer, and a reflux condenser. The flask was charged with alendronic acid monohydrate (25 g, 0.094  
10 mol) and aqueous ethanol. The mixture was heated to boiling with stirring. The aqueous ethanolic sodium hydroxide was added dropwise to the suspension of alendronic acid monohydrate in aqueous ethanol for 3 hours at reflux with vigorously stirring. Then the mixture was stirred at reflux for additional 15 hours. The mixture was cooled to room temperature with stirring. The solid was filtered, washed with absolute ethanol, then with  
15 absolute ethyl ether, and dried overnight in a vacuum oven (10-15 mm Hg, 40-50°C) to give 26.2g of alendronate sodium, having crystalline Form G.

### **Example 11**

#### **Preparation of alendronate sodium Form (G) from Alendronate Sodium Trihydrate**

20 A suspension of alendronate sodium trihydrate 1.0g (3.08 mmol) in aqueous ethanol (10 ml of ethanol + 1.9 ml of water) was boiled at reflux with stirring for 15 hrs. After cooling to ambient temperature the solid was filtered, washed with absolute ethanol and ether, and dried overnight in a vacuum oven (10-15 mm Hg, ambient temperature) to give 0.9 g of alendronate sodium, containing crystal form G.

25

### **Example 12**

#### **Preparation of Alendronate Sodium Form H from Alendronic Acid Monohydrate**

Preparation of aqueous ethanolic sodium hydroxide:

Absolute ethanol (50 ml) and water (6.7 ml, 20x0.019 mol) were mixed.

30 Sodium hydroxide (0.76 g, assay 99%, 0.019 mol) was dissolved in 8.5 ml of this aqueous ethanol. The remaining aqueous ethanol was used to prepare a suspension of alendronic acid monohydrate.

A 250 ml flask was fitted with a mechanical stirrer, a thermometer, a dropping funnel, and a reflux condenser. The flask was charged with alendronic acid monohydrate (5 g, 0.019 mol) and aqueous ethanol. The aqueous ethanolic sodium hydroxide was added dropwise to the suspension of alendronic acid monohydrate in aqueous ethanol for 15 minutes at reflux with vigorously stirring. The mixture was then refluxed for additional 15 hours. The mixture was then cooled to room temperature with stirring. The solid was filtered, washed with absolute ethanol, then with absolute ethyl ether, and dried overnight in a vacuum oven (10-15 mm Hg, ambient temperature) to give 5.2 g of alendronate sodium, having crystalline Form H.

Although certain presently preferred embodiments of the invention have been described herein, it will be apparent to those skilled in the art to which the invention pertains that variations and modifications of the described embodiments may be made without departing from the spirit and scope of the invention. Accordingly, it is intended that the invention be limited only to the extent required by the appended claims and the applicable rules of law.

WE CLAIM:

1. The compound 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt having water content of 1.3 % to 11.7%.
2. A hydrate form of a compound of claim 1 which is any of the hydrate forms selected from the group that consists of 1/4 hydrate, 1/3 hydrate, hemihydrate, 2/3 hydrate, 3/4 hydrate, monohydrate, 5/4 hydrate, 4/3 hydrate, 3/2 hydrate, and dihydrate.
3. Crystalline monosodium alendronate monohydrate.
4. A sample of the crystalline monosodium alendronate monohydrate of claim 3 having a water content of about 6.2% weight.
5. Crystalline monosodium alendronate monohydrate characterized by its stability against dehydration at temperatures up to about 150°C.
6. The crystalline monosodium alendronate monohydrate of claim 5 further characterized by peaks in the powder x-ray diffraction pattern at values of two theta of  $12.7 \pm 0.2$ ,  $16.2 \pm 0.2$ ,  $17.3 \pm 0.2$ ,  $17.6 \pm 0.2$ ,  $24.8 \pm 0.2$ , and  $25.5 \pm 0.2$ .
7. A method of preparing the crystalline monosodium alendronate monohydrate of any of claims 3 through 6 comprising the steps of:
  - a) suspending one equivalent of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid in a lower alkanol,
  - b) adding a solution of one equivalent of a sodium base and from 5 to 200 equivalents of water in a lower alcohol, to the suspension of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid and
  - c) isolating the crystalline monosodium alendronate monohydrate.
8. A method according to claim 7 wherein the compound 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid is in a monohydrate form.

9. A method according to claim 7 wherein the lower alkanol is selected from the group consisting of methanol, ethanol and isopropanol.

10. A method according to claim 7 wherein the sodium base selected from the group consisting of sodium hydroxide, sodium methoxide and sodium ethoxide.

11. A method according to claim 7 wherein the compound 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid is in an anhydrous form.

12. A method of preparing the compound of any of claims 3 through 6 comprising the steps of:

a) treating one equivalent of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic monosodium salt in a lower alkanol with 20-40 equivalents of water; and

b) isolating said compound.

13. A method according to claim 12 wherein the lower alkanol of step a) is ethanol.

14. A method of preparing the compound of any of claims 3 through 6 comprising the steps of:

a) treating one equivalent of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic disodium salt in a lower alkanol with 20-40 equivalents of water, and one equivalent of alendronic acid; and

b) isolating said compound.

15. A method according to claim 14 wherein the lower alkanol of step a) is ethanol.

16. A method of preparing the compound of any of claims 3 through 6 comprising the steps of:

a) treating one equivalent of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic trisodium salt in a lower alkanol with 20-40 equivalents of water and two equivalents of alendronic acid; and

b) isolating said compound.

17. A method according to claim 16 wherein the lower alkanol of step a) is ethanol.
18. A method of preparing the compound of any of claims 3 through 6 comprising the steps of:
  - a) treating one equivalent of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic tetrasodium salt in a lower alkanol with 20-40 equivalents of water, and three equivalents of alendronic acid; and
  - b) isolating said compound.
19. A method according to claim 18 wherein the lower alkanol of step a) is ethanol.
20. A method according to claim 12 in which the 4-amino-1-hydroxybutylidene-1,1-bisphosphonic sodium salt is a monosodium salt trihydrate.
21. Crystalline monosodium alendronate monohydrate characterized by peaks in the powder x-ray diffraction pattern at values of two theta of  $9.3 \pm 0.2$ ,  $12.4 \pm 0.2$ ,  $13.5 \pm 0.2$ ,  $26.3 \pm 0.2$  and  $30.0 \pm 0.2$ .
22. A method of preparing the compound of any of claim 21 comprising the steps of:
  - a) treating 4-amino-1-hydroxybutylidene-1,1-bisphosphonic monosodium trihydrate with an effective amount of a drying agent; and
  - b) isolating said compound of claim 21.
23. A method according to claim 22 wherein the reaction of step a) is performed in ethanol.
24. Alendronate monosodium hemihydrate.
25. The compound 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt having water content of 2.8% to 3.9%.
26. The compound according to claim 25 having water content of about 3.2%.
27. The compound according to claim 25, which is characterized by peaks in the powder x-ray diffraction at values of two theta of  $7.0 \pm 0.2$ ,  $9.3 \pm 0.2$ , and  $14.0 \pm 0.2$ .



28. A method of preparing the compound of claim 24 or 25 comprising the steps of:

a) treating 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid in a lower alkanol with one equivalent of sodium base and 9 to 15 equivalents of water; and

b) isolating said compound of claim 24 or 25.

29. A method according to claim 28 wherein the compound 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid is in a monohydrate form.

30. A method according to claim 28 wherein the lower alkanol is selected from the group consisting of methanol, ethanol and isopropanol.

31. A method according to claim 28 wherein the sodium base is selected from the group consisting of sodium hydroxide, sodium methoxide and sodium ethoxide.

32. A method according to claim 28 wherein the compound 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid is in an anhydrous form.

33. The compound 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt having water content of 2.5% to 3.5%.

34. The compound according to claim 33, which is characterized by peaks in the powder x-ray diffraction at values of two theta of  $9.2 \pm 0.2$ ,  $14.2 \pm 0.2$ ,  $15.0 \pm 0.2$ ,  $17.1 \pm 0.2$ ,  $20.7 \pm 0.2$ ,  $22.0 \pm 0.2$ ,  $22.4 \pm 0.2$ .

35. A method of preparing the compound of claim 2 or 33 comprising the steps of:

a) treating 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid in a lower alkanol with one equivalent of sodium base and 17 to 22 equivalents of water; and

b) isolating said compound of claim 2 or 33.

36. A method according to claim 35 in which the compound 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid is in a monohydrate form.

37. A method according to claim 35 wherein the lower alkanol is selected from the group consisting of methanol, ethanol and isopropanol.

38. A method according to claim 35 wherein the sodium base is selected from the group consisting of sodium hydroxide, sodium methoxide and sodium ethoxide.

39. The compound 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt having water content of 6.4% to 9.0%.

40. The compound according to claim 39, which is characterized by peaks in the powder x-ray diffraction at values of two theta of  $12.2 \pm 0.2$ ,  $13.3 \pm 0.2$ ,  $14.8 \pm 0.2$ ,  $15.8 \pm 0.2$ ,  $16.3 \pm 0.2$ , and  $17.2 \pm 0.2$ .

41. A method of preparing the compound of claim 2 or 39 comprising the steps of:

a) treating 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid in a lower alkanol with one equivalent of sodium base and 0 to 4 equivalents of water; and

b) isolating said compound of claim 2 or 39.

42. A method according to claim 41 in which the compound 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid is in a monohydrate form.

43. A method according to claim 41 wherein the lower alkanol is selected from the group consisting of methanol, ethanol and isopropanol.

44. A method according to claim 41 wherein the sodium base is selected from the group consisting of sodium hydroxide, sodium methoxide and sodium ethoxide.

45. The compound 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt having water content of 3.2% to 5.8%.

46. The compound according to claim 45, which is characterized by peaks in the powder x-ray diffraction at values of two theta of  $13.1 \pm 0.2$ ,  $15.2 \pm 0.2$ ,  $16.3 \pm 0.2$ ,  $22.3 \pm 0.2$ ,  $22.5 \pm 0.2$ ,  $23.4 \pm 0.2$ , and  $23.7 \pm 0.2$ .

47. A method of preparing the compound of 2 or 45 comprising the steps of:

a) treating 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid anhydrous in a lower alkanol with one equivalent of sodium base and 0 to 4 equivalents of water; and

b) isolating said compound of claim 2 or 45.

48. A method according to claim 47 in which the compound 4-amino-1-hydroxybutylidene-1, 1-bisphosphonic acid is in an anhydrous form.

49. A method according to claim 48 wherein the lower alkanol is selected from the group consisting of methanol, ethanol and isopropanol.

50. A method according to claim 48 wherein the sodium base is selected from the group consisting of sodium hydroxide, sodium methoxide and sodium ethoxide.

51. The compound 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt having water content of 1.3 % to 3.1 %.

52. The compound according to claim 51, which is characterized by peaks in the powder x-ray diffraction at values of two theta of  $13.0 \pm 0.2$ ,  $13.4 \pm 0.2$ ,  $14.2 \pm 0.2$ ,  $19.1 \pm 0.2$ , and  $19.4 \pm 0.2$ .

53. A method of preparing the compound of claim 2 or 51 comprising the steps of:

a) treating 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid in a lower alkanol with one equivalent of sodium base and 3 to 20 equivalents of water; and

b) isolating said compound of claim 2 or 51.

54. A method according to claim 53 in which the compound 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid is in a monohydrate form.

55. A method according to claim 53 wherein the lower alkanol is selected from the group consisting of methanol, ethanol and isopropanol.

56. A method according to claim 53 wherein the sodium base is selected from the group

consisting of sodium hydroxide, sodium methoxide and sodium ethoxide.

57. A method according to claim 53 wherein the compound 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid is in an anhydrous form.

58. Alendronate monosodium dihydrate.

59. The compound 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt having water content of about 11.7%.

60. The compound according to claim 59, which is characterized by peaks in the powder x-ray diffraction at values of two theta of  $9.3 \pm 0.2$ ,  $12.4 \pm 0.2$ ,  $13.5 \pm 0.2$ ,  $26.3 \pm 0.2$  and  $30.0 \pm 0.2$ .

61. A method for preparing a compound according to claim 58 or 59 comprising the steps of:

a) treating 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate with an effective amount of drying agent; and

b) isolating 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid the monosodium salt dihydrate.

62. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of any of claims 1, 3, 25, 33, 39, 45 and 51.

63. A method for treating and/or preventing bone loss in a subject, comprising the step of administering to said subject in need thereof an effective amount of the pharmaceutical composition as defined in claim 62.

64. A method of preparing the compound of claim 1 comprising the steps of:

a) reacting one equivalent of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid with one equivalent of sodium base in an aqueous organic solvent selected from the group consisting of acetone, DMSO, DMF, acetonitrile, alcohols, polyalcohols, polyalcohol ethers, pyridine, sulfolane, N-methyl pyrrolidinone and dioxane, and

b) isolating said compound of claim 1.

65. A method of preparing the crystalline monosodium alendronate monohydrate of claim 3 comprising the steps of:

a) suspending one equivalent of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid with one equivalent of sodium base in a solvent mixture comprising an organic solvent selected from the group consisting of acetone, DMSO, DMF, acetonitrile, alcohols, polyalcohols, polyalcohol ethers, pyridine, sulfolane, N-methyl pyrrolidinone and dioxane, and water, and

b) separating the crystalline monosodium alendronate monohydrate from the solvent mixture.

66. A method of preparing the compound of claim 25 comprising the steps of:

a) reacting one equivalent of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid with one equivalent of sodium base in an aqueous organic solvent selected from the group consisting of acetone, DMSO, DMF, acetonitrile, alcohols, polyalcohols, polyalcohol ethers, pyridine, sulfolane, N-methyl pyrrolidinone and dioxane, and

b) isolating said compound of claim 25.

67. A method of preparing the compound of claim 33 comprising the steps of:

a) reacting one equivalent of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid with one equivalent of sodium base in an aqueous organic solvent selected from the group consisting of acetone, DMSO, DMF, acetonitrile, alcohols, polyalcohols, polyalcohol ethers, pyridine, sulfolane, N-methyl pyrrolidinone and dioxane, and

b) isolating said compound of claim 33.

68. A method of preparing the compound of claim 39 comprising the steps of:

a) reacting one equivalent of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid with one equivalent of sodium base in an aqueous organic solvent selected from the group consisting of acetone, DMSO, DMF, acetonitrile, alcohols, polyalcohols, polyalcohol ethers, pyridine, sulfolane, N-methyl pyrrolidinone and dioxane, and

b) isolating said compound of claim 39.

69. A method of preparing the compound of claim 45 comprising the steps of:

a) reacting one equivalent of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid with one equivalent of sodium base in an aqueous organic solvent selected from the group consisting of acetone, DMSO, DMF, acetonitrile, alcohols, polyalcohols, polyalcohol ethers, pyridine, sulfolane, N-methyl pyrrolidinone and dioxane, and

b) isolating said compound of claim 45.

70. A method of preparing the compound of claim 51 comprising the steps of:

a) reacting one equivalent of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid with one equivalent of sodium base in an aqueous organic solvent selected from the group consisting of acetone, DMSO, DMF, acetonitrile, alcohols, polyalcohols, polyalcohol ethers, pyridine, sulfolane, N-methyl pyrrolidinone and dioxane, and

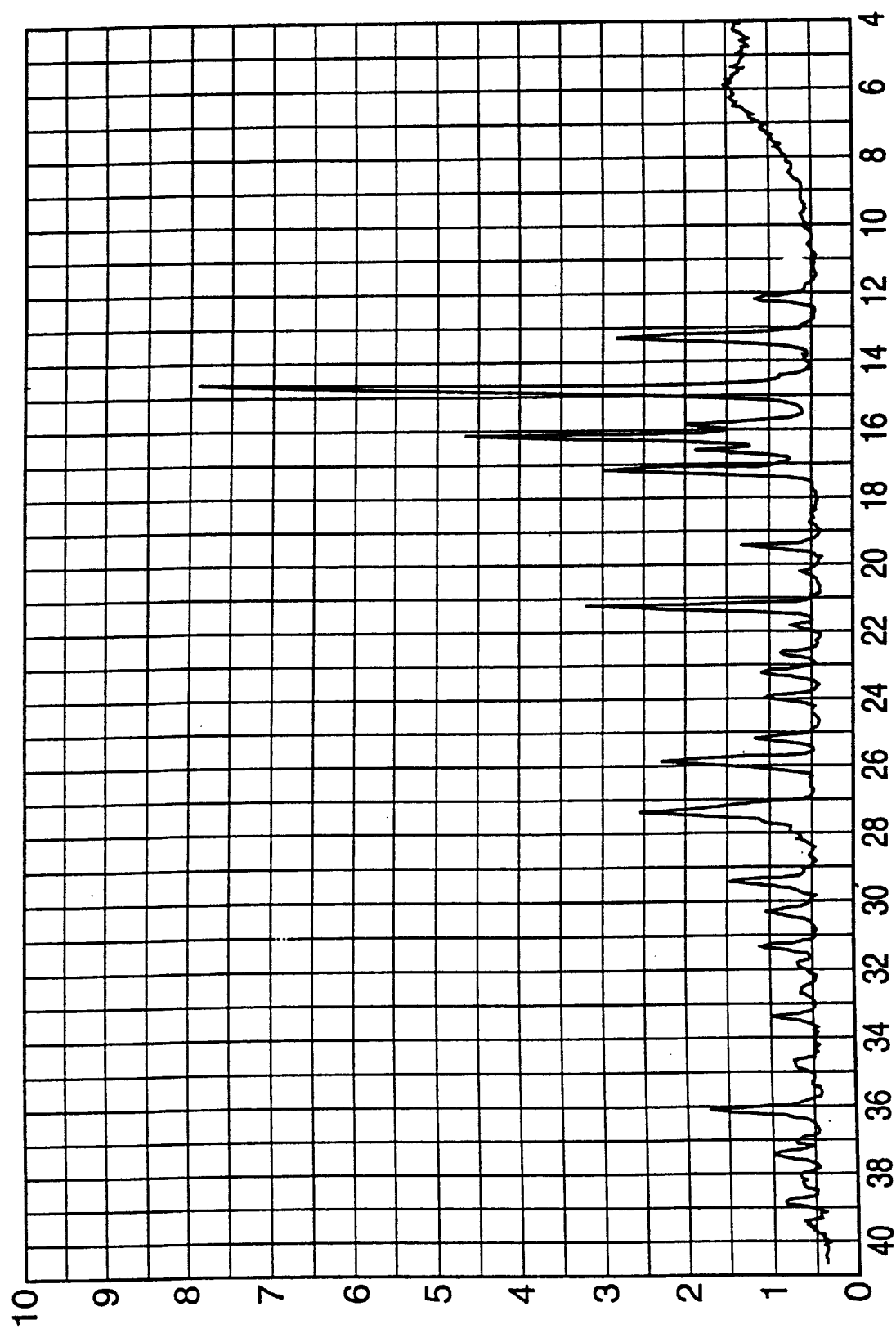
b) isolating said compound of claim 51.

71. A method of preparing the compound of claim 3 comprising the steps of:

a) reacting one equivalent of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid with one equivalent of sodium base in an aqueous organic solvent selected from the group consisting of acetone, DMSO, DMF, acetonitrile, alcohols, polyalcohols, polyalcohol ethers, pyridine, sulfolane, N-methyl pyrrolidinone and dioxane, and

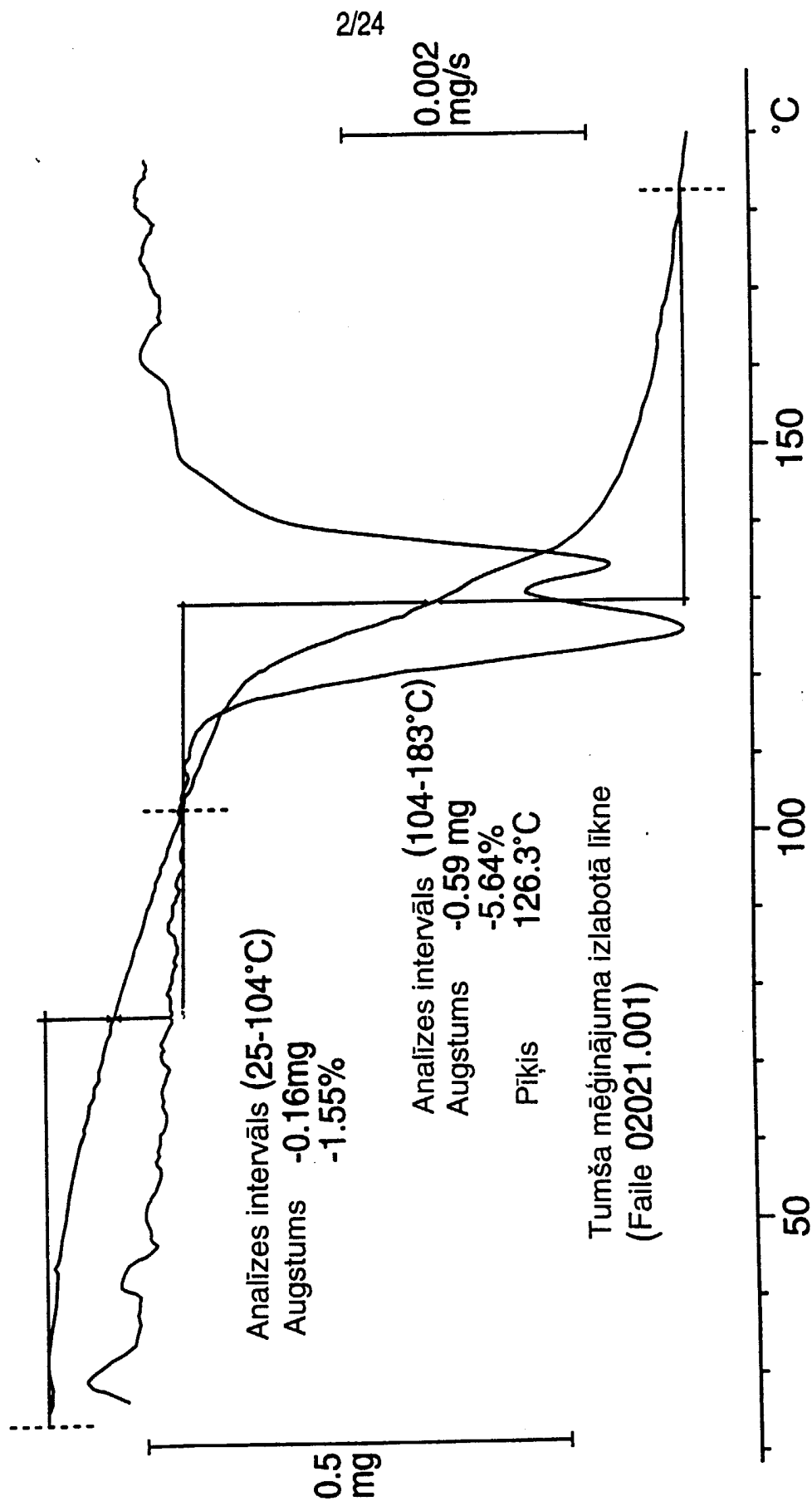
b) isolating said compound of claim 3.

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1a. zīm.

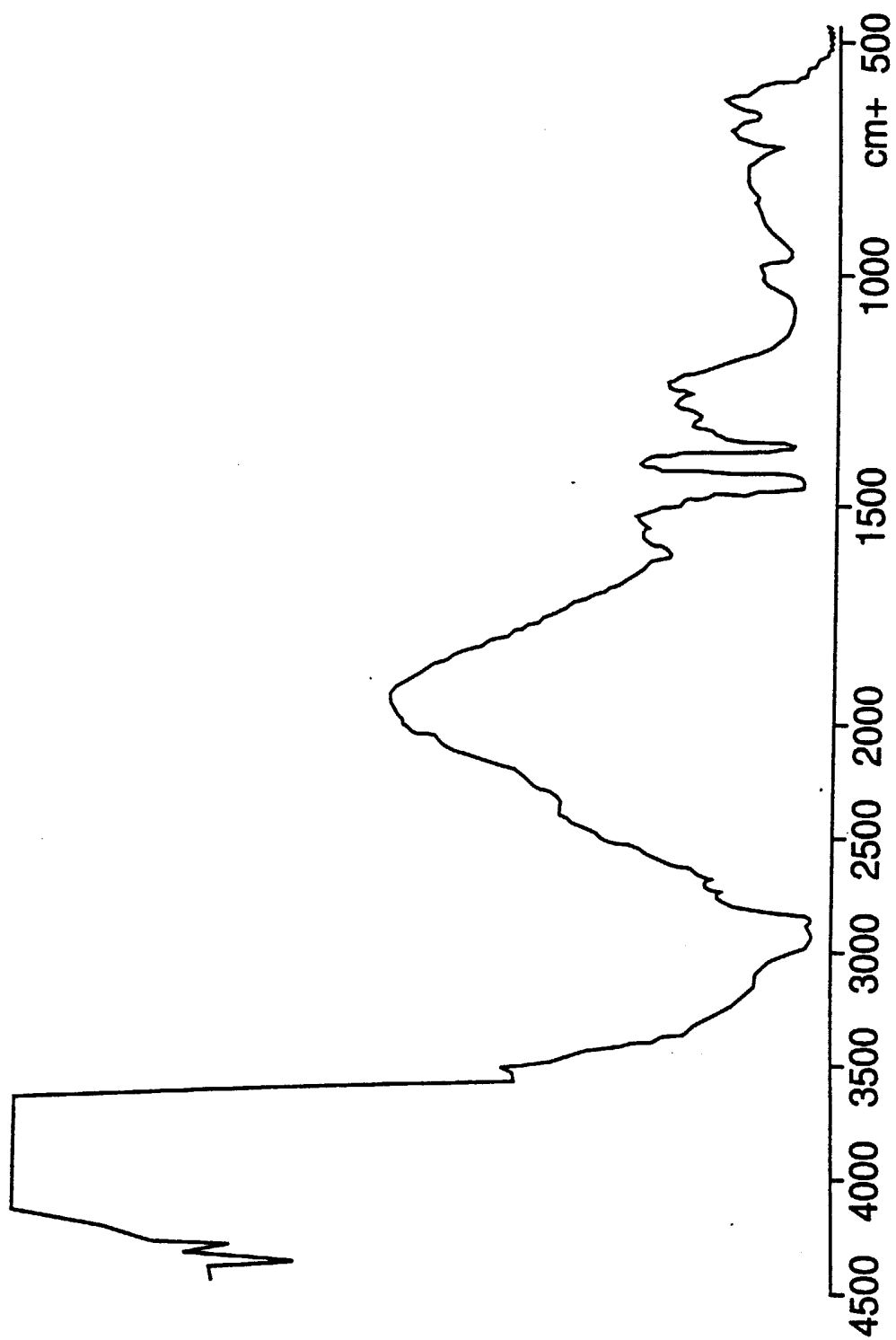
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1b. zīm.

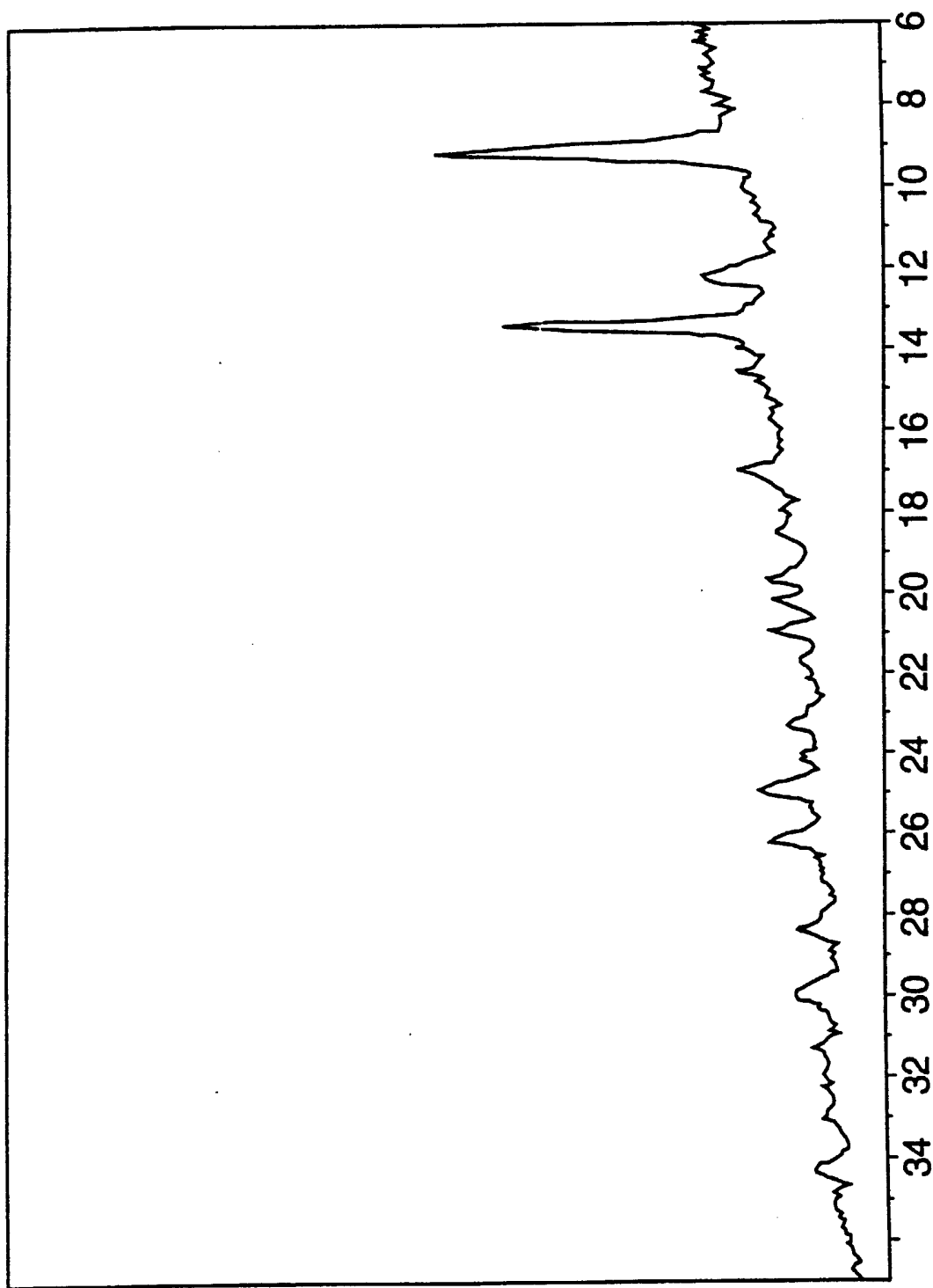


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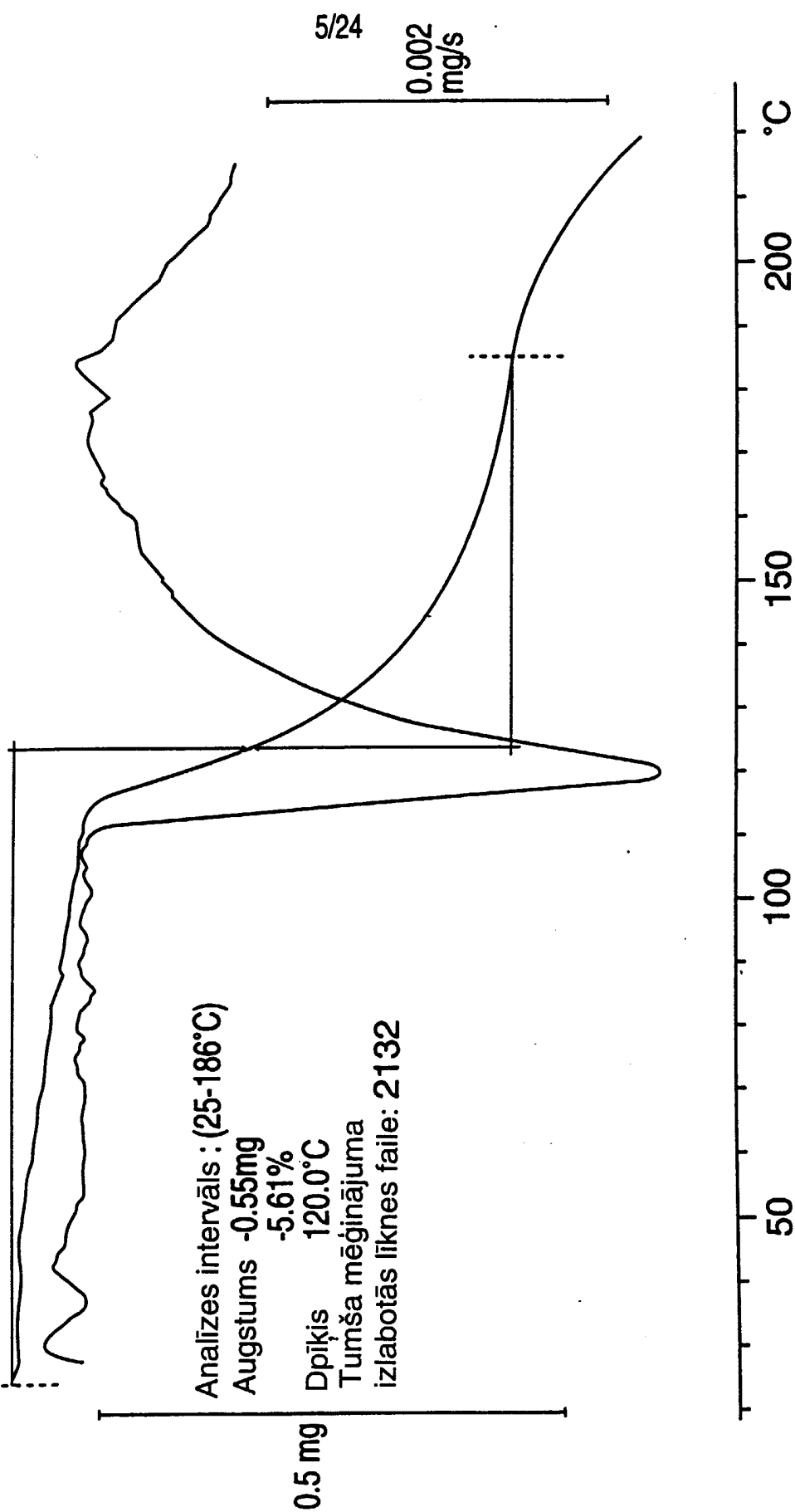
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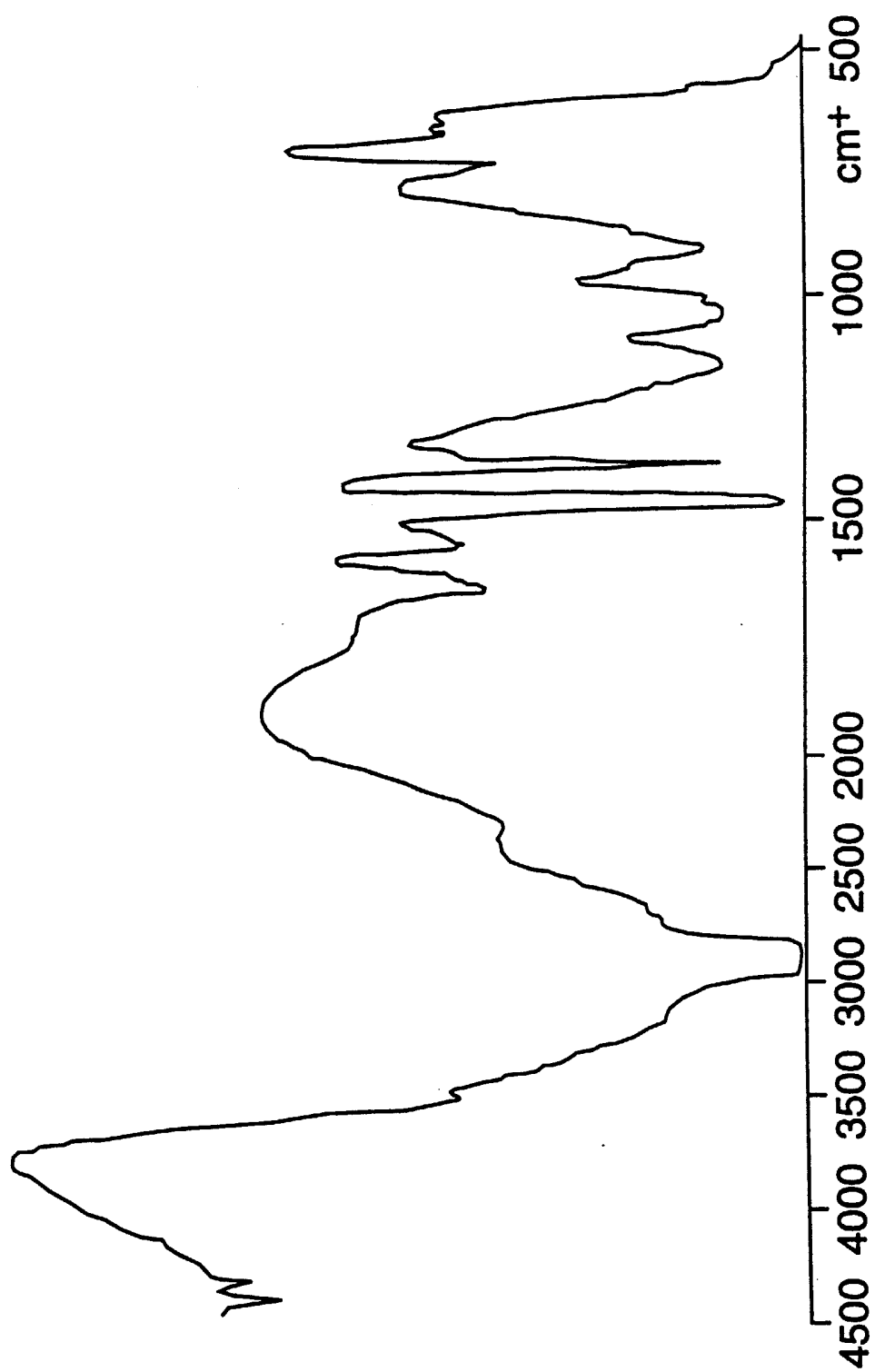
2a. zīm.

Nātrija alendronāta NF-632-9  
9.739 mg Ātrums :10.0 °C/min



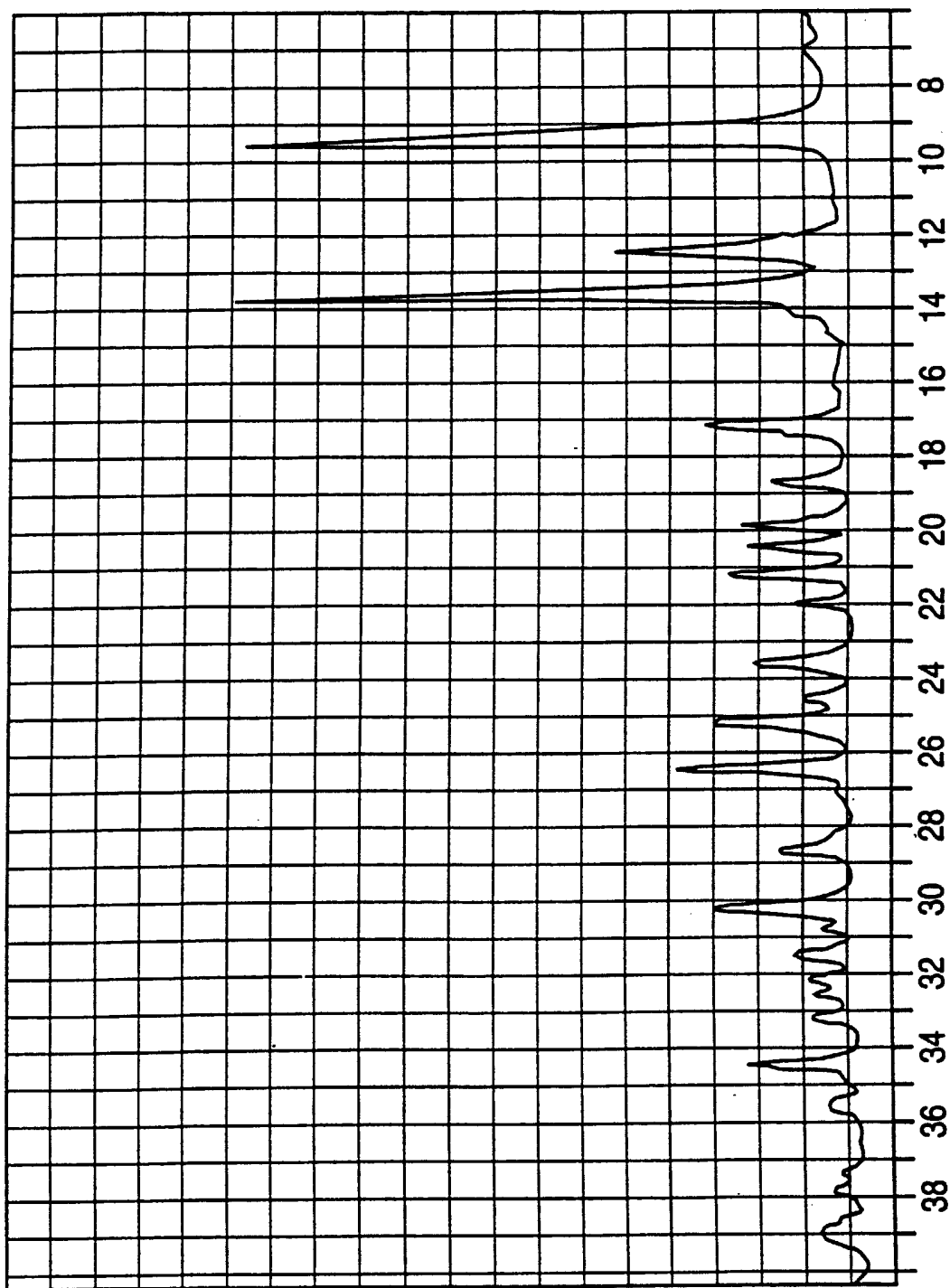
**2b. zīm.**

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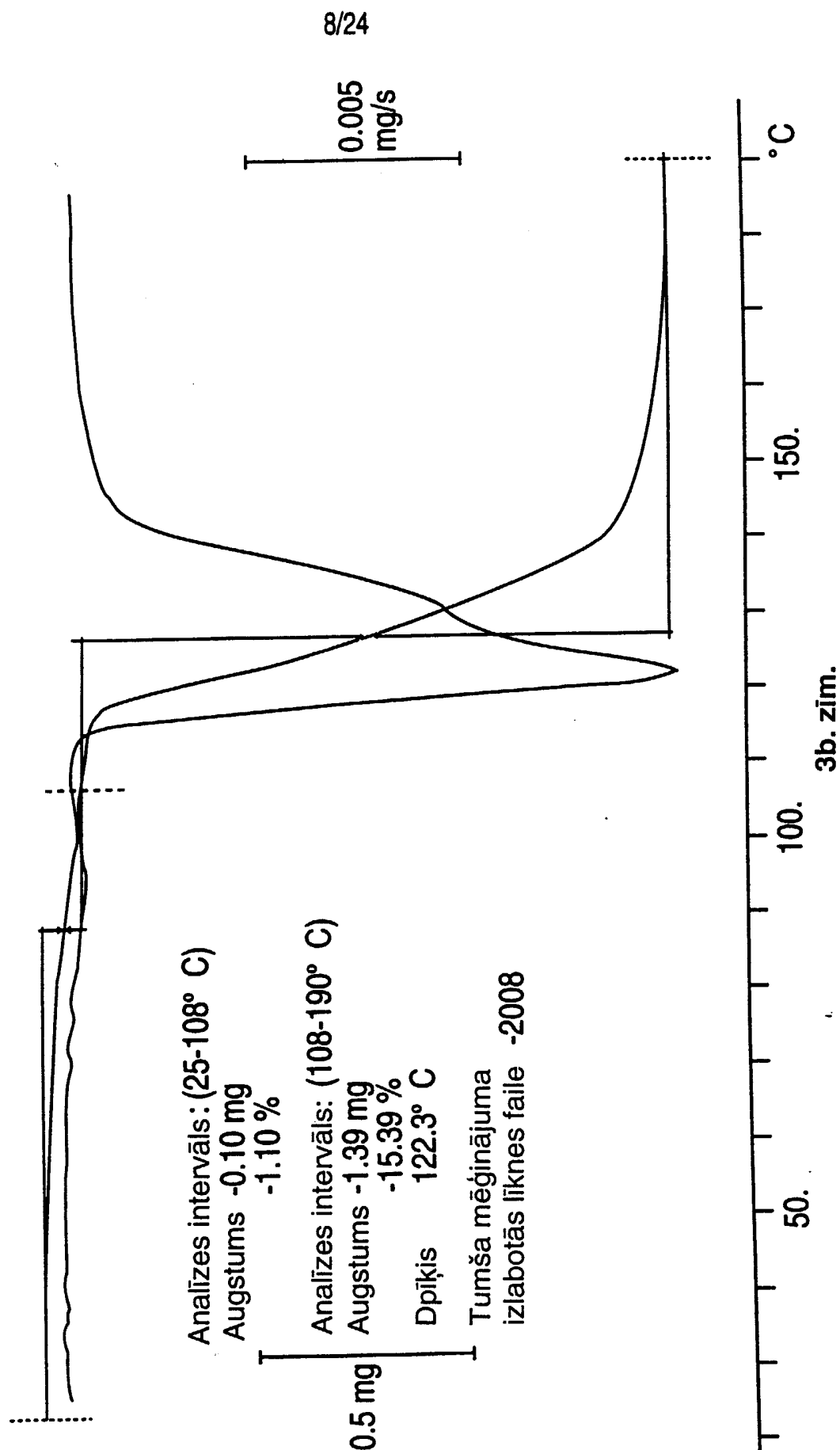
2c. zim.

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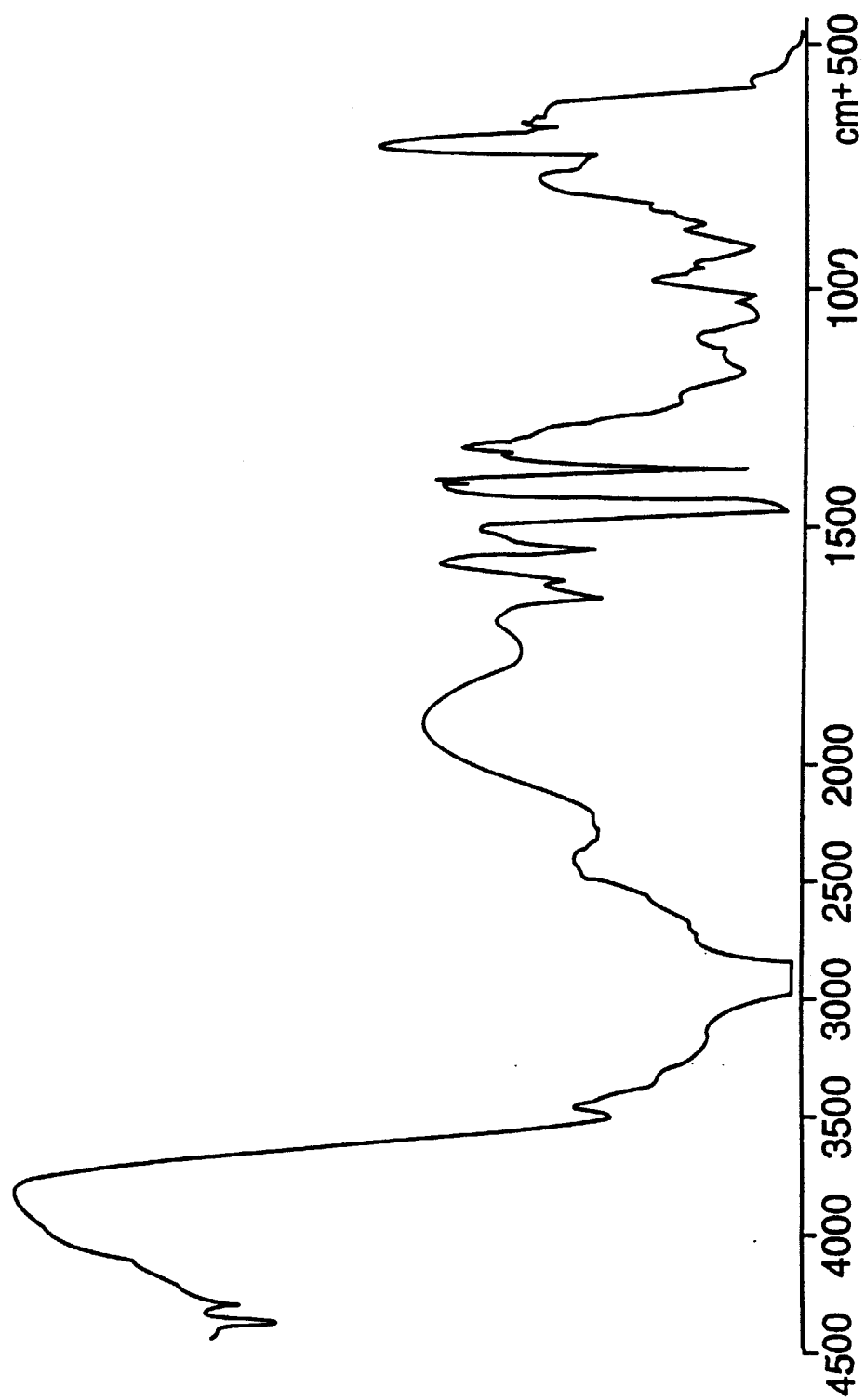


3a. zīm.

Nātrija alendronāta NF-595  
9.038 mg Ātrums: 10.0 °C/min

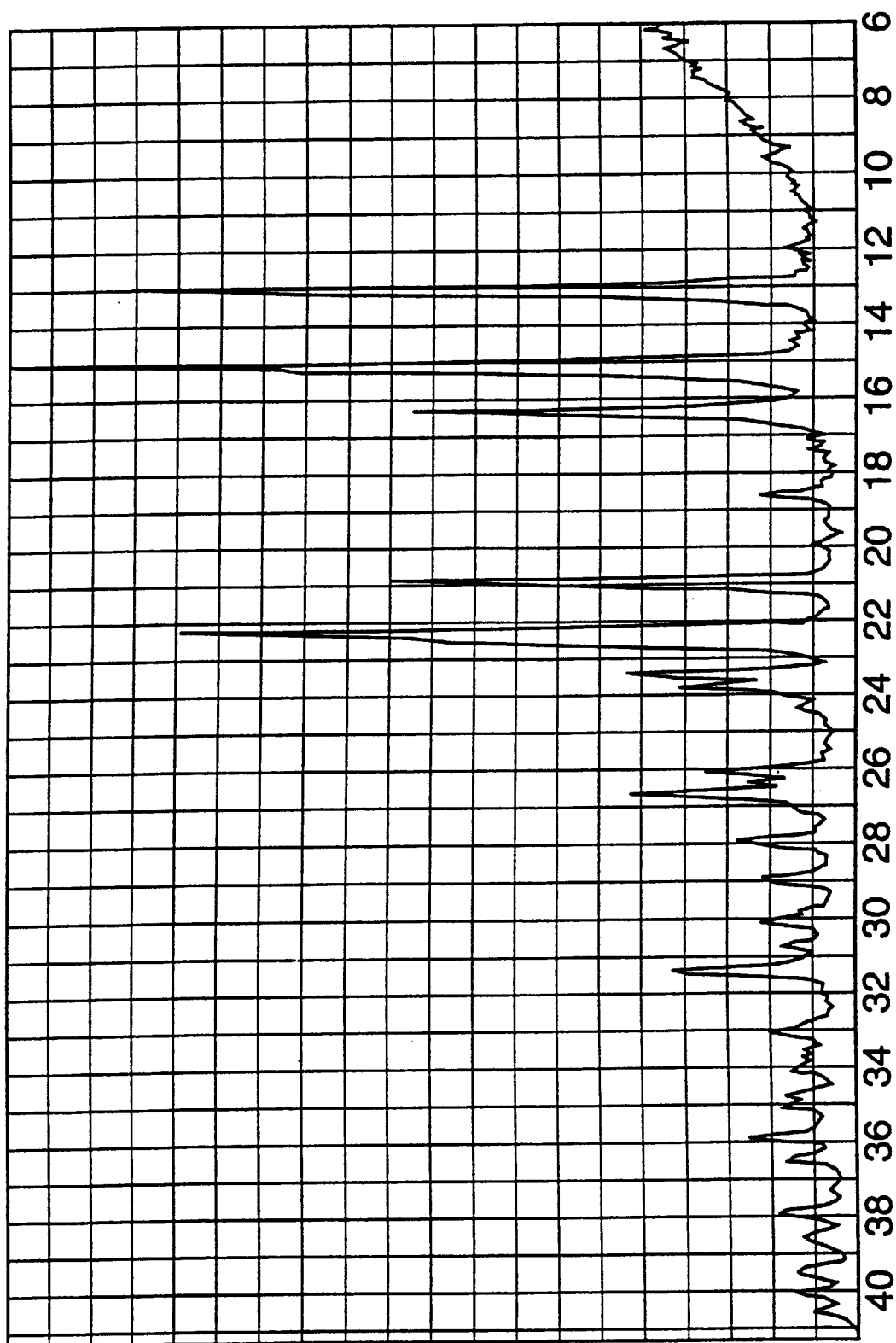


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3c. zim.

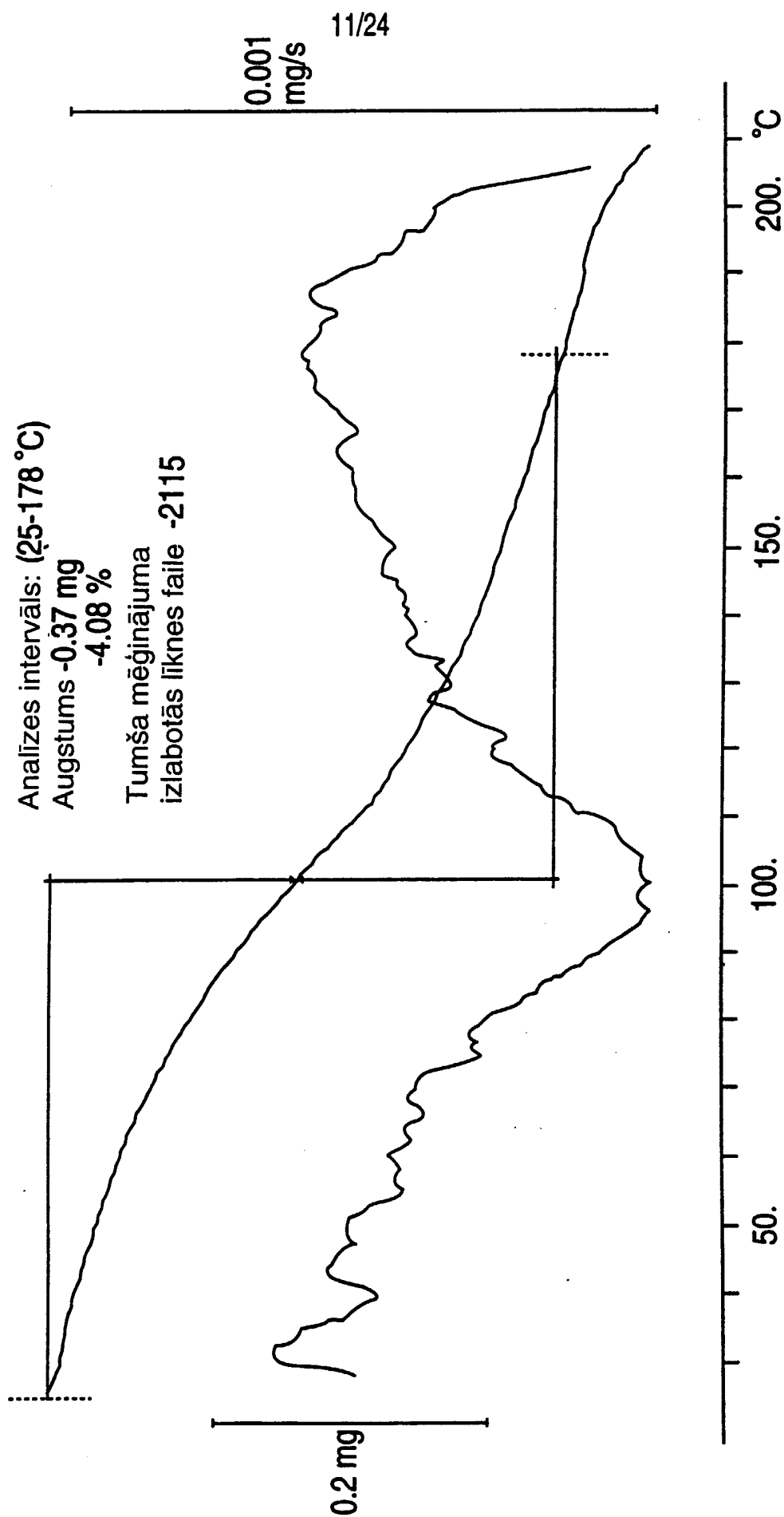
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4a. zim.

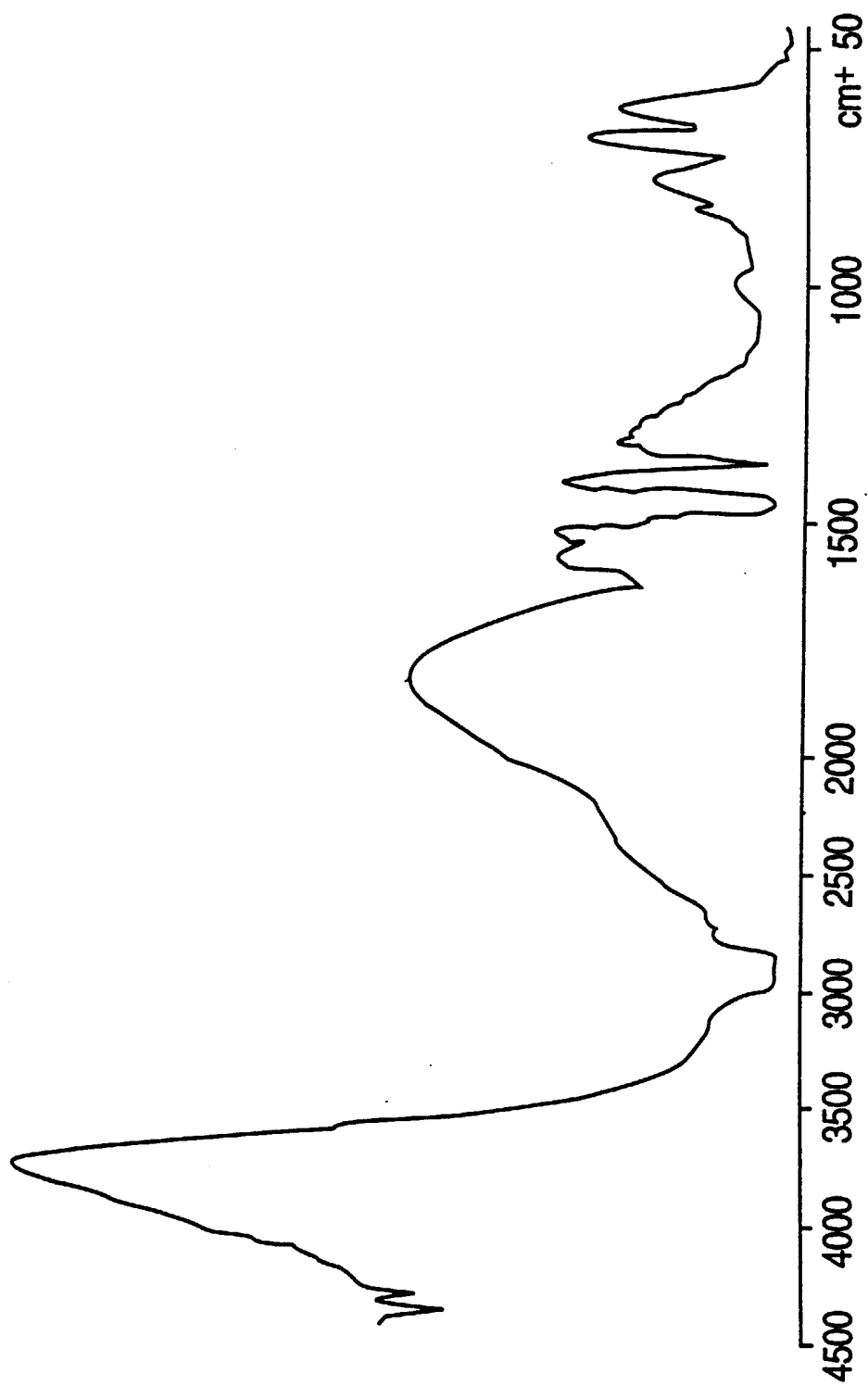


Nātrija alendronāta NF-636  
9.143 mg Ātrums: 10.0 °C/min



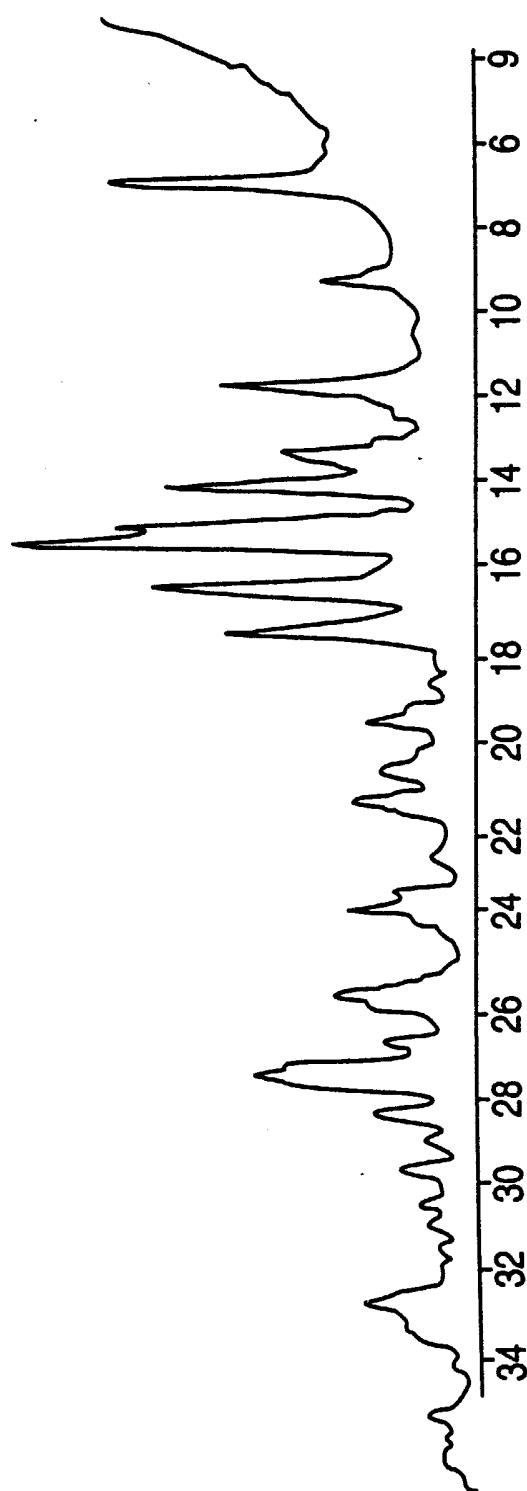
4b. zīm.

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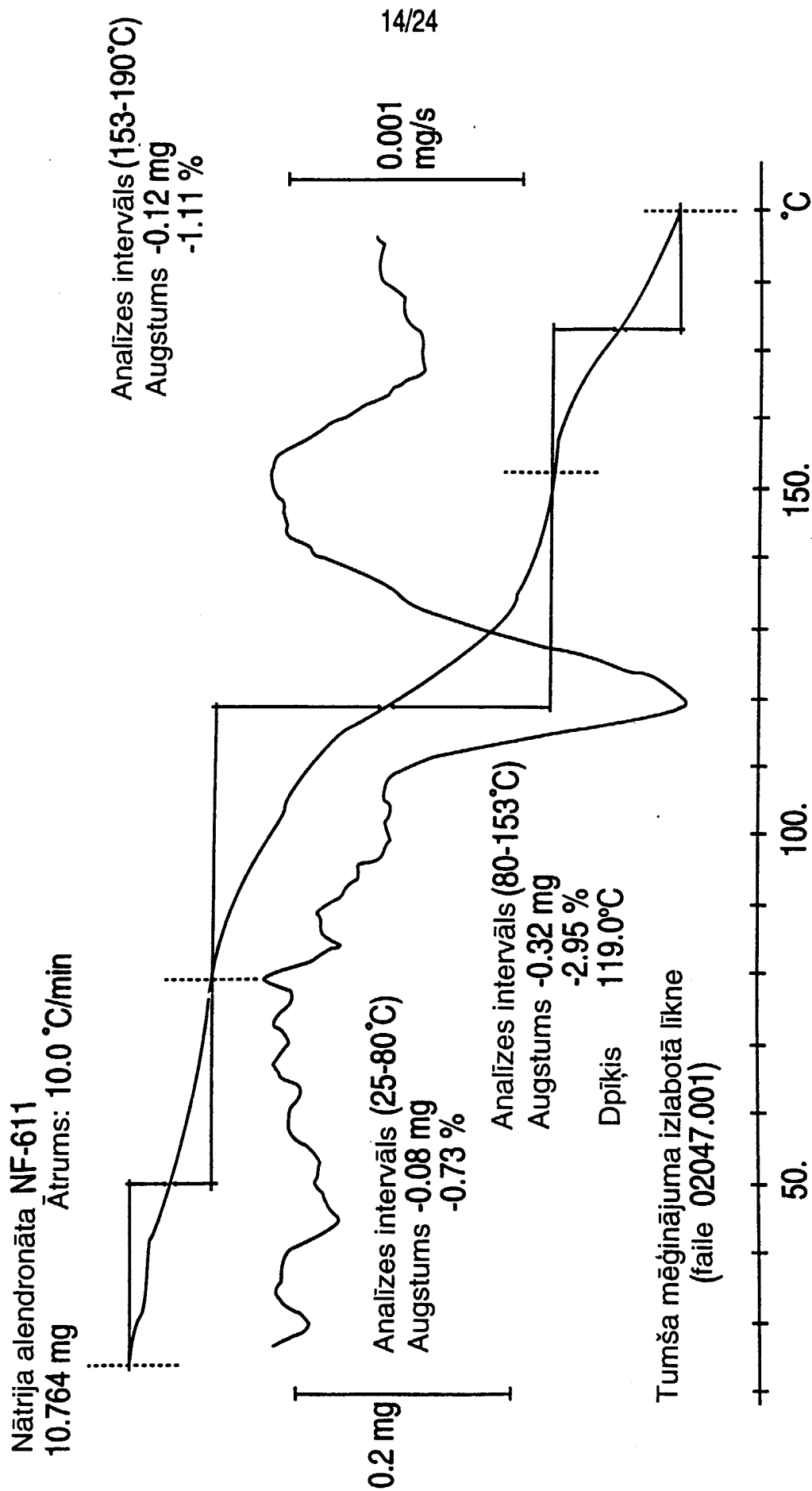


4c. zím.

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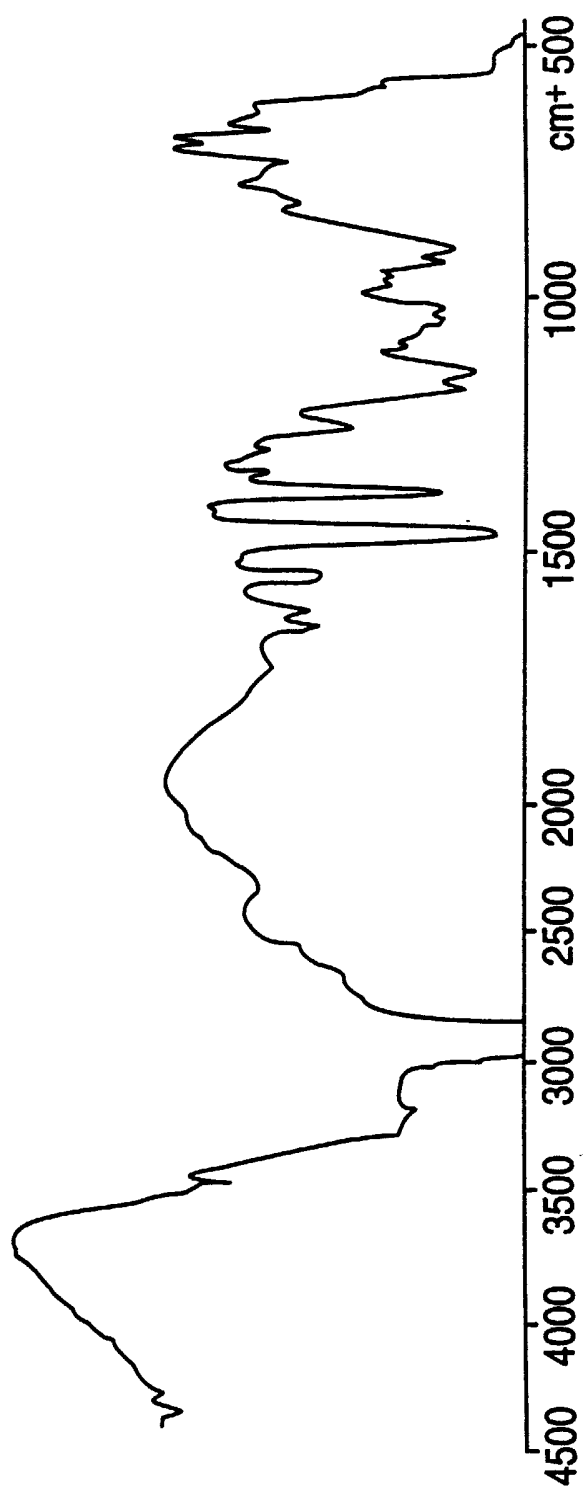


5a. zīm.



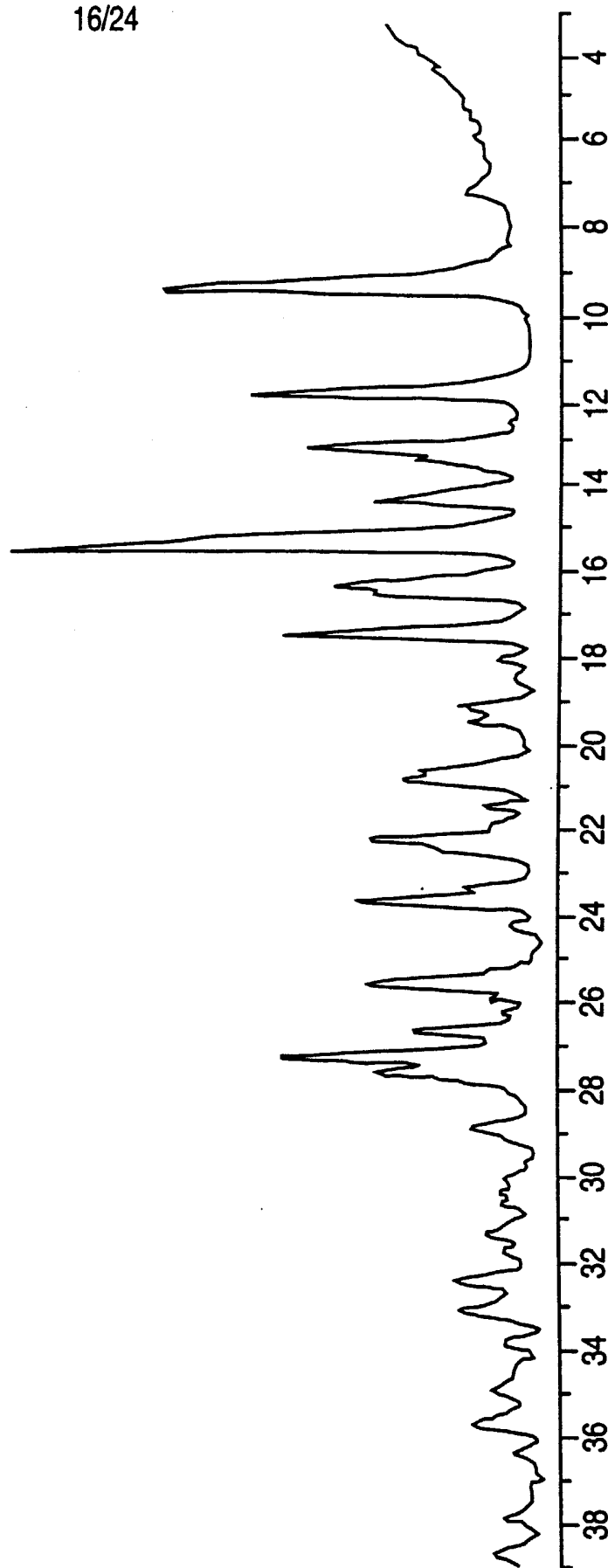
5b. zīm.

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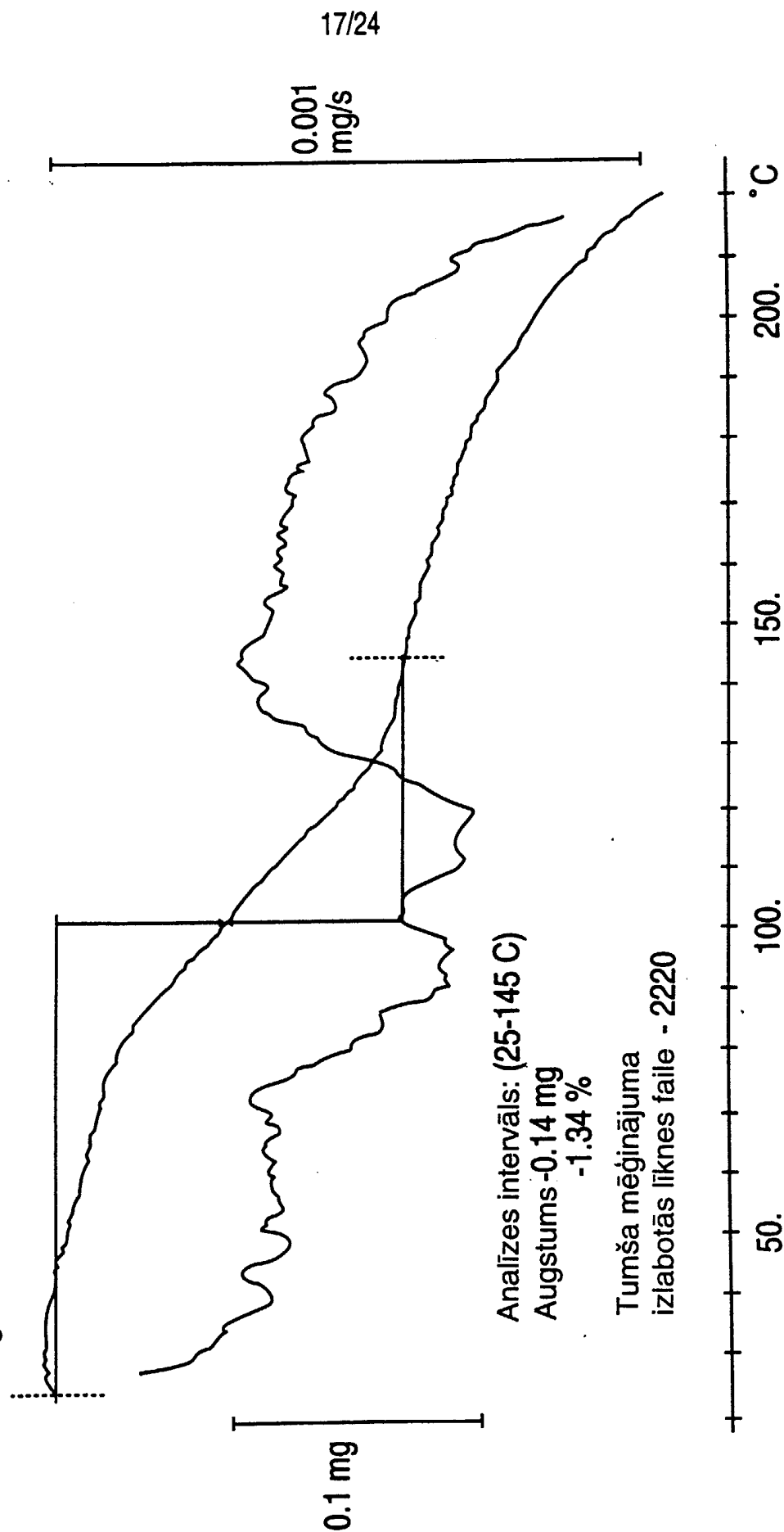
5c. zīm.

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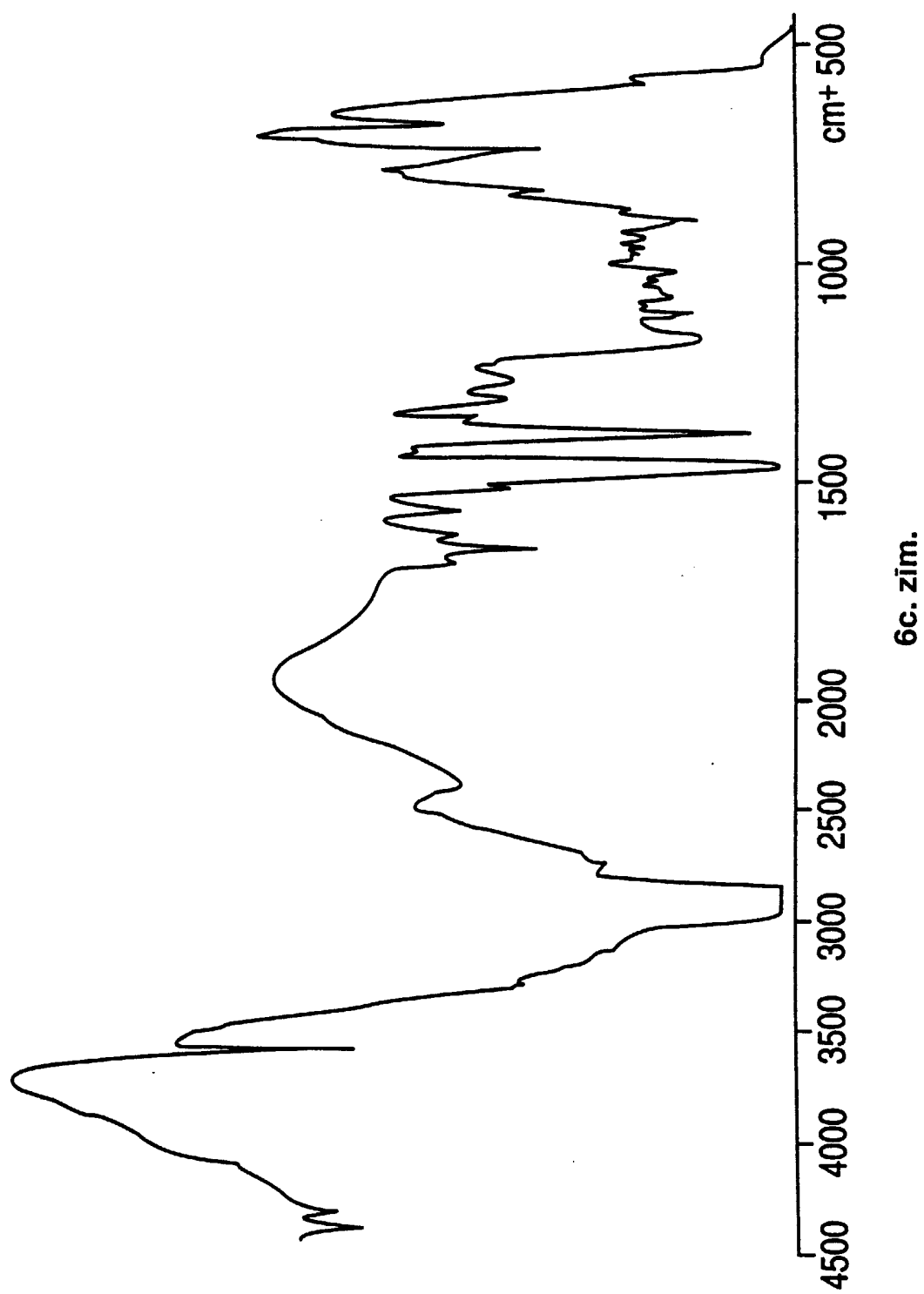
6a. zīm.

Nātrija alendronāta NF-662  
10.450 mg Ātrums: 10.0 °C/min



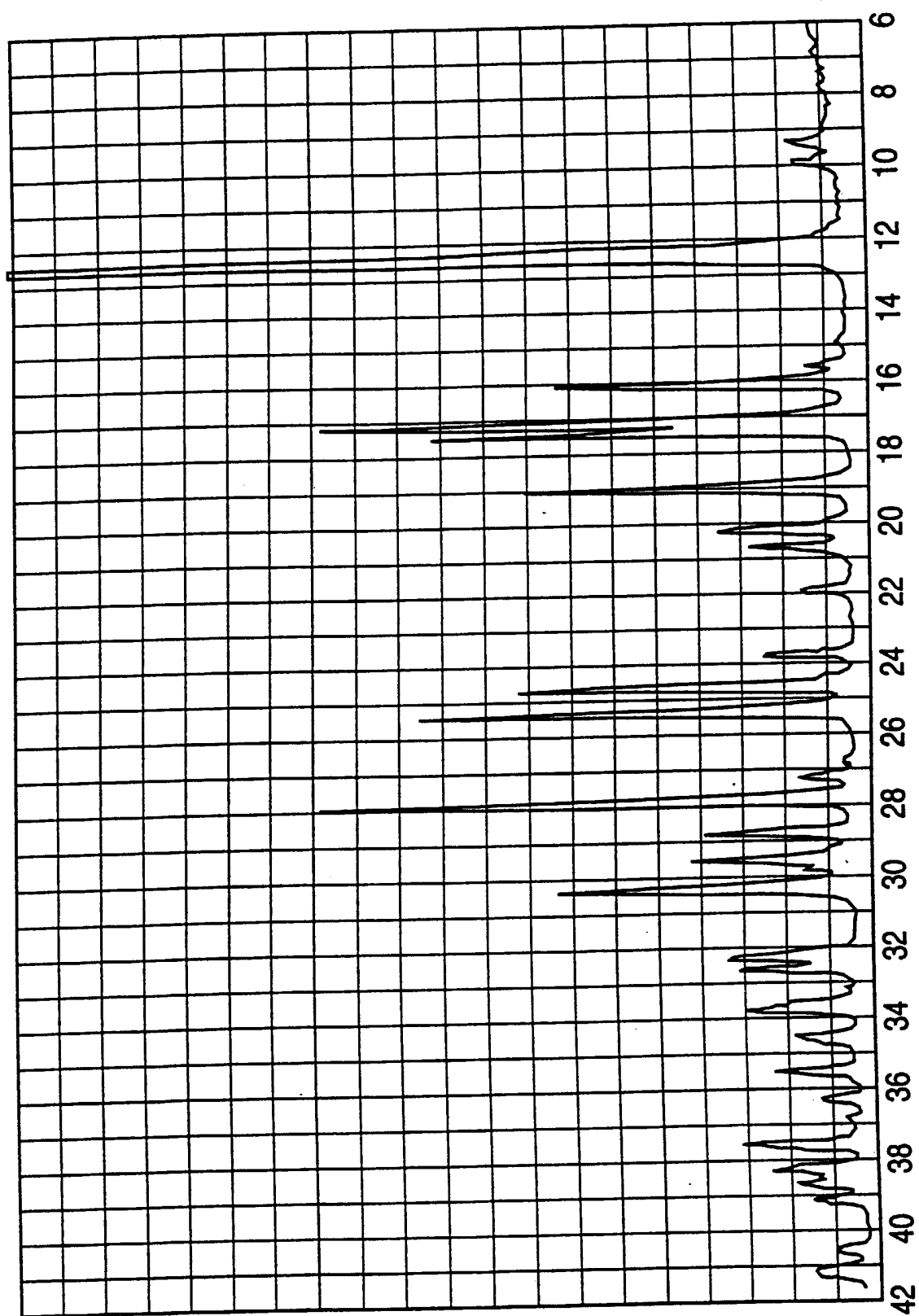
6b. zīm.

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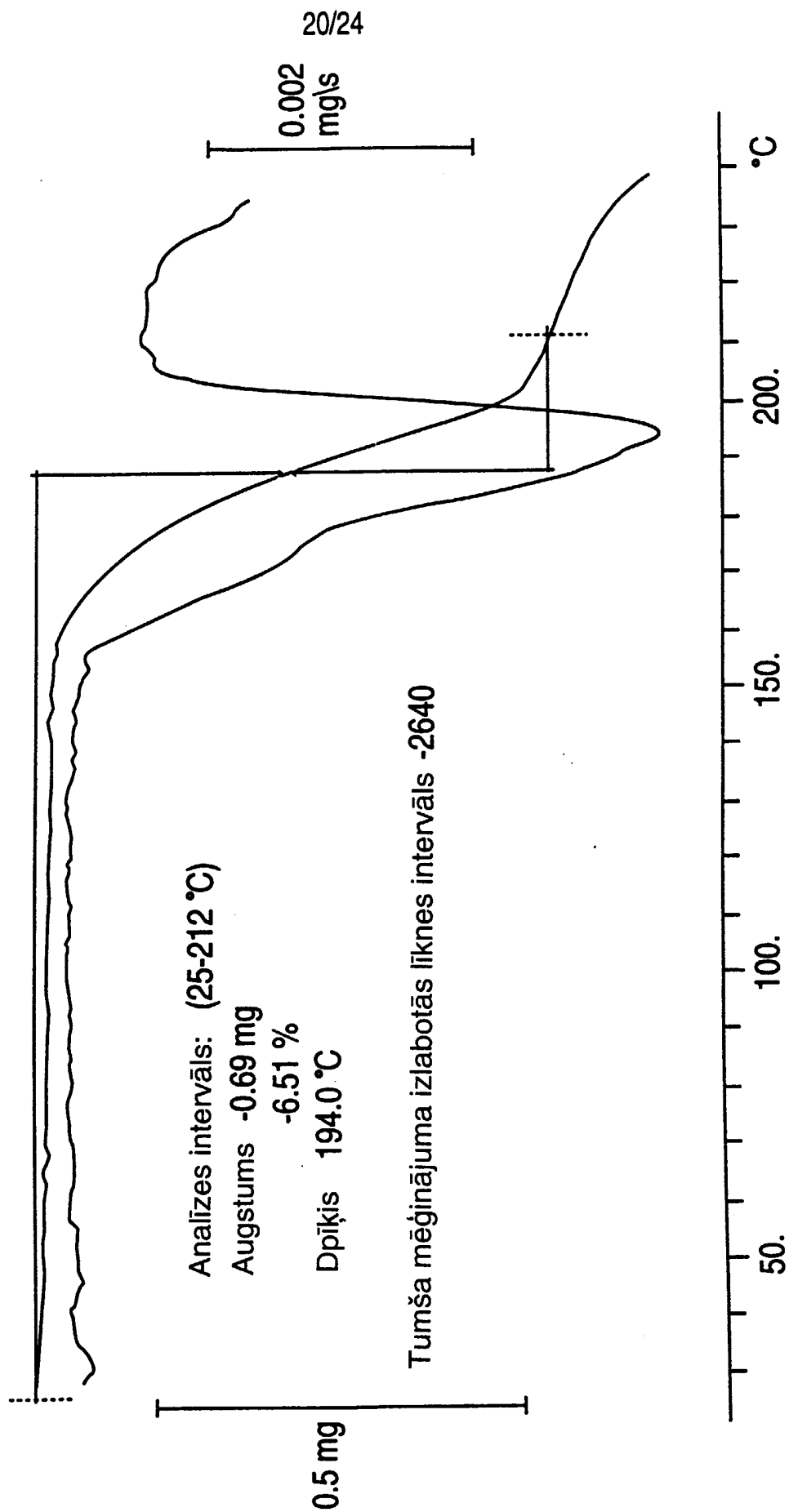
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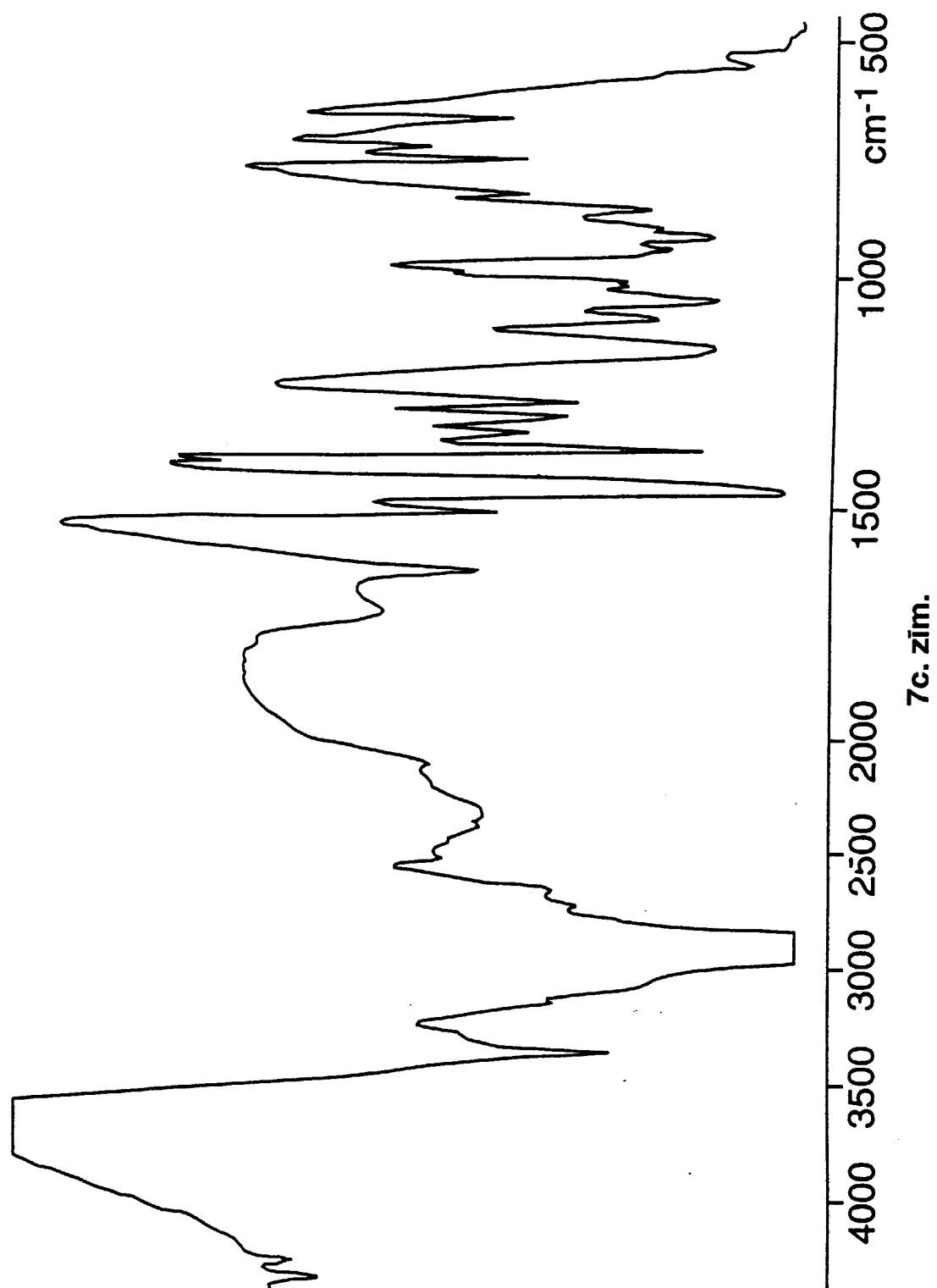
7a. zīm.

Nātrija alendronāta NF-796

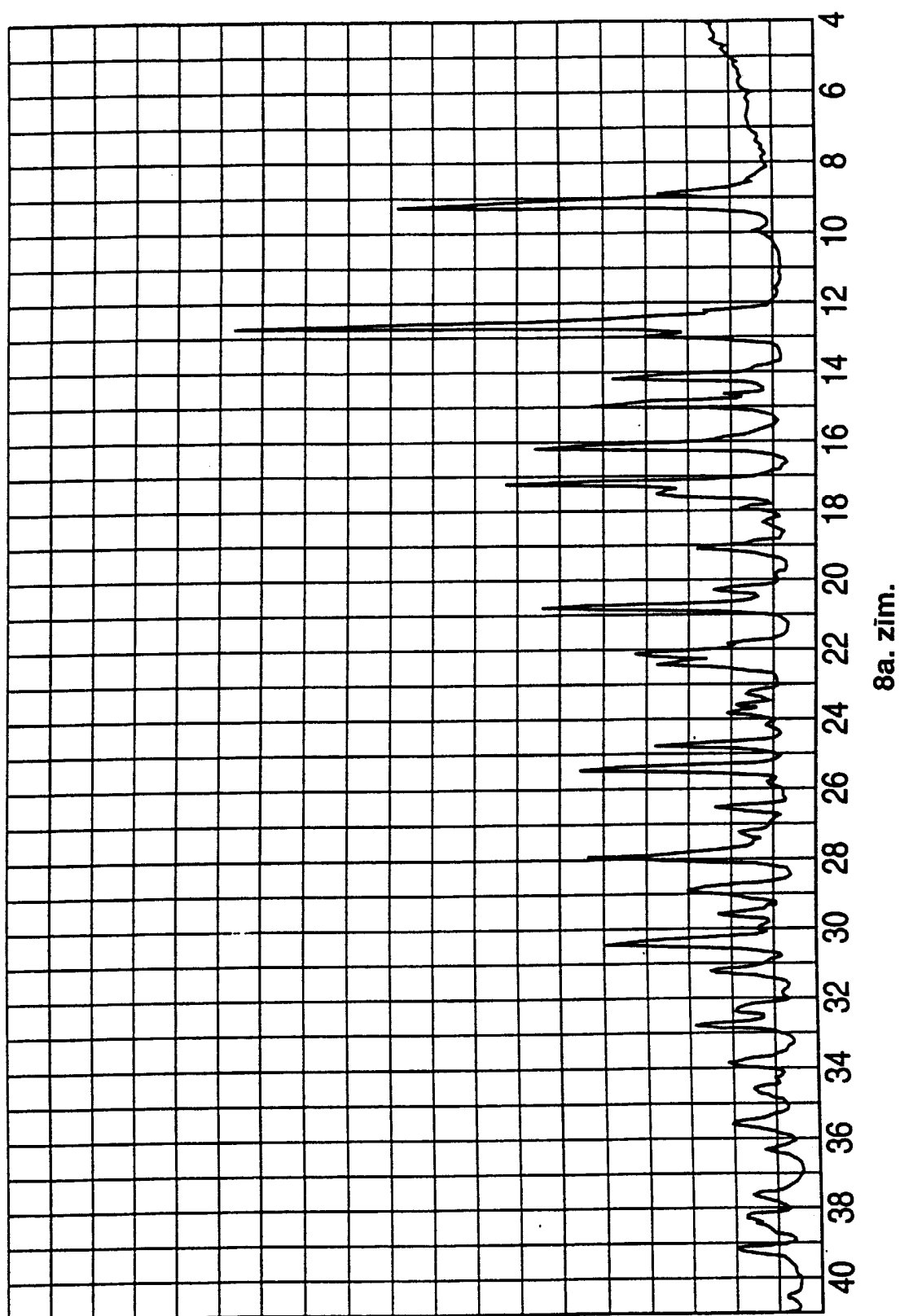
10.673 mg Ātrums: 10.0 °C/min



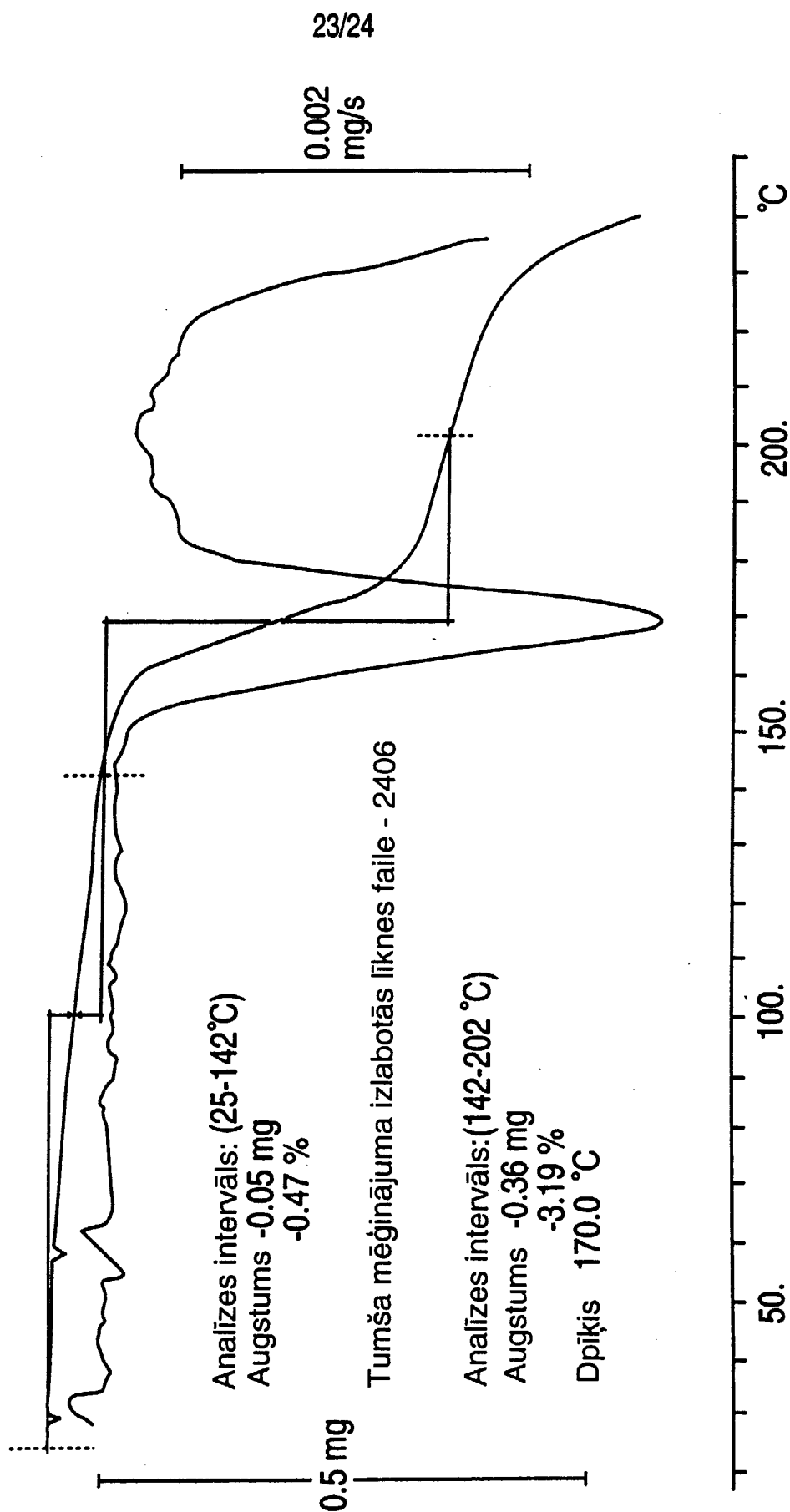
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Nātrija alendronāta PI - 19075 BM - 4103/5  
11.171 mg      Ātrums: 10.0 °C/min



8b. zīm.

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