

|       |                                                 |    |
|-------|-------------------------------------------------|----|
| <110> | HANMI PHARM. CO., LTD.                          |    |
| <120> | INSULINA DE ACCIÓN PROLONGADA Y USO DE LA MISMA |    |
| <130> | OPA14248-PCT                                    |    |
| <150> | KR 10-2014-0006938                              |    |
| <151> | 2014-01-20                                      |    |
| <160> | 40                                              |    |
| <170> | KopatentIn 2.0                                  |    |
| <210> | 1                                               |    |
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| <213> | Secuencia Artificial                            |    |
| <220> |                                                 |    |
| <223> | Cebador                                         |    |
| <400> | 1                                               |    |
|       | gggtccctgc agaagcgtgc gattgtggaa caatgctgt      | 39 |
| <210> | 2                                               |    |
| <211> | 39                                              |    |
| <212> | ADN                                             |    |
| <213> | Secuencia Artificial                            |    |
| <220> |                                                 |    |
| <223> | Cebador                                         |    |
| <400> | 2                                               |    |
|       | acagcattgt tccacaatcg cacgcttctg cagggaccc      | 39 |
| <210> | 3                                               |    |
| <211> | 39                                              |    |
| <212> | ADN                                             |    |
| <213> | Secuencia Artificial                            |    |
| <220> |                                                 |    |
| <223> | Cebador                                         |    |
| <400> | 3                                               |    |
|       | tccctgcaga agcgtggcgc ggtggaacaa tgctgtacc      | 39 |
| <210> | 4                                               |    |
| <211> | 39                                              |    |
| <212> | ADN                                             |    |
| <213> | Secuencia Artificial                            |    |
| <220> |                                                 |    |
| <223> | Cebador                                         |    |
| <400> | 4                                               |    |
|       | ggtacagcat tgttccaccg cgccacgctt ctgcaggga      | 39 |
| <210> | 5                                               |    |
| <211> | 36                                              |    |
| <212> | ADN                                             |    |
| <213> | Secuencia Artificial                            |    |
| <220> |                                                 |    |
| <223> | Cebador                                         |    |
| <400> | 5                                               |    |
|       | ctctaccagc tggaaaacgc gtgtaactga ggatcc         | 36 |
| <210> | 6                                               |    |
| <211> | 36                                              |    |
| <212> | ADN                                             |    |
| <213> | Secuencia Artificial                            |    |
| <220> |                                                 |    |
| <223> | Cebador                                         |    |
| <400> | 6                                               |    |
|       | ggatcctcag ttacacgcgt tttccagctg gtagag         | 36 |
| <210> | 7                                               |    |
| <211> | 39                                              |    |
| <212> | ADN                                             |    |
| <213> | Secuencia Artificial                            |    |
| <220> |                                                 |    |
| <223> | Cebador                                         |    |
| <400> | 7                                               |    |
|       | gttaaccaac acttgtgtgc gtcacacctg gtggaagct      | 39 |

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| <210> | 8                                          |    |  |
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| <220> |                                            |    |  |
| <223> | Cebador                                    |    |  |
| <400> | 8                                          |    |  |
|       | agcttccacc aggtgtgacg cacacaagtg ttggttaac | 39 |  |
| <210> | 9                                          |    |  |
| <211> | 39                                         |    |  |
| <212> | ADN                                        |    |  |
| <213> | Secuencia Artificial                       |    |  |
| <220> |                                            |    |  |
| <223> | Cebador                                    |    |  |
| <400> | 9                                          |    |  |
|       | ctagtgtgcg gggaacgagc gttcttctac acaccaag  | 39 |  |
| <210> | 10                                         |    |  |
| <211> | 39                                         |    |  |
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| <213> | Secuencia Artificial                       |    |  |
| <220> |                                            |    |  |
| <223> | Cebador                                    |    |  |
| <400> | 10                                         |    |  |
|       | cttgggtgtg tagaagaacg ctcgttcccc gcacactag | 39 |  |
| <210> | 11                                         |    |  |
| <211> | 39                                         |    |  |
| <212> | ADN                                        |    |  |
| <213> | Secuencia Artificial                       |    |  |
| <220> |                                            |    |  |
| <223> | Cebador                                    |    |  |
| <400> | 11                                         |    |  |
|       | gtgtgcgggg aacgaggcgc gttctacaca cccaagacc | 39 |  |
| <210> | 12                                         |    |  |
| <211> | 39                                         |    |  |
| <212> | ADN                                        |    |  |
| <213> | Secuencia Artificial                       |    |  |
| <220> |                                            |    |  |
| <223> | Cebador                                    |    |  |
| <400> | 12                                         |    |  |
|       | ggctctgggt gtgtagaacg cgcctcgttc cccgcacac | 39 |  |
| <210> | 13                                         |    |  |
| <211> | 39                                         |    |  |
| <212> | ADN                                        |    |  |
| <213> | Secuencia Artificial                       |    |  |
| <220> |                                            |    |  |
| <223> | Cebador                                    |    |  |
| <400> | 13                                         |    |  |
|       | tgcggggaac gaggcttcgc gtacacaccc aagaccgc  | 39 |  |
| <210> | 14                                         |    |  |
| <211> | 39                                         |    |  |
| <212> | ADN                                        |    |  |
| <213> | Secuencia Artificial                       |    |  |
| <220> |                                            |    |  |
| <223> | Cebador                                    |    |  |
| <400> | 14                                         |    |  |
|       | gcgggtcttg ggtgtgtacg cgaagcctcg ttccccga  | 39 |  |
| <210> | 15                                         |    |  |
| <211> | 37                                         |    |  |
| <212> | ADN                                        |    |  |
| <213> | Secuencia Artificial                       |    |  |
| <220> |                                            |    |  |
| <223> | Cebador                                    |    |  |
| <400> | 15                                         |    |  |
|       | ccagcatctg ctccctcgaa cagctggaga actactg   | 37 |  |

Spanish\_OPA14248 Sequence Listing

|                                                                    |                      |     |
|--------------------------------------------------------------------|----------------------|-----|
| <210>                                                              | 16                   |     |
| <211>                                                              | 37                   |     |
| <212>                                                              | ADN                  |     |
| <213>                                                              | Secuencia Artificial |     |
| <220>                                                              |                      |     |
| <223>                                                              | Cebador              |     |
| <400>                                                              | 16                   |     |
| cagtagttct ccagctgttc gagggagcag atgctgg                           |                      | 37  |
| <210>                                                              | 17                   |     |
| <211>                                                              | 34                   |     |
| <212>                                                              | ADN                  |     |
| <213>                                                              | Secuencia Artificial |     |
| <220>                                                              |                      |     |
| <223>                                                              | Cebador              |     |
| <400>                                                              | 17                   |     |
| cagcatctgc tccctcaacc agctggagaa ctac                              |                      | 34  |
| <210>                                                              | 18                   |     |
| <211>                                                              | 34                   |     |
| <212>                                                              | ADN                  |     |
| <213>                                                              | Secuencia Artificial |     |
| <220>                                                              |                      |     |
| <223>                                                              | Cebador              |     |
| <400>                                                              | 18                   |     |
| gtagttctcc agctgggtga gggagcagat gctg                              |                      | 34  |
| <210>                                                              | 19                   |     |
| <211>                                                              | 258                  |     |
| <212>                                                              | ADN                  |     |
| <213>                                                              | Secuencia Artificial |     |
| <220>                                                              |                      |     |
| <223>                                                              | Análogo 1            |     |
| <400>                                                              | 19                   |     |
| ttcgttaacc aacacttggtg tggctcacac ctggtggaag ctctctacct agtgtgcggg |                      | 60  |
| gaacgaggct tcttctacac acccaagacc cgccgggagg cagaggacct gcagggtggg  |                      | 120 |
| cagggtggagc tgggcggggg ccctggtgca ggcagcctgc agcccttggc cctggagggg |                      | 180 |
| tccctgcaga agcgtgcatg tgtggaacaa tgctgtacca gcatctgctc cctctaccag  |                      | 240 |
| ctggagaact actgcaac                                                |                      | 258 |
| <210>                                                              | 20                   |     |
| <211>                                                              | 86                   |     |
| <212>                                                              | PRT                  |     |
| <213>                                                              | Secuencia Artificial |     |
| <220>                                                              |                      |     |
| <223>                                                              | Análogo 1            |     |
| <400>                                                              | 20                   |     |
| Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr    |                      |     |
| 1 5 10 15                                                          |                      |     |
| Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Arg Arg    |                      |     |
| 20 25 30                                                           |                      |     |
| Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly Pro    |                      |     |
| 35 40 45                                                           |                      |     |
| Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln Lys    |                      |     |
| 50 55 60                                                           |                      |     |
| Arg Ala Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln    |                      |     |
| 65 70 75 80                                                        |                      |     |
| Leu Glu Asn Tyr Cys Asn                                            |                      |     |
| 85                                                                 |                      |     |
| <210>                                                              | 21                   |     |
| <211>                                                              | 258                  |     |
| <212>                                                              | ADN                  |     |
| <213>                                                              | Secuencia Artificial |     |
| <220>                                                              |                      |     |
| <223>                                                              | Análogo 2            |     |
| <400>                                                              | 21                   |     |
| ttcgttaacc aacacttggtg tggctcacac ctggtggaag ctctctacct agtgtgcggg |                      | 60  |

gaacgaggct tcttctacac acccaagacc cgccgggagg cagaggacct gcagggtgggg 120  
 cagggtggagc tgggcggggg ccctggtgca ggcagcctgc agcccttggc cctggagggg 180  
 tccctgcaga agcgtggcgc ggtggaacaa tgctgtacca gcatctgctc cctctaccag 240  
 ctggagaact actgcaac 258

<210> 22  
 <211> 86  
 <212> PRT  
 <213> Secuencia Artificial

<220>  
 <223> Análogo 2

<400> 22  
 Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr  
 1 5 10 15  
 Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Arg Arg  
 20 25 30  
 Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly Pro  
 35 40 45  
 Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln Lys  
 50 55 60  
 Arg Gly Ala Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln  
 65 70 75 80  
 Leu Glu Asn Tyr Cys Asn  
 85

<210> 23  
 <211> 258  
 <212> ADN  
 <213> Secuencia Artificial

<220>  
 <223> Análogo 3

<400> 23  
 ttcgttaacc aacacttggtg tggtcacac ctggtggaag ctctctacct agtgtgcggg 60  
 gaacgaggct tcttctacac acccaagacc cgccgggagg cagaggacct gcagggtgggg 120  
 cagggtggagc tgggcggggg ccctggtgca ggcagcctgc agcccttggc cctggagggg 180  
 tccctgcaga agcgtggcat tgtggaacaa tgctgtacca gcatctgctc cctctaccag 240  
 ctggagaacg cgtgcaac 258

<210> 24  
 <211> 86  
 <212> PRT  
 <213> Secuencia Artificial

<220>  
 <223> Análogo 3

<400> 24  
 Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr  
 1 5 10 15  
 Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Arg Arg  
 20 25 30  
 Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly Pro  
 35 40 45  
 Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln Lys  
 50 55 60  
 Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln  
 65 70 75 80  
 Leu Glu Asn Ala Cys Asn  
 85

<210> 25  
 <211> 258  
 <212> ADN  
 <213> Secuencia Artificial

<220>  
 <223> Análogo 4

<400> 25  
 ttcgttaacc aacacttggtg tgcgtcacac ctggtggaag ctctctacct agtgtgcggg 60  
 gaacgaggct tcttctacac acccaagacc cgccgggagg cagaggacct gcagggtgggg 120  
 cagggtggagc tgggcggggg ccctggtgca ggcagcctgc agcccttggc cctggagggg 180

## Spanish\_OPA14248 Sequence Listing

tccctgcaga agcgtggcat tgtggaacaa tgctgtacca gcatctgctc cctctaccag 240  
ctggagaact actgcaac 258

<210> 26  
<211> 86  
<212> PRT  
<213> Secuencia Artificial

<220>  
<223> Análogo 4

<400> 26  
Phe Val Asn Gln His Leu Cys Ala Ser His Leu Val Glu Ala Leu Tyr  
1 5 10 15  
Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Arg Arg  
20 25 30  
Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly Pro  
35 40 45  
Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln Lys  
50 55 60  
Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln  
65 70 75 80  
Leu Glu Asn Tyr Cys Asn  
85

<210> 27  
<211> 258  
<212> ADN  
<213> Secuencia Artificial

<220>  
<223> Análogo 5

<400> 27  
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gaacgagcgt tcttctacac acccaagacc cgccgggagg cagaggacct gcaggtgggg 120  
caggtggagc tgggcggggg ccctggtgca ggcagcctgc agcccttggc cctggagggg 180  
tccctgcaga agcgtggcat tgtggaacaa tgctgtacca gcatctgctc cctctaccag 240  
ctggagaact actgcaac 258

<210> 28  
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<212> PRT  
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<220>  
<223> Análogo 5

<400> 28  
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr  
1 5 10 15  
Leu Val Cys Gly Glu Arg Ala Phe Phe Tyr Thr Pro Lys Thr Arg Arg  
20 25 30  
Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly Pro  
35 40 45  
Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln Lys  
50 55 60  
Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln  
65 70 75 80  
Leu Glu Asn Tyr Cys Asn  
85

<210> 29  
<211> 258  
<212> ADN  
<213> Secuencia Artificial

<220>  
<223> Análogo 6

<400> 29  
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gaacgaggcg cgttctacac acccaagacc cgccgggagg cagaggacct gcaggtgggg 120  
caggtggagc tgggcggggg ccctggtgca ggcagcctgc agcccttggc cctggagggg 180  
tccctgcaga agcgtggcat tgtggaacaa tgctgtacca gcatctgctc cctctaccag 240

ctggagaact actgcaac

<210> 30  
<211> 86  
<212> PRT  
<213> Secuencia Artificial

<220>  
<223> Análogo 6

<400> 30  
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr  
1 5 10 15  
Leu Val Cys Gly Glu Arg Gly Ala Phe Tyr Thr Pro Lys Thr Arg Arg  
20 25 30  
Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly Pro  
35 40 45  
Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln Lys  
50 55 60  
Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln  
65 70 75 80  
Leu Glu Asn Tyr Cys Asn  
85

<210> 31  
<211> 258  
<212> ADN  
<213> Secuencia Artificial

<220>  
<223> Análogo 7

<400> 31  
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gaacgaggct tcgcgtacac acccaagacc cgccgggagg cagaggacct gcagggtgggg 120  
cagggtggagc tgggcggggg ccctggtgca ggcagcctgc agcccttggc cctggagggg 180  
tccctgcaga agcgtggcat tgtggaacaa tgctgtacca gcatctgctc cctctaccag 240  
ctggagaact actgcaac 258

<210> 32  
<211> 86  
<212> PRT  
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<220>  
<223> Análogo 7

<400> 32  
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr  
1 5 10 15  
Leu Val Cys Gly Glu Arg Gly Phe Ala Tyr Thr Pro Lys Thr Arg Arg  
20 25 30  
Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly Pro  
35 40 45  
Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln Lys  
50 55 60  
Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln  
65 70 75 80  
Leu Glu Asn Tyr Cys Asn  
85

<210> 33  
<211> 261  
<212> ADN  
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<220>  
<223> Análogo 8

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gaacgaggct tcttctacac acccaagacc cgccgggagg cagaggacct gcagggtgggg 120  
cagggtggagc tgggcggggg ccctggtgca ggcagcctgc agcccttggc cctggagggg 180  
tccctgcaga agcgtggcat tgtggaacaa tgctgtacca gcatctgctc cctcgaacag 240  
ctggagaact actgcaactg a 261

<210> 34  
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 <212> PRT  
 <213> Secuencia Artificial

<220>  
 <223> Análogo 8

<400> 34  
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 Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Arg Arg  
 20 25 30  
 Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly Pro  
 35 40 45  
 Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln Lys  
 50 55 60  
 Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Glu Gln  
 65 70 75 80  
 Leu Glu Asn Tyr Cys Asn  
 85

<210> 35  
 <211> 261  
 <212> ADN  
 <213> Secuencia Artificial

<220>  
 <223> Análogo 9

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 gaacgaggct tcttctacac acccaagacc cgccgggagg cagaggacct gcagggtggg 120  
 cagggtggagc tgggcggggg ccctggtgca ggcagcctgc agcccttggc cctggagggg 180  
 tccctgcaga agcgtggcat tgtggaacaa tgctgtacca gcatctgctc cctcaaccag 240  
 ctggagaact actgcaactg a 261

<210> 36  
 <211> 86  
 <212> PRT  
 <213> Secuencia Artificial

<220>  
 <223> Análogo 9

<400> 36  
 Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr  
 1 5 10 15  
 Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr Arg Arg  
 20 25 30  
 Glu Ala Glu Asp Leu Gln Val Gly Gln Val Glu Leu Gly Gly Gly Pro  
 35 40 45  
 Gly Ala Gly Ser Leu Gln Pro Leu Ala Leu Glu Gly Ser Leu Gln Lys  
 50 55 60  
 Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Asn Gln  
 65 70 75 80  
 Leu Glu Asn Tyr Cys Asn  
 85

<210> 37  
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 <212> PRT  
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<220>  
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<220>  
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 <222> (1)  
 <223> Xaa es Gly o Ala

<220>  
 <221> VARIANTE  
 <222> (2)  
 <223> Xaa es Ile o Ala

<220>  
 <221> VARIANTE  
 <222> (14)

<223> Xaa es Tyr, Glu, o Asn

<220>  
 <221> VARIANTE  
 <222> (19)  
 <223> Xaa es Tyr o Ala

<400> 37  
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 Glu Asn Xaa Cys Asn  
 20

<210> 38  
 <211> 30  
 <212> PRT  
 <213> Secuencia Artificial

<220>  
 <223> cadena B del análogo de insulina

<220>  
 <221> VARIANTE  
 <222> (8)  
 <223> Xaa es Gly o Ala

<220>  
 <221> VARIANTE  
 <222> (23)  
 <223> Xaa es Gly o Ala

<220>  
 <221> VARIANTE  
 <222> (24)  
 <223> Xaa es Phe o Ala

<220>  
 <221> VARIANTE  
 <222> (25)  
 <223> Xaa es Phe o Ala

<400> 38  
 Phe Val Asn Gln His Leu Cys Xaa Ser His Leu Val Glu Ala Leu Tyr  
 1 5 10 15  
 Leu Val Cys Gly Glu Arg Xaa Xaa Xaa Tyr Thr Pro Lys Thr  
 20 25 30

<210> 39  
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 <212> PRT  
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<220>  
 <223> cadena A de Insulina

<400> 39  
 Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys Ser Leu Tyr Gln Leu  
 1 5 10 15  
 Glu Asn Tyr Cys Asn  
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<210> 40  
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 <212> PRT  
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<220>  
 <223> cadena B de Insulina

<400> 40  
 Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr  
 1 5 10 15  
 Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr  
 20 25 30