SEQUENCE LISTING

<110> SYNTAXIN LIMITED
IPSEN BIOPHARM LIMITED

<120> Recombinant Clostridium botulinum neurotoxins

<130> P39711WO

<150> GB 1219602.8
<151> 2012-10-31

<160> 3

<170> PatentIn version 3.5

<210> 1
<211> 3759
<212> DNA
<213> Artificial Sequence

<220>
<223> Optimised BoNT/E1 nucleic acid sequence

<400> 1
atgccgaaaa tcaactcttt caactacaac gacccggtta acgaccgtac catcctgtat 60

atcaaaccgg gtggttgcca ggagttctac aaatctttca acatcatgaa aaacatctgg 120

atcatcccgg aacgtaacgt tatcggtacc accccgcagg acttccaccc gccgacctct 180

ctgaaaaacg gtgactcttc ttactacgac ccgaactacc tccagtctga cgaagaaaaa 240

gaccgtttcc tgaaaatcgt taccaaaatc ttcaaccgta tcaacaacaa cctgtctggt 300

ggtatcctgc tggaagaact gtctaaagct aacccgtacc tgggtaacga caacaccccg 360

gacaaccagt tccacatcgg tgacgcttct gctgttgaaa tcaaattctc taacggttct 420

caggacatcc tgctgccgaa cgttatcatc atgggtgctg aaccggacct gttcgaaacc 480

aactcttcta acatctctct gcgtaacaac tacatgccgt ctaaccacgg tttcggttct 540

atcgctatcg ttaccttctc tccggaatac tctttccgtt tcaacgacaa cagcatgaac 600

gagttcatcc aggacccggc tctgaccctg atgcacgaac tgatccactc tctgcacggt 660

ctgtacggtg ctaaaggtat caccaccaaa tacaccatca cccagaaaca gaacccgctg 720

atcaccaaca tccgtggtac caacatcgaa gagttcctga ccttcggtgg taccgacctg 780

aacatcatca cctctgctca gtctaacgac atctacacca acctgctggc tgactacaaa 840

aaaatcgctt ctaaactgtc taaagttcag gtttctaacc cgctgctgaa cccgtacaaa 900

gacgttttcg aagctaaata cggtctggac aaagacgctt ctggtatcta ctctgttaac 960

atcaacaaat tcaacgacat cttcaaaaaa ctgtactctt tcaccgagtt cgacctggcg 1020

accaaattcc aggttaaatg ccgtcagacc tacatcggtc agtacaaata cttcaaactg 1080

tctaacctgc tgaacgactc tatctacaac atctctgaag gttacaacat caacaacctg 1140

aaagttaact tccgtggtca gaacgctaac ctgaacccgc gtatcatcac cccgatcacc 1200

ggtcgtggtc tggttaaaaa aatcatccgt ttctgcaaga atattgtaag cgttaaagga 1260

ataagaaaaa gtatctgcat cgaaatcaac aacggtgaac tgttcttcgt tgcttctgaa 1320

aactcttaca acgacgacaa catcaacacc ccgaaagaaa tcgacgacac cgttacctct 1380

aacaacaact acgaaaacga cctggaccag gttatcctga acttcaactc tgaatctgct 1440

ccgggtctgt ctgacgaaaa actgaacctg accatccaga acgacgctta catcccgaaa 1500

tacgactcta acggtacctc tgacatcgaa cagcacgacg ttaacgaact gaacgttttc 1560

ttctacctgg acgctcagaa agttccggaa ggtgaaaaca acgttaacct gacctcttct 1620

atcgacaccg ctctgctgga acagccgaaa atctacacct tcttctcttc tgagttcatc 1680

aacaacgtta acaaaccggt tcaggctgct ctgttcgttt cttggattca gcaggttctg 1740

gttgacttca ccaccgaagc taaccagaaa tctaccgttg acaaaatcgc tgacatctct 1800

atcgttgttc cgtacatcgg tctggctctg aacatcggta acgaagctca gaaaggtaac 1860

ttcaaagacg ctctggaact gctgggtgct ggtatcctgc tggagttcga accggaactg 1920

ctgatcccga ccatcctggt tttcaccatc aaatctttcc tgggttcttc tgacaacaaa 1980

aacaaagtta tcaaagctat caacaacgct ctgaaagaac gtgacgaaaa atggaaagaa 2040

gtttactctt tcatcgtttc taactggatg accaaaatca acacccagtt caacaaacgt 2100

aaagaacaga tgtaccaggc tctccagaac caggttaacg ctatcaaaac catcatcgaa 2160

tctaaataca actcttacac cctggaagaa aaaaacgaac tgaccaacaa atacgacatc 2220

aaacagatcg aaaacgaact gaaccagaaa gtttctatcg ctatgaacaa catcgaccgt 2280

ttcctgaccg aatcttctat ctcttacctg atgaaactca tcaacgaagt taaaatcaac 2340

aaactgcgtg aatacgacga aaacgttaaa acctacctgc tgaactacat catccagcac 2400

ggttctatcc tgggtgaatc tcagcaggaa ctgaactcta tggttaccga caccctgaac 2460

aactctatcc cgttcaaact gtcttcttac accgacgaca aaatcctgat ctcttacttc 2520

aacaaattct ttaaacgcat taagagttca tcggttctga atatgcggta caaaaatgat 2580

aaatatgtcg atacttctgg atatgatagc aatatcaaca ttaacggcga cgtgtataaa 2640

tatccgacaa ataaaaacca gtttgggata tataacgaca agctgtcgga ggtcaatatt 2700

tctcaaaacg actatatcat ttacgataat aaatataaaa actttagcat tagtttttgg 2760

gttcgtatac ctaattatga caataaaatt gtaaatgtga ataacgagta taccattata 2820

aactgtatgc gcgacaataa cagtggttgg aaggtatcgc tgaaccataa tgagattatc 2880

tggaccctgc aggataatgc aggtataaac cagaaactgg cttttaacta tggaaacgca 2940

aatgggatct cagattacat taataaatgg atttttgtta ccattacgaa cgatcgctta 3000

ggcgactcaa aactttatat taatggcaat ctgatagatc agaaatcaat cttaaatttg 3060

ggcaatattc atgtctctga taacatcttg ttcaagatcg ttaattgcag ttacactcgt 3120

tatattggca ttcgttactt taatatcttc gataaagaac tggacgagac ggaaatccag 3180

actctgtatt caaacgagcc caatactaat atattgaaag atttttgggg taactatctt 3240

ttatatgata aagaatacta tctcctgaat gtattgaagc caaacaattt catagataga 3300

cgcaaggata gcacattaag tatcaacaat atcagatcta ctatactgtt agcaaatcgc 3360

ctctactccg gtattaaagt gaagattcag cgggttaata actccagtac caatgataat 3420

ctggtccgta agaacgatca ggtatacatc aatttcgtcg cgagcaaaac tcatctcttc 3480

ccgctttacg ccgatacagc tacgacaaac aaggaaaaaa ccataaaaat ttccagctcc 3540

ggaaacagat tcaatcaagt agttgtaatg aactctgtgg gtaataattg tacgatgaac 3600

tttaagaata acaatgggaa caatattgga cttttgggct tcaaagccga cacagtggtg 3660

gcgtccacct ggtattacac gcacatgcgg gaccatacga attcgaacgg ttgcttctgg 3720

aactttatct cggaagaaca cgggtggcaa gaaaaataa 3759

<210> 2
<211> 1252
<212> PRT
<213> Clostridium botulinum

<400> 2

Met Pro Lys Ile Asn Ser Phe Asn Tyr Asn Asp Pro Val Asn Asp Arg
1 5 10 15

Thr Ile Leu Tyr Ile Lys Pro Gly Gly Cys Gln Glu Phe Tyr Lys Ser
20 25 30

Phe Asn Ile Met Lys Asn Ile Trp Ile Ile Pro Glu Arg Asn Val Ile
35 40 45

Gly Thr Thr Pro Gln Asp Phe His Pro Pro Thr Ser Leu Lys Asn Gly
50 55 60

Asp Ser Ser Tyr Tyr Asp Pro Asn Tyr Leu Gln Ser Asp Glu Glu Lys
65 70 75 80

Asp Arg Phe Leu Lys Ile Val Thr Lys Ile Phe Asn Arg Ile Asn Asn
85 90 95

Asn Leu Ser Gly Gly Ile Leu Leu Glu Glu Leu Ser Lys Ala Asn Pro
100 105 110

Tyr Leu Gly Asn Asp Asn Thr Pro Asp Asn Gln Phe His Ile Gly Asp
115 120 125

Ala Ser Ala Val Glu Ile Lys Phe Ser Asn Gly Ser Gln Asp Ile Leu
130 135 140

Leu Pro Asn Val Ile Ile Met Gly Ala Glu Pro Asp Leu Phe Glu Thr
145 150 155 160

Asn Ser Ser Asn Ile Ser Leu Arg Asn Asn Tyr Met Pro Ser Asn His
165 170 175

Gly Phe Gly Ser Ile Ala Ile Val Thr Phe Ser Pro Glu Tyr Ser Phe

180 185 190

Arg Phe Asn Asp Asn Ser Met Asn Glu Phe Ile Gln Asp Pro Ala Leu
195 200 205

Thr Leu Met His Glu Leu Ile His Ser Leu His Gly Leu Tyr Gly Ala
210 215 220

Lys Gly Ile Thr Thr Lys Tyr Thr Ile Thr Gln Lys Gln Asn Pro Leu
225 230 235 240

Ile Thr Asn Ile Arg Gly Thr Asn Ile Glu Glu Phe Leu Thr Phe Gly
245 250 255

Gly Thr Asp Leu Asn Ile Ile Thr Ser Ala Gln Ser Asn Asp Ile Tyr
260 265 270

Thr Asn Leu Leu Ala Asp Tyr Lys Lys Ile Ala Ser Lys Leu Ser Lys
275 280 285

Val Gln Val Ser Asn Pro Leu Leu Asn Pro Tyr Lys Asp Val Phe Glu
290 295 300

Ala Lys Tyr Gly Leu Asp Lys Asp Ala Ser Gly Ile Tyr Ser Val Asn
305 310 315 320

Ile Asn Lys Phe Asn Asp Ile Phe Lys Lys Leu Tyr Ser Phe Thr Glu
325 330 335

Phe Asp Leu Ala Thr Lys Phe Gln Val Lys Cys Arg Gln Thr Tyr Ile
340 345 350

Gly Gln Tyr Lys Tyr Phe Lys Leu Ser Asn Leu Leu Asn Asp Ser Ile
355 360 365

Tyr Asn Ile Ser Glu Gly Tyr Asn Ile Asn Asn Leu Lys Val Asn Phe
370 375 380

Arg Gly Gln Asn Ala Asn Leu Asn Pro Arg Ile Ile Thr Pro Ile Thr
385 390 395 400

Gly Arg Gly Leu Val Lys Lys Ile Ile Arg Phe Cys Lys Asn Ile Val
405 410 415

Ser Val Lys Gly Ile Arg Lys Ser Ile Cys Ile Glu Ile Asn Asn Gly
420 425 430

Glu Leu Phe Phe Val Ala Ser Glu Asn Ser Tyr Asn Asp Asp Asn Ile
435 440 445

Asn Thr Pro Lys Glu Ile Asp Asp Thr Val Thr Ser Asn Asn Asn Tyr

```
    450                 455                 460

Glu Asn Asp Leu Asp Gln Val Ile Leu Asn Phe Asn Ser Glu Ser Ala
465                 470                 475                 480

Pro Gly Leu Ser Asp Glu Lys Leu Asn Leu Thr Ile Gln Asn Asp Ala
                485                 490                 495

Tyr Ile Pro Lys Tyr Asp Ser Asn Gly Thr Ser Asp Ile Glu Gln His
            500                 505                 510

Asp Val Asn Glu Leu Asn Val Phe Phe Tyr Leu Asp Ala Gln Lys Val
        515                 520                 525

Pro Glu Gly Glu Asn Asn Val Asn Leu Thr Ser Ser Ile Asp Thr Ala
    530                 535                 540

Leu Leu Glu Gln Pro Lys Ile Tyr Thr Phe Phe Ser Ser Glu Phe Ile
545                 550                 555                 560

Asn Asn Val Asn Lys Pro Val Gln Ala Ala Leu Phe Val Ser Trp Ile
                565                 570                 575

Gln Gln Val Leu Val Asp Phe Thr Thr Glu Ala Asn Gln Lys Ser Thr
            580                 585                 590

Val Asp Lys Ile Ala Asp Ile Ser Ile Val Val Pro Tyr Ile Gly Leu
        595                 600                 605

Ala Leu Asn Ile Gly Asn Glu Ala Gln Lys Gly Asn Phe Lys Asp Ala
    610                 615                 620

Leu Glu Leu Leu Gly Ala Gly Ile Leu Leu Glu Phe Glu Pro Glu Leu
625                 630                 635                 640

Leu Ile Pro Thr Ile Leu Val Phe Thr Ile Lys Ser Phe Leu Gly Ser
                645                 650                 655

Ser Asp Asn Lys Asn Lys Val Ile Lys Ala Ile Asn Asn Ala Leu Lys
            660                 665                 670

Glu Arg Asp Glu Lys Trp Lys Glu Val Tyr Ser Phe Ile Val Ser Asn
        675                 680                 685

Trp Met Thr Lys Ile Asn Thr Gln Phe Asn Lys Arg Lys Glu Gln Met
    690                 695                 700

Tyr Gln Ala Leu Gln Asn Gln Val Asn Ala Ile Lys Thr Ile Ile Glu
705                 710                 715                 720

Ser Lys Tyr Asn Ser Tyr Thr Leu Glu Glu Lys Asn Glu Leu Thr Asn
```

725 730 735

Lys Tyr Asp Ile Lys Gln Ile Glu Asn Glu Leu Asn Gln Lys Val Ser
740 745 750

Ile Ala Met Asn Asn Ile Asp Arg Phe Leu Thr Glu Ser Ser Ile Ser
755 760 765

Tyr Leu Met Lys Leu Ile Asn Glu Val Lys Ile Asn Lys Leu Arg Glu
770 775 780

Tyr Asp Glu Asn Val Lys Thr Tyr Leu Leu Asn Tyr Ile Ile Gln His
785 790 795 800

Gly Ser Ile Leu Gly Glu Ser Gln Gln Glu Leu Asn Ser Met Val Thr
805 810 815

Asp Thr Leu Asn Asn Ser Ile Pro Phe Lys Leu Ser Ser Tyr Thr Asp
820 825 830

Asp Lys Ile Leu Ile Ser Tyr Phe Asn Lys Phe Phe Lys Arg Ile Lys
835 840 845

Ser Ser Ser Val Leu Asn Met Arg Tyr Lys Asn Asp Lys Tyr Val Asp
850 855 860

Thr Ser Gly Tyr Asp Ser Asn Ile Asn Ile Asn Gly Asp Val Tyr Lys
865 870 875 880

Tyr Pro Thr Asn Lys Asn Gln Phe Gly Ile Tyr Asn Asp Lys Leu Ser
885 890 895

Glu Val Asn Ile Ser Gln Asn Asp Tyr Ile Ile Tyr Asp Asn Lys Tyr
900 905 910

Lys Asn Phe Ser Ile Ser Phe Trp Val Arg Ile Pro Asn Tyr Asp Asn
915 920 925

Lys Ile Val Asn Val Asn Asn Glu Tyr Thr Ile Ile Asn Cys Met Arg
930 935 940

Asp Asn Asn Ser Gly Trp Lys Val Ser Leu Asn His Asn Glu Ile Ile
945 950 955 960

Trp Thr Leu Gln Asp Asn Ala Gly Ile Asn Gln Lys Leu Ala Phe Asn
965 970 975

Tyr Gly Asn Ala Asn Gly Ile Ser Asp Tyr Ile Asn Lys Trp Ile Phe
980 985 990

Val Thr Ile Thr Asn Asp Arg Leu Gly Asp Ser Lys Leu Tyr Ile Asn

995 1000 1005

Gly Asn Leu Ile Asp Gln Lys Ser Ile Leu Asn Leu Gly Asn Ile
1010 1015 1020

His Val Ser Asp Asn Ile Leu Phe Lys Ile Val Asn Cys Ser Tyr
1025 1030 1035

Thr Arg Tyr Ile Gly Ile Arg Tyr Phe Asn Ile Phe Asp Lys Glu
1040 1045 1050

Leu Asp Glu Thr Glu Ile Gln Thr Leu Tyr Ser Asn Glu Pro Asn
1055 1060 1065

Thr Asn Ile Leu Lys Asp Phe Trp Gly Asn Tyr Leu Leu Tyr Asp
1070 1075 1080

Lys Glu Tyr Tyr Leu Leu Asn Val Leu Lys Pro Asn Asn Phe Ile
1085 1090 1095

Asp Arg Arg Lys Asp Ser Thr Leu Ser Ile Asn Asn Ile Arg Ser
1100 1105 1110

Thr Ile Leu Leu Ala Asn Arg Leu Tyr Ser Gly Ile Lys Val Lys
1115 1120 1125

Ile Gln Arg Val Asn Asn Ser Ser Thr Asn Asp Asn Leu Val Arg
1130 1135 1140

Lys Asn Asp Gln Val Tyr Ile Asn Phe Val Ala Ser Lys Thr His
1145 1150 1155

Leu Phe Pro Leu Tyr Ala Asp Thr Ala Thr Thr Asn Lys Glu Lys
1160 1165 1170

Thr Ile Lys Ile Ser Ser Ser Gly Asn Arg Phe Asn Gln Val Val
1175 1180 1185

Val Met Asn Ser Val Gly Asn Asn Cys Thr Met Asn Phe Lys Asn
1190 1195 1200

Asn Asn Gly Asn Asn Ile Gly Leu Leu Gly Phe Lys Ala Asp Thr
1205 1210 1215

Val Val Ala Ser Thr Trp Tyr Tyr Thr His Met Arg Asp His Thr
1220 1225 1230

Asn Ser Asn Gly Cys Phe Trp Asn Phe Ile Ser Glu Glu His Gly
1235 1240 1245

Trp Gln Glu Lys

1250

<210> 3
<211> 3759
<212> DNA
<213> Clostridium botulinum

<400> 3
atgccaaaaa ttaatagttt taattataat gatcctgtta atgatagaac aattttatat 60
attaaaccag gcggttgtca agaattttat aaatcattta atattatgaa aaatatttgg 120
ataattccag agagaaatgt aattggtaca acccccaag attttcatcc gcctacttca 180
ttaaaaaatg gagatagtag ttattatgac cctaattatt tacaaagtga tgaagaaaag 240
gatagatttt taaaaatagt cacaaaaata tttaatagaa taaataataa tctttcagga 300
gggattttat tagaagaact gtcaaaagct aatccatatt tagggaatga taatactcca 360
gataatcaat tccatattgg tgatgcatca gcagttgaga ttaaattctc aaatggtagc 420
caagacatac tattacctaa tgttattata atgggagcag agcctgattt atttgaaact 480
aacagttcca atatttctct aagaaataat tatatgccaa gcaatcacgg ttttggatca 540
atagctatag taacattctc acctgaatat tcttttagat ttaatgataa tagtatgaat 600
gaatttattc aagatcctgc tcttacatta atgcatgaat taatacattc attacatgga 660
ctatatgggg ctaaagggat tactacaaag tatactataa cacaaaaaca aaatccccta 720
ataacaaata taagaggtac aaatattgaa gaattcttaa cttttggagg tactgattta 780
aacattatta ctagtgctca gtccaatgat atctatacta atcttctagc tgattataaa 840
aaaatagcgt ctaaacttag caaagtacaa gtatctaatc cactacttaa tccttataaa 900
gatgtttttg aagcaaagta tggattagat aaagatgcta gcggaattta ttcggtaaat 960
ataaacaaat ttaatgatat ttttaaaaaa ttatacagct ttacggaatt tgatttagca 1020
actaaatttc aagttaaatg taggcaaact tatattggac agtataaata cttcaaactt 1080
tcaaacttgt taaatgattc tatttataat atatcagaag gctataatat aaataattta 1140
aaggtaaatt ttagaggaca gaatgcaaat ttaaatccta gaattattac accaattaca 1200
ggtagaggac tagtaaaaaa aatcattaga ttttgtaaaa atattgtttc tgtaaaaggc 1260
ataaggaaat caatatgtat cgaaataaat aatggtgagt tatttttttgt ggcttccgag 1320
aatagttata atgatgataa tataaatact cctaaagaaa ttgacgatac agtaacttca 1380
aataataatt atgaaaatga tttagatcag gttatttttaa attttaatag tgaatcagca 1440
cctggacttt cagatgaaaa attaaattta actatccaaa atgatgctta tataccaaaa 1500
tatgattcta atggaacaag tgatatagaa caacatgatg ttaatgaact taatgtattt 1560
ttctatttag atgcacagaa agtgcccgaa ggtgaaaata atgtcaatct cacctcttca 1620
attgatacag cattattaga acaacctaaa atatatacat ttttttcatc agaatttatt 1680
aataatgtca ataaacctgt gcaagcagca ttatttgtaa gctggataca acaagtgtta 1740
gtagatttta ctactgaagc taaccaaaaa agtactgttg ataaaattgc agatatttct 1800

atagttgttc catatatagg tcttgcttta aatataggaa atgaagcaca aaaaggaaat 1860
tttaaagatg cacttgaatt attaggagca ggtattttat tagaatttga acccgagctt 1920
ttaattccta caattttagt attcacgata aaatcttttt taggttcatc tgataataaa 1980
aataaagtta ttaaagcaat aaataatgca ttgaaagaaa gagatgaaaa atggaaagaa 2040
gtatatagtt ttatagtatc gaattggatg actaaaatta atacacaatt taataaaaga 2100
aaagaacaaa tgtatcaagc tttacaaaat caagtaaatg caattaaaac aataatagaa 2160
tctaagtata atagttatac tttagaggaa aaaaatgagc ttacaaataa atatgatatt 2220
aagcaaatag aaaatgaact taatcaaaag gtttctatag caatgaataa tatagacagg 2280
ttcttaactg aaagttctat atcctattta atgaaattaa taaatgaagt aaaaattaat 2340
aaattaagag aatatgatga gaatgtcaaa acgtatttat tgaattatat tatacaacat 2400
ggatcaatct tgggagagag tcagcaagaa ctaaattcta tggtaactga taccctaaat 2460
aatagtattc cttttaagct ttcttcttat acagatgata aaattttaat ttcatatttt 2520
aataaattct ttaagagaat taaaagtagt tcagttttaa atatgagata taaaaatgat 2580
aaatacgtag atacttcagg atatgattca aatataaata ttaatggaga tgtatataaa 2640
tatccaacta ataaaaatca atttggaata tataatgata aacttagtga agttaatata 2700
tctcaaaatg attacattat atatgataat aaatataaaa attttagtat tagtttttgg 2760
gtaagaattc ctaactatga taataagata gtaaatgtta ataatgaata cactataata 2820
aattgtatga gagataataa ttcaggatgg aaagtatctc ttaatcataa tgaaataatt 2880
tggacattgc aagataatgc aggaattaat caaaaattag catttaacta tggtaacgca 2940
aatggtattt ctgattatat aaataagtgg atttttgtaa ctataactaa tgatagatta 3000
ggagattcta aactttatat taatggaaat ttaatagatc aaaaatcaat tttaaattta 3060
ggtaatattc atgttagtga caatatatta tttaaaatag ttaattgtag ttatacaaga 3120
tatattggta ttagatattt taatattttt gataaagaat tagatgaaac agaaattcaa 3180
actttatata gcaatgaacc taatacaaat attttgaagg atttttgggg aaattatttg 3240
ctttatgaca aagaatacta tttattaaat gtgttaaaac caaataactt tattgatagg 3300
agaaaagatt ctactttaag cattaataat ataagaagca ctattctttt agctaataga 3360
ttatatagtg gaataaaagt taaaatacaa agagttaata atagtagtac taacgataat 3420
cttgttagaa agaatgatca ggtatatatt aattttgtag ccagcaaaac tcacttattt 3480
ccattatatg ctgatacagc taccacaaat aaagagaaaa caataaaaat atcatcatct 3540
ggcaatagat ttaatcaagt agtagttatg aattcagtag gaaataattg tacaatgaat 3600
tttaaaaata ataatggaaa taatattggg ttgttaggtt tcaaggcaga tactgtagtt 3660
gctagtactt ggtattatac acatatgaga gatcatacaa acagcaatgg atgtttttgg 3720
aactttattt ctgaagaaca tggatggcaa gaaaaataa 3759