<별지2>

<안전성·유효성 심사관련 제출자료목록>

○ 관련규정 : 생물학적제제등의허가및심사에관한규정 (식품의약품안전청고시 제2003-26호, 2003.5.23.) 제19조제1항 및 [별표2] III. 5. 기타 따로 분류되지 않은 품목

구분 \ 자료번호	1	2	3		4						5			6		7	8
			가	나	가	나	다	라	마	바	가	나	다	가	나		
1. 제출자료	○	○	○	△	○	△	△	△	△	△	○	△	△	○	×	○	○
2. 제출여부	○	○	○	○	○	○	○	○	×	○	○	○	○	○	×	○	○
3. 면제사유	4호마목의 자료는 면제사유서로 갈음																

○ 제출자료목록

1. 기원 또는 발견 및 개발경위에 관한 자료

2. 구조결정·물리화학적 성질 및 생물학적 성질에 관한 자료(자사기준및시험방법 포함)

3. 안정성에 관한 자료
   가. 장기보존시험 또는 가속시험자료 :
      1) 24개월 장기보존시험자료
      2) 12개월 가속시험자료
   나. 가혹시험자료 :
      1) 3개월 가혹시험자료
      2) 광 가혹시험자료 (146.4 시간, 1.48 million Lux / hours)

4. 독성에 관한 자료
   가. 단회투여독성시험자료
      1) Single dose subcutaneous toxicity study in Sprague-Dawley Rat
      2) Single dose intravenous toxicity study in Sprague-Dawley Rat
      3) Single dose subcutaneous toxicity study in NMRI mice
      4) Single dose intraveneous toxicity study in NMRI mice

나. 반복투여독성시험자료

1) Six Month Subcutaneous Toxicity Study in the Dog
2) Addendum D (NN980224): Toxicokinetics from: Six Month Subcutaneous Toxicity in the Dog
3) Addendum E (NN980011): Antibodies against NN304 in Sample from Study NN960241 (Six Month Subcutaneous Toxicity in the Dog)
4) Twelve Month Subcutaneous Toxicity Study in the Dog
5) Addendum D (NN980169): Antibodies against NN304 in Samples from Study NN960242 (Twelve Month Subcutaneous Toxicity in the Dog)
6) Addendum E (NN990052): Toxicokinetics from: Twelve Month Subcutaneous Toxicity in the Dog
7) Four week subcutaneous toxicity study in the rats
8) Antibody against NN304 in samples from study No. NN960243 (six months subcutaneous toxicity study in the rat)
9) NN304 investigation of the proliferation activity in mammary tisssue from female rats in the study NN960243
10) 2 week subcutaneous dose range finding study in Sprague-Dawley rats
11) Maximum tolerated dose study by subcutaneous administration to Beagle dog
12) Four week subcutaneous toxicity study in the dog
13) A pilot study in the female rabbit by subcutaneous administration
14) Three month subcutaneous toxicity study in the rat followed by a four week recovery period
15) Three month subcutaneous toxicity study in the dog followed by a four-week recovery period
16) Toxicokinetics from : Maximum tolerated dose (MTD) followed by a 4-7 weeks fixed dose subcutaneous toxicity study in the dog
17) Analysis report concerning anti-NN304 antibody and quantification of NN304 in serum from rats from study No. NN950175
18) Analysis report concerning anti-NN304 antibodies and quantification of NN304 in plasma from dogs from study no. 950423
19) Assessment of blood glucose levels in rats given high or low energy diet after dosing with NN304 for 4 days
20) Toxicokinetics from: Four weeks subcutaneous toxicity study in th rats
21) Six months subcutaneous toxicity in the rat

22) Toxicokinetics from: four weeks subcutaneous toxicity study in the dog
23) Toxicokinetics from: A pilot study by subcutaneous administration in the female rabbits
24) Quantification of NN304 and anti-NN304 antibodies in serum from study NN960007 (three months subcutaneous toxicity study in the dog followed by a four week recovery period)
25) Toxicokinetics from: Three month toxicity study in the dog followed by a four week recovery period
26) Toxicokinetics from NN304: Three month toxicity study in the rat followed by four week recovery study
27) Toxicokinetics from: six months subcutaneous toxicity study in the rat

다. 생식·발생독성시험자료

1) A Range Finding Study of Effects on Fertility and Embryofeotal Development in the Rat by Subcutaneous Injection
2) Toxicokinetics from: A Range Finding Study on Fertility and Embryofoetal Development by Subcutaneous Administration in the Rat
3) A Study of Effects on Fertility and Embryofoetal Development in the Rat by Subcutaneous Injection
4) Toxicokinetics from: A Study of Fertility and Embryofoetal Development by Subcutaneous Administration in the Rat
5) A Dose Range Finding Study in the Pregnant Rabbit by Subcutaneous Injection
6) Toxicokinetics from: A Dose Range Finding Study by Subcutaneous Administration in the Pregnant Rabbit
7) A Study of Effects on Embryofoetal Development in the Rabbit by Subcutaneous Injection
8) Toxicokinetics from: A Study for Effects on Embryofoetal Development by Subcutaneous Administration in the Rabbit
9) Preliminary Study of Effects on the Pre-and Post-Natal Development in CD Rats by Subcutaneous Administration
10) Appendix 19 to NN990122: Toxicokinetics from: Preliminary Study of Effects on Pre- and Post-Natal Development in CD Rats by Subcutaneous Administration
11) Study of Effects on the Pre- and Post-Natal Development in CD Rats by Subcutaneous Administration

라. 유전독성시험자료

1) Reverse Mutation in four Histidine-Requiring Strains of *Salmonella typhimurium* and two Tryptophan-Requiring Strains of *Escherichia coli*
2) Induction of Chromosome Abberation in Cultured Human Peripheral Blood Lymphocytes
3) Induction of Micronuclei in the Bone Marrow of Treated Mice

마. 기타독성시험자료

1) Local Toxicity 2 and 5 Days after Subcutaneous Injection in Pigs
2) Insulin Detemir 1200 and 2400nmol/ml. Local Toxicity 2 and 5 Days after Subcutaneous Injection in Pigs

5. 약리작용에 관한 자료

가. 효력시험자료

1) 정상혈당클램프 쥐에서의 NN304의 효력(Potency of NN304 in euglycaemic clamped rats)
2) 개에서의 NN304의 대사지연의 메카니즘: 알부민에 의한 NN304 체류
3) NN304 또는 Protaphane의 피하투여 후의 정상 혈당 clamp 시험(Euglycemic glucose clamp after s.c. injection of NN304 or Protaphane)

나. 일반약리시험자료

1) Assessment of effects in the Lrwin observation test following subcutaneous administration to NMRI mice.
2) Effect on the sleeping time induced by hexobarbitone in the mouse.
3) Effect on the sleeping time induced by alcohol in the mouse.
4) Assessment of potential anti-convulsion activity following single subcutaneous administration to CD-1 mice.
5) Assessment of potential pro-convulsion activity following single subcutaneous administration to CD-1 mice.
6) Assessment of potential analgesic effects on acetic acid induced writhing following single subcutaneous administration to CD-1 mice.
7) Effect on the body temperature in the rat.
8) Effect on the cardiovascular and respiratory system in the rat.
9) Plasma levels following subcutaneous administration to the anesthetized rat.
10) Effect on the cardiovascular and respiratory system in the dog.
11) Effect on the renal function in the rats.
12) Effect on the isolated ileum of the guinea pig.
13) Effect in the intestinal mobility (Chacoal propulsion) in the mouse.

다. 흡수, 분포, 대사, 배설시험자료

1) Absorption, distribution, metabolism and excretion of radioactivity following subcutaneous administration of ^{125}I-Tyr(A14)-NN304 and ^{14}C-tetradecanoyl (Lys B29)-NN304 to Rats (NN960497)
2) The disposition of total radioactivity in the dog following subcutaneous administration of ^{125}I-Tyr(A14)-NN304 and ^{14}C-tetradecanoyl(Lys B29)-NN304 (NN97005)
3) The disposition of total radioactivity in the dog following subcutaneous administration of ^{125}I-Tyr(A14)-NN304 and ^{14}C-tetradecanoyl(Lys B29)-NN304 (NN980077)
4) Pharmacokinetics of NN304 in male and female beagle dongs after single intravenous and subcutaneous dosing (NN95033).
5) Pharmacokinetics and plasma glucose reduction in the dog following sigle IV and SC administration (NN960271)
6) 암컷과 수컷 MVM mice에 단회 iv와 sc 투여 후의 NN304의 약동학 (Pharmacokinetics of NN304 in Male and Female MVM mice after Single Intravenous and Subcutameous dosing.)
7) ^{125}I-Tyr(A14)-NN304 and ^{14}C-tetradecanoyl(Lys[B29])-NN304. Absorption, Distribution, Metabolism and Excretion of Radioactivity Following Subcutaneous Administration to Rats. (NN970177)
8) ^{125}I-Tyr(A14)-NN304 and ^{14}C-tetradecanoyl(Lys[B29])-NN304. Absorption, Distribution, Metabolism and Excretion of Radioactivity Following Subcutaneous Administration to Rats HLS Study number NVO 138 Novo Nordisk Study No. 960497, Pharmacokinetics study No 980326
9) Distribution, Excretion, Placental Transfer and Metabolism of ^{14}C-NN304 in the Rat after Repeated Subcutaneous Administration.
10) Pharmacokinetics of NN304 in Male and Female Spraque-Dawlay Rats after Single Intravenous and Subcutaneous Dosing.
11) Pharmacokinetics of NN304 after Single SC and Single IV Administration in th Rat.
12) Detemination of In vitro Protein Binding of ^{125}I-labelled NN304 in Dog, Pig, Rat, Mouse and Rabbit Plasma by Equilibrium Dialysis.
13) Detemination of In vitro Protein Binding of ^{125}I-labelled NN304 in Human Plasma by Equilibrium Dialysis.
14) Detemination of In vitro Protein Binding of Insulin detemir in Plasma of

Decreasing Concentrations and to HSA and AAGP.

15) Albumin binding of $N^{\in B29}$tetradecanoyl des-(B30) inslulin(NN304)

16) Albumin binding of insulins acylated with fatty acids: characterization of the ligand-protein interaction and correlation between binding affinity and timing of the insulin effect in vivo.

17) Albumin binding and time action of acylated insulins in various species

18) Effect of fatty acids and selected drugs on the albumin bindind of a long-acting, acylated insulin alalogue

19) The Effect of NN304 on Hepatic Cytochrome P450s in Male and Female Sprague-Dawley rats after Subcutameous Administration at 1 and 50 units/kg/day

20) In vitro metabolite profile of ^{14}C-NN304after incubation with monolayer hepatocytes from CD-1 mouse, Sprague-Dauley rat, New Zealand white rabbit, beagle dog, Yucatan mini-pig, cynomolgus monkey, and humans.

21) Indentification of Urine Metabolites following Single Subcutaneous Administration of ^{14}C-NN304 to the Rat at Nominal Dose Level of 6000 nmol/kg.

22) In vitro Metabolic Profile and Metabolite Identification of ^{14}C-Insulin Detemir and Human Insulin after Incubation with either Cytosol, Hepatocytes or Protein Disulfide Isomerase from the Species: Rat, Dog, Pig, and Human and in Kidney S9 Mixture form Human and Rat.

23) Investigation of Stability of Insulin Detemir in Plasma and Whole Blood.

6. 임상시험성적에 관한 자료

가. 임상시험자료집

1) Insulin determir의 건강한 일본계 미국인과 백인 피험자의 증가경향 용량에 대한 약물동력학(PK)의 open-label 비교

2) 건강한 지원자를 대상으로 Insulin aspart와 insulin detemir의 혼합투여와 분리투여 시의 약동학에 미치는 영향에 대한 무작위배정, 단독기관, 개방형, 두 기간 교차시험

3) 건강한 일본계와 백인인종 피험자 간의 insulin detemir 2400nmol/ml와 NPH insulin의 단회투여의 약동학적, 약력학적 비교를 위한 무작위 배정, 단독 기관, 두 기간 교차시험

4) A single-center, randomised, double-blind, two-period cross-over trial to compare serum glucose following single doses of insulin detemir given at

dinner and insulin detemir at bedtime in subjects with Type I diabetes on a basal/bolus regimen

5) A multicentre, uncontrolled, open, titration study of the new long/intermediate action insulin analogue NN304 in a basal/bolus regimen in Type I diabetic patients.
6) A multicentre, open, randomised, crossover trial to compare the blood glucose lowering effect of NN304 with NPH insulin in Type I diabetic subjects.
7) 1일 1회 저녁에 투여하는 insulin detemir(NN304) 또는 human insulin NPH의 Metformin과의 병용투여: 이전에 metformin 단독 또는 병용투여 경험이 있는 2형 당뇨병 환자에서의 안전성과 효력 비교- 무작위 추출, 6개월, open-label, 평행그룹 다기관 시험.
8) 1형 당뇨 환자에 대한 insulin detemir의 아침, 저녁식사 전 투여, 또는 아침, 취침시 투여, 또는 NPH insulin의 아침 취침 시 투여.
9) 1형 당뇨병환자를 대상으로 16주간의 다기관, 다국적, 개방, 무작위배정 3그룹 평행 시험으로 insulin detemir의 12시간 간격 투여, insulin detemir의 아침과 취침시 투여, NPH의 아침과 취침시 투여를 비교

7. 외국의 사용현황 등에 관한 자료

가. EMEA 허가사항

8. 국내 유사제품과의 비교검토 및 당해 의약품등의 특성에 관한 자료. 끝.