

## <안전성·유효성 심사관련 제출자료목록>

- 페라미플루주15밀리리터, 녹십자

○ 관련규정 : 의약품등의품목허가·신고·심사규정(식품의약품안전청고시 제2009-222호, 2009.12.31) 제5조1항 및 [별표1] **신약 1.화학구조 또는 본질조성이 전혀 새로운 신물질 의약품**

구분 \ 제출자료	자 료 번 호																			
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### ○ 제출자료 목록

#### 1. 기원 또는 발견 및 개발경위에 관한 자료

#### 3. 안정성에 관한 자료

##### 가. 원료의약품에 관한 자료

- 1) 장기보존시험, 가속시험자료
- 2) 가혹시험자료

##### 나. 완제의약품에 관한 자료

- 1) 장기보존시험, 가속시험자료
- 2) 가혹시험자료

#### 4. 독성에 관한 자료

##### 가. 단회투여독성시험자료

- 1) Single Intravenous Toxicity Study of Peramivir trihydrate in Rats (PMV-TF-016-L, SG07084)
- 2) Single Intravenous Infusion Toxicity Study of Peramivir trihydrate in Monkeys (PMV-TF-017-L, SG07083)
- 3) Single Intravenous Infusion Toxicity study of Peramivir trihydrate in Monkeys (PMV-TF-044-L, SG07217)

##### 나. 반복투여독성시험자료

- 1) Twenty-eight day intravenous GLP toxicity study of BCX-1812 in Rats (0527-07232)
- 2) One-Month Continuous Intravenous Infusion Toxicity Study of Peramivir trihydrate

in Rats (S-021812-TF-112-L, SG08337-1)

- 3) Twenty-eight day intravenous GLP toxicity study of BCX-1812 in cynomolgus monkeys (0527- 07233)
- 4) One-Month Continuous Intravenous Infusion Toxicity Study of Peramivir trihydrate in Monkeys (S-021812-TF-091-L, SG08078-1)
- 5) SEVEN-DAY INTRAVENOUS TOXICITY STUDY OF RWJ-270201-162 IN RATS (STUDY DS99318) : non-GLP
- 6) A 14-Day Continuous Intravenous Infusion Toxicity Study of RWJ-270201-162 in Rats (Study DS99031)
- 7) 2-week intravenous toxicity study of peramivir in cynomolgus monkeys with 2-week recovery (806-023)

#### 다. 유전독성시험자료

- 1) In Vitro Mutagenicity Testing of RWJ-270201-162 in The Bacterial/Microsomal Activation Assay (DS98322)
- 2) In Vitro Chromosome Aberration Assay of RWJ-270201-162 using CHO-K1 Cells (DS98321)
- 3) Micronucleus Test of Peramivir trihydrate with Mouse Bone Marrow Cells (PMV-TF-040-L, SG07209)

#### 라. 생식발생독성시험자료

##### 수태능 및 초기배발생시험

- 1) Intravenous Fertility and General Reproductive Toxicity Study of RWJ-270201-162 in Male Rats (DS99307, 213-023)
- 2) Intravenous Fertility and General Reproductive Toxicity Study of RWJ-270201-162 in Female Rats (DS99309, 213-024)

##### 배·태아발생시험

- 3) Intravenous Development Toxicity Study of RWJ-270201-162 in Rats (DS99316, 213-021)
- 4) Intravenous Dosage-Range Developmental Toxicity Study of RWJ-270201-162 in Rats (DS99402, 213-021P)
- 5) A Continuous Intravenous Infusion Developmental Toxicity Study of RWJ-270201-162 in Rat (DS00312, 96844)
- 6) Intravenous Developmental Toxicity Study of RWJ-270201-162 in Rabbits (DS99317, 213-020)
- 7) Intravenous Dosage-Range Developmental Toxicity Study of RWJ-270201-162 in Rabbits (DS99403, 213-020P)

##### 출생 전·후의 발생 및 모체기능시험

- 8) Intravenous Developmental And Perinatal/Postnatal Reproduction Toxicity Study of

RWJ-270201-162 In Rats, Including a Postnatal Behavioral/Functional Evaluation (DS99310, 213-022)

발육기 동물에 대해 평가한 시험

- 9) Single Intravenous Toxicity Study of Peramivir trihydrate in Juvenile Rats (S-021812-TF-109-L, SG08296)
- 10) One-Month Intravenous Toxicity Study of Peramivir trihydrate in Juvenile Rats (S-021812-TF-110-L, SG08297)

마. 기타독성시험

항원성시험

- 1) Antigenicity Study in Guinea Pigs: Systemic Anaphylaxis and Passive Cutaneous Anaphylaxis Reactions (DS00320)

기전독성시험

- 2) Single Intravenous Nephrotoxicity Study of Peramivir trihydrate in Rabbits (S-021812-TF-068-L, SG07394)
- 3) One-Week Intravenous Nephrotoxicity Study of Peramivir trihydrate in Rabbits (S-021812-TF-094-L, SG08109)

## 5. 약리작용에 관한 자료

가. 효력시험자료

- 1) Inhibition Effect of Peramivir trihydrate on Neuraminidase of Influenza A and B viruses using Glycoprotein (Fetuin) as Substrate (S-021812-EB-116-N)
- 2) Inhibitory Effect of Peramivir trihydrate on Neuraminidase of Influenza A and B Viruses (PMV-EB-037-N)
- 3) Inhibitory Effect of Peramivir trihydrate on Neuraminidase of Influenza A and B Viruses (2) (S-021812-EB-111-N)
- 4) Inhibitory Effect of Peramivir trihydrate on Neuraminidase of Avian Influenza Viruses (PMV-EB-033-N)
- 5) Inhibitory Effect of Peramivir trihydrate on Bacterial Neuraminidase (PMV-EB-032-N)
- 6) Inhibitory Effect of Peramivir trihydrate on Human Sialidases (S-021812-EB-130-N)
- 7) Binding activity of Peramivir trihydrate on Various Receptors (S-021812-EF-127-N, AL-4143-G)
- 8) Inhibitory Effect of Peramivir trihydrate on Replication Activity of Influenza A and B Viruses (Clinically-isolated Strains) (PMV-EB-035-N)
- 9) Inhibitory Effect of Peramivir trihydrate on Plaque Formation in Laboratory Strains of Influenza A and B Viruses (S-021812-EB-115-N)

- 10) Inhibitory Effect of Peramivir trihydrate on Plaque Formation in Clinical Isolates of Influenza A and B Viruses (S-021812-EB-108-N)
- 11) Inhibitory Effect of Peramivir trihydrate on Replication Activity of Influenza A and B Viruses (Laboratory Strains) (PMV-EB-034-N)
- 12) Inhibitory Effect of Intravenous Administration of Peramivir trihydrate on Influenza A Virus-infected Mice (PMV-EB-038-N)
- 13) Therapeutic Effect of Peramivir trihydrate after Intravenous Dosing in Mice Infected by Influenza A Virus (A/PR/8/34) (S-021812-EB-103-N)
- 14) Therapeutic Effect of Peramivir trihydrate after Intravenous Dosing in Mice Infected by Influenza A Virus (A/Kumamoto/Y5/67) (S-021812-EB-104-N)
- 15) Therapeutic Effect of Peramivir trihydrate after Intravenous Dosing in Mice Infected by Influenza A Virus (A/Victoria/3/75) (S-021812-EB-105-N)
- 16) Inhibitory Effect of Intravenous Administration of Peramivir trihydrate on Influenza B Virus-infected Mice (PMV-EB-039-N)
- 17) Therapeutic Effect of Peramivir trihydrate after Intravenous Dosing in Mice Infected by Influenza B Virus (B/Lee/40) (S-021812-EB-106-N)
- 18) Therapeutic Effect of Peramivir trihydrate on Influenza A virus-infected Mice after Delayed Dosing (S-021812-EB-058-N)
- 19) Inhibitory Effect of Peramivir trihydrate after Intravenous Dosing on Viral Replication in Mice infected by Influenza A Virus (S-021812-EB-123-N)
- 20) On-site Dissociation of Peramivir trihydrate from the N9 Neuraminidase (PMV-EB-036-N)
- 21) Pharmacodynamic Effect of Intravenous Administration of Peramivir trihydrate on Influenza A virus-infected Mice (S-021812-EB-052-N)
- 22) Pharmacokinetic and Pharmacodynamic Analysis of Peramivir trihydrate Using Influenza A Virus-infected Mice (S-021812-EB-053-N)
- 23) Inhibitory Effect of Peramivir trihydrate on Neuraminidase of Influenza Viruses Isolated in Yokohama from 2005 to 2008 (S-021812-EB-117-N)
- 24) Inhibitory Effect of Peramivir trihydrate on Neuraminidase with H274Y Mutation of Influenza A Viruses (S-021812-EB-135-N)
- 25) Therapeutic Effect of Peramivir trihydrate after Intravenous Dosing on Mice Infected by Influenza A Virus Carrying NA H274Y Mutation (S-021812-EB-134-N)
- 26) Inhibitory Effect of Peramivir trihydrate on Recombinant Neuraminidase of Influenza A and B Viruses Carrying Oseltamivir- or Zanamivir-Resistant Mutation (S-021812-EB-133-N)
- 27) Therapeutic Effect of Peramivir trihydrate after Intravenous Dosing on Immunocompromised Mice Infected by Influenza A Virus (S-021812-EB-131-N)

- 28) Inhibitory Effect of Peramivir trihydrate on Neuraminidase of Highly Pathogenic Avian Influenza Viruses (S-021812-EB-060-N)
- 29) Inhibitory Effect of Peramivir trihydrate on Replication of Highly Pathogenic Avian Influenza Viruses (S-21812-EB-061-N)
- 30) Therapeutic Effect of Peramivir trihydrate after Intravenous Dosing in Mice infected by Highly Pathogenic Avian Influenza Virus (A/Hong Kong/483/97) (S-021812-EB-082-N)
- 31) On-site Dissociation of Peramivir, Oseltamivir carboxylate and Zanamivir from the N9 Neuraminidase Enzyme (PB001-CSA63005)

#### 나. 안전성약리시험

- 1) Effect of Peramivir trihydrate on Central Nervous System in Rats (PMV-SF-004-L, SG07086)
- 2) Effect of Peramivir trihydrate in Respiratory System in Rats (PMV-SF-005-L, SG07087)
- 3) Influence of RWJ-270201-162 on Pulmonary Function in the Anaesthetized Ventilated Guinea-Pig (DS00321)
- 4) Effect of Peramivir trihydrate on Cardiovascular system in Conscious Monkeys (PMV-SF-006-L, SG07088)
- 5) Effects of Peramivir trihydrate on Action Potential in Guinea Pig Papillary Muscles (PMV-SF-007-L, B070292)
- 6) Effects of BCX-1812 on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells (070117.CDS)

#### 다. 흡수, 분포, 대사 및 배설시험자료

##### 분석방법과 밸리데이션 보고서

##### 흡수

- 1) Plasma Concentration Following single Administration of [<sup>14</sup>C]-Peramivir trihydrate in Rats (PMV-PF-025-N, PBC055-032)
- 2) Dose-linearity of Plasma Concentration Following Single Administration of Peramivir trihydrate in Rats (S-021812-PF-027-N, PBC055-039)
- 3) Pharmacokinetics and Disposition Following Single Administration of [<sup>14</sup>C]-Peramivir trihydrate in Monkeys (PMV-PF-028-N, PBC055-036)
- 4) Dose-Linearity of Plasma Concentration Following Single Administration of Peramivir trihydrate in Monkeys (PMV-PB-029-N)
- 5) Dose-linearity of Plasma Concentration Following Single administration of Peramivir trihydrate in Mice (PMV-PF-026-N, PBC055-040)
- 6) Dose-linearity of Plasma Concentration Following Single administration of Peramivir trihydrate in influenza A Virus-infected Mice (S-021812-PB-055-N)

- 7) Plasma Concentration Following Repeated Intravenous Administration of [<sup>14</sup>C]-Peramivir trihydrate in Rats (PMV-PF-030-N, PBC055-042)

#### 분포

- 8) Quantitative Whole Body Autoradiography of Rats Following Single or Multiple Intravenous or Single Intramuscular Administration of [<sup>14</sup>C]-Peramivir (6425-149)
- 9) Quantitative Whole-body Autoradiography Following Single Intravenous Administration of [<sup>14</sup>C]-Peramivir trihydrate in Pregnant Rats (S-021812-PF-096-N, 1920/048)
- 10) Tissue Distribution Following Single Intravenous Administration of [<sup>14</sup>C]-Peramivir trihydrate in Juvenile and Mature Rats (S-021812-PF-093-N, B080344)
- 11) Tissue Distribution after Single Intravenous Administration of [<sup>14</sup>C]-Peramivir trihydrate at High Dose in Juvenile and Mature Rats (S-021812-PF-120-N, B090020)

#### 대사

- 12) Study on the in vivo Major Metabolites of [<sup>14</sup>C]-Peramivir trihydrate in Rats (PMV-PF-021-N, PBC055-034)
- 13) Study on the in vivo Major Metabolites of [<sup>14</sup>C]-Peramivir trihydrate in Monkeys (PMV-PF-022-N, PBC055-037)
- 14) Study on the in vivo Major Metabolites of [<sup>14</sup>C]-Peramivir trihydrate in Mice (PMV-PF-023-N, PBC055-035)

#### 배설

- 15) Urinary, Fecal and Biliary Excretion Following Single Intravenous Administration of [<sup>14</sup>C]-Peramivir trihydrate in Rats (PMV-PF-020-N, PBC055-033)
- 16) Urinary and Fecal Excretion Following Repeated Intravenous Administration of [<sup>14</sup>C]-Peramivir trihydrate in Rats (S-021812-PF-031-N, PBC055-043)
- 17) Excretion into Milk Following Single Intravenous Administration of [<sup>14</sup>C]-Peramivir trihydrate in Nursing Rats (S-021812-PF-099-N, PBC055-079)
- 18) Effect of Probenecid on Plasma Concentration after Single Intravenous administration of Peramivir trihydrate in Rats (S-021812-PF-121-N, PBC055-124)
- 19) Effect of Probenecid on Plasma Concentration after Single Intravenous administration of Peramivir trihydrate in Rabbits (S-021812-PB-122-N)

#### 라. 약물상호작용 등에 관한 자료

- 1) Study on P-glycoprotein Mediated Drug interaction of Peramivir trihydrate (S-021812, 7SHIOP2)

### 6. 임상시험성적에 관한 자료

#### 가. 임상시험자료집

생물약제학시험보고서

인체시료를 이용한 약동학과 관련된 시험보고서

인체약동학 시험보고서

- 1) S-021812 의 건강한 성인 남자를 대상으로 한 제1상 정맥내 반복투여임상시험 (0712T0611)
- 2) S-021812 건강한 성인 남자를 대상으로 한 제1상 정맥내 단회·반복투여시험 -고용량 (800 mg1 일 1 회투어) 으로의 검토-
- 3) A Phase I Double-Blind, Placebo-Controlled, Dose-Escalating Study to Evaluate the Safety and Tolerability of Intravenous Peramivir in Healthy Subjects (Hi-05-101)
- 4) A Phase I Double-Blind, Placebo-Controlled, Dose-Escalating Study to Evaluate the Safety and Tolerability of Intravenous Peramivir Administered Twice Daily in Healthy Subjects (Hi-06-102)
- 5) A Phase 1, Double-Blind, Placebo-Controlled, Dose-Escalating Study to Evaluate the Safety and Tolerability of Intravenous Peramivir Administered Once Daily For One Day and as Repeat Doses for Ten Days in Healthy Subjects (Hi-06-103, BCX1812-103)
- 6) A phase 1, Double-Blind, Multiple-Dose, Randomized, Placebo-Controlled, Single Center Study to Evaluate the Safety and Pharmacokinetics of Intravenous Permivir Administered in Elderly Subjects ( $\geq 65$  years of age) (Hi-06-104, BCX1812-104)
- 7) A Phase 1, Open-Label, Multi-Center Study to Evaluate the Safety and Pharmacokinetics of Intravenous Peramivir (2mg/kg) Administered in Subjects with Impaired Renal Function (Hi-06-105), BCX1812-105)
- 8) A phase 1, Open-Label, Single-Dose, Single-Center, Treatment Sequence-Randomized, Parallel-Group Study to Evaluate the Pharmacokinetics, Bioavailability and safety of intramuscular Permivir administered to Healthy subjects (Him-06-111, BCX1812-111)

9) 집단 약동학 시험보고서

인체약력학 시험 보고서

- 10) A Randomized, Double-Blind, Phase I, Placebo- and Positive-Controlled, 4-Period Crossover, Thorough QT/QTc Interval Study of Single Intravenous Doses of Peramivir in Healthy Subjects (BCX1812-106)

유효성과 안전성 시험보고서

- 11) S-021812 단회 정맥내투여에 의한 인플루엔자 바이러스 감염증을 대상으로한 제 2 상 임상시험 -이중눈가림 병행군간 비교에 의한 용량설정임상시험 - (0722T0621)
- 12) Phase III Clinical Study of Single-Dose Intravenous S-021812 in Patients with Influenza Virus Infection - A Double-Blind, Parallel Group, Comparative Study with

Oseltamivir Phosphate - (0815T0631)

13) A Phase 2, multicenter, randomized, double-mask, double-dummy study comparing the efficacy and safety of peramivir administered intravenously once daily versus oseltamivir administered orally twice daily in adults with acute serious or potentially life-threatening influenza (BCX1812-201)

14) 인플루엔자 바이러스 감염증을 대상으로 S-021812 정맥내 투여 제 3 상 임상시험 - 고위험 인자를 보유한 환자에 대한 검토 - (0816T0632)

#### Literature References

#### 나. 가교자료

#### 7. 외국의 사용현황 등에 관한 자료

- 일본 (2010.1.13)

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

- 타미플루, 리렌자로타디스크