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[Table] Approved Biosimilars

Drug	Approval Agency				
	EMA	FDA	HEALTH CANADA	PMDA	MFDS
Erythropoietin	■ Abseamed (2007) ■ Binocrit (2007) ■ Epoetin alfa hexal (2007) ■ Retacrit (2007) ■ Silapo (2007)			■ Epoetin alfa BS (JCR, 2010)	
Filgrastim	■ Tevasgrastim (2008) ■ Ratiograstim (2008) ■ Biograstim (2008) ■ Zarzio (2009) ■ Filgrastim hexal (2009) ■ Nivestim (2010) ■ Accofil (2014) ■ Grastofil (2014)	■ Zarxio (2015)		■ FilgrastimBS (Fuji, 2012) ■ FilgrastimBS (Teva, Nippon Kayaku 2013) ■ FilgrastimBS (Sandoz, 2014)	
Somatropin	■ Omnitrope (2006)		■ Omnitrope (2009)	■ Somatropin BS (Sandoz, 2009)	■ SciTropin A (2014)
Insulin	■ Abasaglar (2014)			■ Insulin glargine BS (Lilly, 2014) ■ Insulin glargine BS (Fuji Film, 2016)	
Infliximab	■ Remsima (2013) ■ Inflectra (2014)		■ Inflectra (2014) ■ Remsima (2014)	■ Infliximab BS (Celltrion, Nippon Kayaku, 2014)	■ Remsima (2012)
Trastuzumab					■ Herzuma (2014)
Etanercept					■ Davigtrel (2014)

ERYTHROPOIETIN - EMA		
Approved Year	**2007**	**2007**
Products Name	**Abseamed, Binocrit, Epoetin alfa Hexal**	**Retacrit, Silapo**
Study Type	**5 PK/PD studies** **(1 pilot study, 2 pivotal study)**	**2 PK studies**
Objectives	Equivalence in PK + PD	Equivalence in PK + Safety
Subjects	Healthy Adult Male	Healthy Adults
Study Design	Randomized, two-center, open, **parallel-group study** - Multiple IV 100 IU/kg TIW Randomized, monocentric, open, **parallel-group study** - Multiple SC 100 IU/kg TIW	**2-period cross-over study** - Single-dose IV bolus injection **3-period cross-over study** - Single-dose SC bolus injection
Primary Endpoints	***[PK]*** AUCτ of EPO	***[PK]*** $AUC_{0\text{-tlast}}$
	[PD] Absolute Hgb response (AUEC)	***[PD]*** Reticulocyte count
Equivalence Margin	**The post hoc acceptance range of 80-125%**	**The post hoc acceptance range of 80-125% for AUC & 70-143% for Cmax**
Clinical Efficacy / Safety Studies		
Study Type	**1 pivotal comparative study,** **1 supportive non-comparative study**	**2 pivotal comparative studies,** **2 supportive, uncontrolled safety studies** ****1 additional comparative SC study (2009) for Retacrit® only**
Objectives	Therapeutic equivalence in efficacy + safety	Therapeutic equivalence in efficacy + safety
Study Subjects	Renal anemia on HD	Renal anemia on HD
Study Design	Randomized, double blind, multicenter, **parallel-group** - IV study	[Correction phase IV study] Randomized, double-blind, multi-center, verum-controlled, **parallel-group study** - Multiple-dose IV [Maintenance phase IV study] Randomized, double-blind, multi-national, verum-controlled, **cross-over study** - Multiple-dose IV **[Additional maintenance phase SC study] Randomized, double-blind, multi-national, **parallel-group study** - Multiple-dose SC

Primary Endpoints	***[Efficacy]*** Mean absolute change in Hgb levels between the screening/baseline period and the evaluation period ***[Safety]*** Incidence of adverse events, serious adverse event, treatment-emergent adverse events, death, physical exam, clinical lab tests	***[Efficacy]*** [Correction phase IV study] - Mean Hgb levels during the last four -weeks of treatment - Mean weekly dosage of EPO per kg body weight during the last four weeks of treatment [Maintenance phase IV study] - Intra-individual change (test-reference) in mean weekly dosage per kg body weight of each product during the double-blind treatment period - Intra-individual change (test-reference) in mean Hgb level during double-blind treatment with each study drug **[Maintenance phase SC study] - Mean Hgb levels during the last four -weeks of treatment - Mean weekly dosage of EPO per kg body weight during the last four weeks of treatment ***[Safety]*** Occurrence of anti-epoetin antibodies, incidence of Hgb levels above 13 g/dl, ratings of tolerability, evaluation of adverse events
Statistics; Equivalence Margin	Equivalence; equivalence margin of ± 0.5 g/dl in Hgb (mean baseline Hgb = < 11.5 and > 11/5 g/dl) **Pre-defined acceptance ranges for equivalence margin*	[Correction phase IV study] Equivalence; 95% CI of the difference between both treatment groups of the primary endpoints; equivalence margin of ± 1g/dl in Hgb and ± 45 IU/kg/week (*corrected from 14 IU/kg/week) for mean weekly EPO dosage [Maintenance phase IV study] Equivalence; 2-sided 95% CI of the intra-individual change (test-reference); Equivalence margin of ± 0.6 g/dl in Hgb and ± 14 IU/kg/week for mean weekly EPO dosage [Maintenance phase SC study] Equivalence; 95% CI of the difference between both treatment groups of the primary endpoints; equivalence margin of ± 0.5 g/dl in Hgb and ± 45 IU/kg/week for EPO dosage **Pre-defined acceptance ranges for equivalence margin*

Abbreviations: AUEC, area under the effect curve; AUC, area under the concentration-time curve; CI, confidence interval; Cmax, maximum serum concentration; EPO, epoetin; HD, hemodialysis Hgb, hemoglobin; IU, international unit; IV, intravenous; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous; TIW, three times a week

FILGRASTIM - ① EMA				
Approved Year	**2008**	**2009**	**2010**	**2014**
Products Name	**Biograstim, Ratiograstim, Tevagrastim**	**Zarzio, Filgrastim Hexal**	**Nivestim**	**Accofil, Grastofil**
Clinical Pharmacokinetic / Pharmacodynamic Studies				
Study Type	**2 PK/PD studies**	**4 PK/PD studies**	**2 PK/PD studies**	**4 PK/PD studies**
Objectives	Equivalence in PD + PK	Equivalence in PD/PK + Safety	Equivalence in PD/PK + Safety	Equivalence in PD/PK + Safety
Subjects	Healthy Male/ Healthy Adults	Healthy Adults	Healthy Adults	Healthy Adults
Study Design	Randomised, single-centre, single-blind, 2-period, **2-arm crossover** - Single SC 5, 10 μg/kg - Single IV 5, 10 μg/kg	Randomised, double-blind, **2-way crossover** - Single SC 1 μg/kg - Multiple SC 2.5, 5 μg/kg/day - Multiple SC 10 μg/kg/day - Single IV 5 μg/kg	Randomised, single-centre, open-label, active-controlled, **2-way crossover** - Single IV & SC 10 μg/kg Randomised, single-centre, double-blind, active-controlled, **2-way crossover** - Multiple SC 5 or 10 μg/kg	Randomised, double-blind, active controlled, **2-way cross-over** - Single SC 75, 150 μg - Single IV 5 μg/kg Randomised, double-blind, active and placebo-controlled **parallel group** - Single SC 5 μg/kg Randomized, single-center, double-blind, active-controlled, **3-arm crossover** - Multiple SC 300 μg
Primary Endpoints	***[PK]*** AUCt of filgrastim	***[PK]*** AUCt and Cmax of filgrastim	***[PK]*** AUCt of filgrastim	***[PK]*** AUCt and Cmax of filgrastim
	[PD] AUCt and Cmax of ANC	***[PD]*** AUC of ANC	***[PD]*** AUC of ANC at Day 5	***[PD]*** AUCt and Cmax of ANC
Equivalence Margin	**90% CI** for the test/reference ratio of the primary PK/PD endpoint needs to be within **80-125%** of the reference product *(Different equivalence margins are defined in PD studies of Zarzio and Filgrastim Hexal. 2.5 μg/kg/day: 87.25~114.61%, 5 and 10 μg/kg/day: 86.50~115.61%)*			
Clinical Efficacy / Safety Studies				
Study Type	**1 pivotal, 2 supportive comparative studies**	**1 supportive non-comparative study**	**1 pivotal study**	**1 non-comparative study**
Objectives	Equivalence in efficacy + Safety, PK subgroup	Safety + Efficacy	Equivalence in efficacy + Safety	Safety + Efficacy
Study Subjects	Chemotherapy-naïve breast cancer (Stage II, III, IV) patients receiving docetaxel & doxorubicin (supportive studies: in patients with lung cancer and NHL focused on safety)	Chemotherapy-naïve breast cancer patients (stage 2, 3, 4 according to AJCC classification) receiving **docetaxel & doxorubicin**		Chemotherapy-naïve breast cancer receiving docetaxel & doxorubicin & *cyclophosphamide*
Study Design	Randomised, multinational, multicentre, placebo- and active- controlled	Randomised, multicenter, open-label, single-arm	Randomised, multicentre, double-blind, active-controlled	Randomised, multicenter, open-label
Primary Endpoints	***[Efficacy]*** DSN (ANC <0.5x10^9 /L) in days in cycle 1 ***[Safety]*** Incidence of adverse events, vital signs, formation of G-SCF antibodies, lab results	***[Efficacy]*** Incidence and DSN in cycles 1 to 4 ***[Safety]*** Incidence of adverse events, vital signs, formation of G-SCF antibodies, lab results	***[Efficacy]*** DSN (ANC <0.5x10^9 /L) in days in cycle 1 ***[Safety]*** Incidence of adverse events, vital signs, formation of G-SCF antibodies, lab results	
Statistics; Equivalence Margin	Equivalence; 2-sided 95% CI for least square mean difference in DSN (Test−Neupogen) lies entirely in **[-1day(-SD), +1day(+SD)]**	N/A	Equivalence; 2-sided 95% CI for least square mean difference in DSN (Test−Neupogen) lies entirely in **[-1day(-SD), +1day(+SD)]**	N/A

Abbreviation: AJCC, American Joint Committee on Cancer; ANC, absolute neutrophil count; AUC, area under the concentration-time curve; CI, confidence interval; Cmax, maximum serum concentration; DSN, duration of severe neutropenia; IV, intravenous; N/A, not applicable; NHL, non-Hodgkin lymphoma; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous; SD, standard deviation

FILGRASTIM - ② PMDA			
Approved Year	**2012 (PMDA)**	**2013 (PMDA)**	**2014 (PMDA)**
Products Name	**Filgrastim BS (Fuji), Filgrastim BS (Mochida)**	**Filgrastim BS (Teva),Filgrastim BS (Nippon Kayaku)**	**Filgrastim BS (Sandoz)**
Study Type	**1 PK/PD, 2 PK, 1 PD studies**	**3 PK, 2 PD studies**	**2 PK/PD, 2 PD studies**
Objectives	Equivalence in PD or PK + Safety	Equivalence in PD or PK + Safety	Equivalence in PD or PK + Safety
Subjects	Healthy Male		
Study Design	Randomised, open-label, active-controlled, 2-period, **2-arm rossover** (PK/PD) Single SC 400 μg/m^2 Randomised, double-blind, active-controlled, 2-period, **2-arm crossover** (2PK) single IV 200 μg/m^2 (PD) multiple SC 400 μg/m^2/day	Randomised, single-blind, 2-period, **2-arm crossover** (3PK) - Single SC 300 μg/m^2 , 150 μg/m^2 , 300 μg/m^2 (2PD) - Single SC 300 μg/m^2 - Multiple SC 300 μg/m^2/day	Randomized, double blind, 2-period-**2-way crossover** (2PK/PD) Single-dose SC 5 μg/kg, IV 2.5 μg/kg (2PD) Multiple doses SC 5 μg/kg/day, BID, for 3days
Primary Endpoints	***[PK]*** AUCt and Cmax of filgrastim	***[PK]*** AUCt and Cmax of filgrastim	***[PK]*** AUCt and Cmax of filgrastim
	[PD] Cmax of ANC & $CD34^+$cell	***[PD]*** Cmax of ANC & $CD34^+$cell	***[PD]*** AUECt and Emax of ANC(& $CD34^+$ cell)
Equivalence Margin	**90% CI** for the test/reference ratio of the primary PK/PD endpoint needs to be within **80-125%** of the reference product (Cmax of $CD34^+$: **95%** CI for the test/reference ratio of PD endpoint needs to be within 80-125% of the reference product)		**90% CI** for the test/reference ratio of the primary PK endpoint needs to be within **80-125%** of the reference product (PD endpoint: **95%** CI for the test/reference ratio needs to be within 80-125% of the reference product)
Clinical Efficacy / Safety Studies			
Study Type	**1 non-comparative study**	*The applicant did not conduct any efficacy clinical trials. Just submitted overseas clinical study data as reference for safety evaluation. Safety study data of Tevagrastim® (Teva Pharmaceutical, Israel) submitted as reference for safety evaluation*	*The applicant did not conduct any efficacy clinical trials. Just submitted overseas clinical study data as reference for safety evaluation. Safety study data of EP06-301(clinical efficacy and safety study of Zarzio®) submitted as reference for safety evaluation*
Objectives	Safety + Efficacy of test drug		
Study Subjects	Chemotherapy-naïve breast cancer patients receiving epirubicin & 5-FU & cyclophosphamide for pre- or postoperative chemotherapy		
Study Design	Non-randomised, multicenter, open-label study		
Primary Endpoints	***[Efficacy]*** DN (ANC <1x10^9 /L) in days in chemotherapy cycle 2 ***[Safety]*** Incidence of adverse events, vital signs, formation of G-SCF antibodies, lab results		
Statistics; Equivalence Margin	N/A		

Abbreviation: ANC, absolute neutrophil count; AUEC, area under the effect curve; BID, twice a day; CI, confidence interval; Cmax, maximum serum concentration; DN, duration of severe neutropenia; IV, intravenous; N/A, not applicable; NHL, non-Hodgkin lymphoma; PD, pharmacodynamics, PK, pharmacokinetics; SC, subcutaneous; 5-FU, fluorouracil

INFLIXIMAB - ① EMA[1]		
Approved Year	**2013**	**2014**
Products Name	**Remsima (Celltrion)**	**Inflectra (Hospira)**
Reference Product	**Remicade (Janssen)**	
Clinical Pharmacokinetic / Pharmacodynamic Studies		
Study Type	**1 pivotal study** (+ Supportive PK data were generated from the pivotal efficacy trial)	
Objectives	Equivalence in PK	
Subjects	AS patients with active disease	
Study Design	Prospective Phase 1, randomised, double-blind, multicentre, multiple single-dose Ⅳ infusion, parallel-group	
Primary Endpoints	***[PK]*** AUCτ, Cmax,ss between Weeks 22 and 30	
	[PD] (supportive study: markers of disease activity: CRP, rheumatoid factor, ESR, anti-CCP concentration at Week 14 and 30)	
Equivalence Margin	Equivalence; 2-sided equivalence margin of 80% to 125% for AUCτ and Cmax,ss in all-randomised population	
Clinical Efficacy / Safety Studies		
Study Type	**1 pivotal study (+** Supportive efficacy data were collected in the pivotal PK trial conducted in AS patients)	
Objectives	Equivalence in efficacy and safety	
Study Subjects	RA patients with active disease and inadequate response to MTX while receiving MTX	
Study Design	Prospective Phase 3, randomised, double-blind, multicentre, multiple single-dose IV infusion, parallel-group	
Primary Endpoints	***[Efficacy]*** % patients achieving ACR20 response at week 30 (supportive study: proportion of patients achieving clinical response according to the ASAS20 and ASAS40 criteria at Week 14 and 30) ***[Safety] -*** Adverse events, death, hypersensitivity via vital signs, electrocardiogram, physical examination, clinical laboratory tests, concomitant medications, signs and symptoms of tuberculosis, pregnancy, infections, infusion-related reactions, safety issues of special interest for infliximab - Anti-drug antibodies, neutralising anti-drug antibodies	
Statistics; Equivalence Margin	Equivalence; 95% CI for the difference in ACR20 contained within the equivalence margin of 15% in per-protocol population	

Abbreviation: ACR, American College of Rheumatology; anti-CCP, antibodies against cyclic citrullinated peptide; AS, ankylosing spondylitis; ASAS, Assessment of Spondyloarthritis International Society; AUCτ, area under the concentration-time curve over the dosing interval; CI, confidence interval; Cmax,ss, maximum serum concentration at steady state; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IV, intravenous; MTX, methotrexate; PD, pharmacodynamics; PK, pharmacokinetics; RA, rheumatoid arthritis

[1] Additionally, 1 pilot study (CT-P13 1.2) was also conducted. This study (randomised, double-blind, parallel-group, Phase 1) was designed to provide preliminary data on the initial pharmacokinetics, efficacy, and safety of CT-P13 compared with Remicade when co-administered with methotrexate in patients with active rheumatoid arthritis.

INFLIXIMAB - ② Health Canada		
Approved Year	**2014**	**2014**
Products Name	**Remsima (Celltrion)**	**Inflectra (Hospira)**
Reference Product	**Remicade (Janssen)**	
Clinical Pharmacokinetic / Pharmacodynamic Studies		
Study Type	**1 pivotal PK study**	
Objectives	Equivalence in PK	
Subjects	Patients with active AS	
Study Design	Randomised, double-blind, multicentre, parallel-group	
Primary Endpoints	***[PK]*** AUCτ, Cmax,ss	
	[PD] N/A	
Equivalence Margin	N/A	
Clinical Efficacy / Safety Studies		
Study Type	**1 pivotal study (** + Supportive efficacy data were collected in the pivotal PK trial conducted in AS patients)	
Objectives	Equivalence in efficacy and safety	
Study Subjects	RA patients with active disease and inadequate response to MTX while receiving MTX	
Study Design	Randomized, double-blind, multicentre, parallel-group	
Primary Endpoints	***[Efficacy]*** Proportion of ACR20 responders at Week 30 (supportive study: proportions of patients achieving an ASAS20 response (an improvement of ≥20%) at Week 30) ***[Safety]*** Adverse events, serious adverse event, treatment-emergent adverse events	
Statistics; Equivalence Margin	Equivalence; minimal treatment differences with 95% CIs falling within the ACR20 (Week 30) comparability margins of -15% to 15% in per-protocol population	

Abbreviation: ACR, American College of Rheumatology; AS, ankylosing spondylitis; ASAS, Assessment of Spondyloarthritis International Society; AUCτ, area under the concentration-time curve over the dosing interval; CI, confidence interval; Cmax,ss, maximum serum concentration at steady state; MTX, methotrexate; N/A, not applicable; PD, pharmacodynamics; PK, pharmacokinetics