Attachment 2: Biosimilar Products Approved with Extrapolated Indications

ERYTHROPOIETIN					
Agency	**Reference**		**Agency**	**Biosimilar**	
	EMA	**PMDA**		**EMA**	**PMDA**
Product Name (Applicant)	Eprex/Erypo, Epoetin alfa (Janssen-Cilag GmbH)	ESPO, Epoetin alfa (Kyowa Hakko Kirin)	**Product Name (Applicant)**	Abseamed (Medice Arzneimittel Pütter) Binocrit (Sandoz) Epoetin alfa hexal (Hexal) Retacrit (Hospira) Silapo (Stada)	Epoetin alfa BS (JCR Pharmaceuticals)
Approved Indications	■ Anemia in CRF patient ○ Adult on HD	■ Renal anemia undergoing HD	***Tested Model**	■ Anemia in CRF patient ○ Adult on HD	■ Renal anemia undergoing HD
	■ Anemia in CRF patient ○ Pediatric on HD ○ Adult on PD ○ Adult not yet on dialysis ■ Chemotherapy-induced anaemia in adult cancer patient ■ Increase the yield of PAD ■ Reduction of need for allogenic blood transfusions in adult prior to surgery	■ Renal anemia undergoing PD ■ Anemia of prematurity	**Extrapolated Indications**	■ Anemia in CRF patient ○ Pediatric on HD ○ Adult on PD ○ Adult not yet on dialysis ■ Chemotherapy-induced anemia in adult cancer patient ■ Increase the yield of PAD ■ Reduction of need for allogenic blood transfusions in adult prior to surgery[1]	■ Renal anemia undergoing PD ■ Anemia of prematurity

* Tested in the clinical efficacy and safety study

[1]Indications added in 2010

Abbreviations
CRF, chronic renal failure; HD, hemodialysis; PD, peritoneal dialysis; PAD, pre-operative autologous blood of donation

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<table>
<tr><th colspan="6">FILGRASTIM</th></tr>
<tr><th rowspan="2">Agency</th><th colspan="3">Reference</th><th rowspan="2">Agency</th><th colspan="2">Biosimilar</th></tr>
<tr><th>EMA</th><th>FDA</th><th>PMDA</th><th>EMA</th><th>FDA</th><th>PMDA</th></tr>
<tr><td>Product Name (Applicant)</td><td>Neupogen (Amgen)</td><td>Neupogen (Amgen)</td><td>Gran (Kyowa Hakko Kirin)</td><td>Product Name (Applicant)</td><td>Biograstim (CT Arzneimittel)
Ratiograstim (Ratiopharm)
Tevagrastim (Teva)
Zarzio (Sandoz)
Filgrastim Hexal (Hexal AG)
Nivestim (Hospira)
Accofil (Accord Healthcare)
Grastofil (Apotex)</td><td>Zarxio (Sandoz)</td><td>Filgrastim BS (Fuji Pharma),(Mochida)

Filgrastim BS (Teva Pharma Japan) ,(Nippon Kayaku)

Filgrastim BS (Sandoz)</td></tr>
<tr><td rowspan="2">Approved Indications</td><td colspan="2">■ Patients with nonmyeloid malignancies receiving myelosuppressive CTX

■ Patients with Acute Myeloid Leukemia
■ Cancer patients receiving myeloablative CTX followed by bone marrow transplantation
■ Cancer patients receiving PBPC collection & therapy
■ Severe congenital, cyclic, or idiopathic neutropenia
■ Patients with HIV infection</td><td></td><td>*Tested Model</td><td colspan="2">■ Patients with nonmyeloid malignancies receiving myelosuppressive CTX</td><td></td></tr>
<tr><td></td><td>■ Neutropenia associated with myelodysplastic syndromes or aplastic anemia</td><td>Extrapolated Indications</td><td colspan="2">■ Patients with Acute Myeloid Leukemia
■ Cancer patients receiving myeloablative CTX followed by bone marrow transplantation
■ Cancer patients receiving PBPC collection & therapy
■ Severe congenital, cyclic, or idiopathic neutropenia
■ Patients with HIV infection</td><td>■ Neutropenia associated with myelodysplastic syndromes or aplastic anemia</td></tr>
</table>

* Tested in the clinical efficacy and safety study

Abbreviations

CTX, chemotherapy; HIV, human immunodeficiency virus; PBPC, peripheral blood progenitor cells

Attachment 2: Biosimilar Products Approved with Extrapolated Indications

INFLIXIMAB							
Agency	**Reference Drug**		**Agency**	**Biosimilar**			
	PMDA	**All the Other**		**MFDS**	**EMA**	**Health Canada**	**PMDA**
Product Name (Applicant)	Remicade (Janssen Biotech[4])		**Product Name (Applicant)**	Remsima (Celltrion)	Remsima (Celltrion) Inflectra (Hospira)	Remsima (Celltrion) Inflectra (Hospira)	Infliximab BS (Celltrion),(Nippon Kayaku)
Approved Indications	■ AS ■ RA ■ CD ■ UC ■ Psoriatic Arthritis ■ Psoriasis ■ Behcet's Uveitis	■ AS ■ RA ■ Adult CD ■ Pediatric CD ■ Adult UC ■ Paediatric UC ■ Psoriatic arthritis ■ Psoriasis	**Tested Model**	■ AS[1] ■ RA[2]		■ RA	
			Extrapolated Indications	■ Adult CD ■ Pediatric CD[3] ■ Adult UC ■ Pediatric UC[3] ■ Psoriatic arthritis ■ Psoriasis	■ Adult CD ■ Pediatric CD ■ Adult UC ■ Pediatric UC ■ Psoriatic arthritis ■ Psoriasis	■ Psoriatic arthritis ■ Psoriasis	■ CD ■ UC ■ Psoriatic arthritis[3] ■ Psoriasis[3]

[1] Pivotal pharmacokinetic and supportive clinical efficacy and safety study
[2] Pivotal clinical efficacy and safety and supportive pharmacokinetic study
[3] Indications added in 2015
4 In Japan, Tanabe Mitsubishi

Notes

The extrapolated indications of infliximab vary by agencies, which is mainly based on the interpretation discrepancies about different *in vitro* ADCC activities.

- MFDS: *Not mentioned*
- EMA: The difference detected has no clinically relevant impact on the efficacy and safety, in particular in IBD.
- Health Canada: While ADCC is not an important mechanism in psoriatic arthritis and psoriasis, it cannot be ruled out as a mechanism of action in IBD and the differences in ADCC activities could have an impact on the clinical safety and efficacy in IBD.
- PMDA: The reference drug and its biosimilar have comparable biological activities, efficacy and safety and are considered to have similar pharmacological activities based on the fact that RA, CD and UC share a common pathologic mechanism and infliximab's mechanism of action. (*Not mentioned about psoriatic diseases.*)

Abbreviations

ADCC, antibody-dependent cell-mediated cytotoxicity; AS, ankylosing spondylitis; CD, Crohn's disease; IBD, inflammatory bowel disease; RA, rheumatoid arthritis; UC, ulcerative colitis

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SOMATROPIN								
Agency	**Reference Drug**			**Agency**	**Biosimilar**			
	EMA PMDA	**MFDS**	**Health Canada**		**PMDA**	**Health Canada**	**EMA**	**MFDS**
Product Name (Applicant)	Genotropin (Pfizer)			**Product Name (Applicant)**	Somatropin BS (Sandoz)	Omnitrope (Sandoz)		Scitropin (SciGen Korea)
Approved Indications	■ GHD in pediatric	■ GHD in pediatric	■ GHD in pediatric	***Tested Model**	■ GHD in pediatric			
	■ GHD in adult ■ PWS ■ SGA ■ TS ■ Growth Disturbance in CRF	■ GHD in adult ■ PWS ■ SGA ■ TS ■ Growth Disturbance in CRF ■ ISS[1]	■ GHD in adult ■ SGA[2] ■ TS[2] ■ ISS[2]	**Extrapolated Indications**	■ GHD in adult[4] ■ PWS[2] ■ SGA[2] ■ TS ■ Growth Disturbance in CRF	■ GHD in adult ■ SGA[3] ■ TS[3] ■ ISS[3]	■ GHD in adult ■ PWS ■ SGA ■ TS ■ Growth Disturbance in CRF	■ GHD in adult ■ PWS ■ SGA ■ TS ■ Growth Disturbance in CRF ■ ISS

* Tested in the clinical efficacy and safety study

[1]Indications added in 2009
[2]Indications added in 2013
[3]Indications added in 2014
[4]Indications added in 2011

Abbreviations

CRF, chronic renal failure; GHD, growth hormone deficiency; ISS, idiopathic short stature; PWS, Prader-Willi syndrome; SGA, small for gestational age; TS, Turner syndrome