

Supplementary table 1: Product examples for half-life extension / decreased dosing frequency

Products based on depot formulations

Parent drug	Drug/carrier	Indication	Commercial Stage
Goserelin	Goserelin acetate implant / PLGA (Zoladex)	Prostate cancer	Approved 1989
Leuprolide	Leuprolide acetate for depot suspension / PLGA (Lupron Depot)	Prostate cancer; endometriosis; uterine fibroids	Approved 1989
Octreotide	Octreotide acetate for injectable suspension / PLGA (Sandostatin LAR)	Acromegaly	Approved 1998
Lanreotide	Lanreotide / PLGA (Somatuline LA)	Acromegaly; Thyrotropic Adenomas; Neuroendocrine Tumours	Approved 1998
Human growth hormone	Somatropin for injectable suspension / PLGA (Nutropin Depot)	Growth hormone deficiency in pediatric patients	Approved 1999; discontinued 2004
Buserelin	Buserelin / PLGA (Suprefact Depot)	Prostate cancer; endometriosis	Approved 2000
Triptorelin	Triptorelin / PLGA (Decapeptyl SR)	Prostate cancer	Approved 2000
Triptorelin pamoate	Triptorelin pamoate for injectable suspension/ PLGA (Trelstar)	Prostate cancer	Approved 2000
Leuprolide	Leuprolide acetate implant/PLGA(Viadur)	Prostate cancer	Approved 2000
BMP-7	Eptotermin alfa/Collagen(Osigraft)	For the treatment of tibial nonunions where autograft has failed or is unfeasible	Approved 2001
Leuprolide	Leuprolide acetate for injectable suspension/ PLGA (Eligard)	Prostate cancer	Approved 2002
BMP-2	rhBMP-2/ACS /Collagen(INFUSE BoneGraft)	For use in anterior lumbar interbody spinal fusion procedures	Approved 2002
Abarelix	Abarelix depot for injectable suspension / carboxymethylcellulose (Plenaxis)	Prostate cancer	Approved 2003; discontinued 2006
Exenatide	Exenatide extended release for injectable suspension / PLGA (Bydureon)	Type 2 diabetes	Approved 2012
Pasireotide	Pasireotide pamoate / PLGA (Signifor)	Acromegaly	Phase III
Human growth hormone	SR-hGH, LB03002 / hyaluronic acid	Pediatric Growth Hormone Deficiency; Adult Growth Hormone Deficiency	Phase III
Leuprolide	Fluid Crystal leuprolide acetate / Lipid (Prosenze, CAM2032)	Prostate cancer; endometriosis	Phase II
IFN-alpha	Controlled release interferon alpha 2b/ poly (ether ester) (Locteron)	Hepatitis C	Phase II
IFN-alpha	Medusa interferon alpha-2b XL / polyglutamate-vitamin E conjugate	Hepatitis C	Phase II
Interleukin-2	Medusa IL-2XL / polyglutamate-vitamin E conjugate	Renal cell carcinoma	Phase I/II
Octreotide	Fluid Crystal octreotide/ Lipid (CAM2029)	Acromegaly; neuroendocrine tumors	Phase I

Pegylated biopharmaceuticals

Parent drug	Drug	Indication	Commercial Stage
Adenosine deaminase	Pegademase bovine (Adagen)	Severe combined immunodeficiency disease (SCID)	Approved 1990
L-Asparaginase	Pegaspargase (Oncaspar)	Acute lymphoblastic leukemia	Approved 1994
Interferon a-2b	Peginterferon alfa-2b (Peg-Intron)	Hepatitis C	Approved 2000
Interferon a-2b	Peginterferon alfa-2b (Pegasys)	Hepatitis C	Approved 2002
G-CSF	Pegfilgrastim (Neulasta)	Chemotherapy-induced neutropenia	Approved 2002
Human growth hormone antagonist	Pegvisomant (Somavert)	Acromegaly	Approved 2002
Erythropoietin	mPEG-epoetin beta (Mircera)	Anemia	Approved 2007
Anti-TNF Fab	Certolizumab pegol (Cimzia)	Crohn's disease	Approved 2008
Uricase	Pegloticase (Krystexxa)	Chronic gout	Approved 2010
EPO mimetic peptide	Peginesatide, Hematide (Omontys)	Anemia	Approved 2012; discontinued 2013
G-CSF	Lipegfilgrastim (Lonquex)	Chemotherapy-induced neutropenia	Approved 2013 (in Europe)
Interferon b-1a	Peginterferon beta-1a (Plegridy)	Relapsing-remitting multiple sclerosis (RRMS)	Phase III
Factor IX	PEG-rFIX N9-GP	Hemophilia B	Phase III
Insulin	Peglispro, Basal insulin lispro, BIL	Type 1 and Type 2 diabetes	Phase III
Consensus interferon	Pegylated Recombinant Consensus Interferon Variant Solution for Injection, PEG-IFN-SA	Chronic Hepatitis C	Phase III
Factor VIII	Site-specific PEGylated recombinant human factor VIII, BAY 94-9027	Hemophilia A	Phase III
Tumor necrosis factor type I	PEG sTNF-RI, Pegsunercept	Rheumatoid arthritis	Phase II
Phenylalanine ammonia lyase	rAvPAL- PEG	Phenylketonuria	Phase II
IL-29	PEG rIL-29	Hepatitis C	Phase II
Anti-VEGF DARPIn	Abicipar pegol	Macular degeneration	Phase II
Human growth hormone	TransCon PEG hGH, ACP-001	Pediatric Growth Hormone Deficiency; Adult Growth Hormone Deficiency	Phase II
Uricase	Pegsiticase, Uricase PEG-20	Gout	Phase I
Human growth hormone	Pegylated hGH, NNC126-0083	Adult Growth Hormone Deficiency	Phase I

N-glycosylation and hyper-/polysialylation

Parent drug	Drug	Indication	Commercial Stage
Erythropoietin	Darbepoetin alfa (Aranesp)	Anemia	Approved 2001
Erythropoietin	PSA-EPO (ErepoXen)	Anemia	Phase II
Insulin	PSA-insulin (SuliXen)	Diabetes	Phase I

Long-circulating biopharmaceuticals based on albumin

Parent drug	Drug	Indication	Commercial Stage
Albumin Fusion Proteins			
GLP-1 (7-36)	Albiglutide	Type 2 diabetes	Approved April 2014
Interferon alpha-2b	Albinterferon alfa-2b (Albuferon)	Hepatitis C	Phase III; discontinued 2010*
G-CSF	Neugranin	Chemotherapy-induced neutropenia	Phase III
FVIII	rVIII-SingleChain	Hemophilia A	Phase III
FIX	rFIX-FP	Hemophilia B	Phase III
HER2 + HER3 specific single-chain Fv	MM-111 (scFv-HSA-scFv)	Cancer	Phase II
Human growth hormone	Albutropin, TV-1106	Pediatric Growth Hormone Deficiency	Phase II
Extracellular EphB4	sEphB4-HSA	Solid tumors	Phase I
FVIIa	rFVIIa-FP (CSL689)	Hemophilia A or B	Phase I
Interferon beta	Albuferon beta	Multiple sclerosis	Phase I
Albumin binding through a conjugated fatty acid chain			
Insulin	Insulin detemir (Levemir)	Diabetes	Approved 2005
Glucagon-like peptide-1	Liraglutide (Victoza)	Type 2 diabetes	Approved 2009
Albumin chemical conjugates			
Exendin-4	CJC-1134-PC	Type 2 diabetes	Phase II
* Albuferon, the interferon alpha-2b albumin fusion, was dropped from development in 2010 despite having met Phase III non-inferiority endpoints against Pegasys. It is not clear that immunogenicity of the fusion construct was involved, although poor tolerability compared to Pegasys was cited as a contributing factor.			

Long-circulating biopharmaceuticals based on fusion with the IgG Fc domain

Parent drug	Drug	Indication	Commercial Stage
TNF receptor 2 (TNFR75)	Etanercept (Enbrel)	Rheumatoid arthritis, ankylosing spondylitis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, plaque psoriasis	Approved 1998
LFA-3	Alefacept (Amevive)	Severe chronic plaque psoriasis	Approved 2003
CTLA-4	Abatacept (Orenica)	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis	Approved 2005
IL-1R	Rilonacept (Arcalyst)	Cryopyrin-associated periodic syndromes	Approved 2008
Thrombopoietin binding peptide	Romiplostim (Nplate)	Chronic idiopathic thrombocytopenia purpura	Approved 2008
VEGFR 1 + 2	Aflibercept (Eylea); ziv-aflibercept (Zaltrap)	Wet age-related macular degeneration; metastatic colorectal cancer	Approved 2011, 2012
CTLA-4	Belatacept (Nulojix)	Prophylaxis of organ rejection in adults receiving a kidney transplant	Approved 2011
Factor IX	rFIXFc (Alprolix)	Hemophilia B	Approved March 2014
Factor VIII	rFVIII-Fc (Eloctate)	Hemophilia A	Approved June 2014
sIL-4R	Altrakcept (Nuvance)	Asthma	Phase III
Angiopoietin 1 and 2 binding peptide	Trebananib (AMG386)	Cancer (various)	Phase III
B cell activating factor	Blisibimod, A-623	Systemic lupus erythematosus	Phase III
TNFR55	Lenercept	Rheumatoid arthritis, severe sepsis	Phase III
Tumor necrosis factor receptor superfamily member 13B (TACI)	Atacept	Systemic lupus erythematosus; multiple sclerosis	Phase II/III
VEGFR 1 + 2	KH902	AMD-associated choroidal neovascularization	Phase II
CD4	PRO542	HIV	Phase II
Activin Receptor IIA extracellular domain	Sotatercept, ACE-011	Anemia	Phase II
Soluble activin type IIB receptor	ACE-031	Duchenne muscular dystrophy	Phase II
Cytotoxic T-lymphocyte antigen 4 (CTLA-4)	ASP2408	Rheumatoid arthritis	Phase II
Lymphotoxic-beta receptor	Baminercept alfa, BG-9924	Sjögren's Syndrome Rheumatoid arthritis	Phase II
Activin receptor-like kinase 1 (ALK1)	Dalantercept, ACE-041	Advanced renal cell carcinoma; advanced hepatocellular carcinoma; recurrent endometrial carcinoma	Phase II
Recombinant P-selectin glycoprotein ligand	YPSL, TS-1	Ischemia reperfusion injury	Phase II
Fibroblast growth factor receptor 1c	FP-1039, GSK3052230	Squamous non-small cell lung cancer; mesothelioma	Phase I
CD95 receptor extracellular domain	APG101	Myelodysplastic syndromes Glioblastoma	Phase I

Long-circulating biopharmaceuticals based on alternative genetic fusion approaches

Parent drug	Drug	Indication	Commercial Stage
Follicle stimulating hormone	Corifollitropin alfa, FSH-CTP (Elonva)	Controlled Ovarian Stimulation in women participating in in vitro fertilization	Approved 2010
Human growth hormone	Human growth hormone-XTEN, VRS-371	Pediatric Growth Hormone Deficiency	Phase II
Human growth hormone	hGH-CTP, MOD-4023	Pediatric Growth Hormone Deficiency	Phase II
GLP-1	GLP1-ELP, PB1023	Type 2 diabetes	Phase II
GLP-1	Exenatide-XTEN, VRS-859	Type 2 diabetes	Phase I

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