MAXIMUM DOSAGE

Policy Number: 2019D0034T **Effective Date**: March 1, 2019

Instructions for Use

Table of Contents **Page**

Related Commercial Policies

- Complement Inhibitors (Soliris® & Ultomiris™)
- Entyvio® (Vedolizumab)
- Infliximab (Remicade® ,Inflectra™, Renflexis™)
- Ophthalmologic Policy: Vascular Endothelial Growth Factor (VEGF) Inhibitors
- Rituxan® (Rituximab)
- Stelara® (Ustekinumab)
- White Blood Cell Colony Stimulating Factors
- Xolair® (Omalizumab)

COVERAGE RATIONALE

See Benefit Considerations

This policy provides information about the maximum dosage per administration for certain medications administered by a medical professional.

Drug Products:

- bevacizumab (Avastin®)
- eculizumab (Soliris®)
- infliximab (Remicade®)
- infliximab-dyyb (Inflectra™)
- infliximab-abda (Renflexis™)
- omalizumab (Xolair®)
- pegfilgrastim (Neulasta®)
- pegfilgrastim-jmdb (Fulphila™)
- rituximab (Rituxan®)
- trastuzumab (Herceptin®)
- ustekinumab (Stelara®)
- vedolizumab (Entyvio®)
- zoledronic acid (zoledronic acid, Reclast® and Zometa®)

Most medications have a maximum dosage based upon body surface area or patient weight or a set maximal dosage independent of patient body size, and are proven when used according to labeled indications or when otherwise supported by published clinical evidence.

The medications included in this policy when given beyond maximum dosages based upon body surface area or patient weight or a set maximal dosage independent of patient body size are not supported by package labeling or published clinical evidence and are unproven.

This policy creates an upper dose limit based on the clinical evidence and the 95th percentile for adult body weight (128 kg) and body surface area (2.59 meters^2) in the U.S. (adult male, 30 to 39 years, Fryar, 2016). In some cases, the maximum allowed units and/or vials may exceed the upper level limit as defined within this policy due to an individual patient body weight > 128 kg or body surface area > 2.59 meters^2.

Medication Name		Diagnosis	Maximum Dosage per Administration	HCPCS Code	Maximum Allowed
Brand	Generic				
Avastin	bevacizumab		15 mg/kg	J9035	192 HCPCS units (10 mg per unit)

Medication Name		Diagnosis	Maximum Dosage per Administration	HCPCS Code	Maximum Allowed
Brand	Generic				
Entyvio	vedolizumab		300 mg	J3380	300 HCPCS units (1 mg per unit)
Herceptin	trastuzumab		8 mg/kg	J9355	103 HCPCS units (10 mg per unit)
Neulasta	pegfilgrastim		6 mg total dose	J2505	1 HCPCS unit (6 mg per unit)
Fulphila	pegfilgrastim-jmdb		6 mg total dose	Q5108	12 HCPCS unit (0.5mg per unit)
Reclast	zoledronic acid		5 mg total dose	J3489	5 HCPCS units (1 mg per unit)
zoledronic acid			5 mg total dose		
			4 mg total dose		
Zometa			4 mg total dose		
Remicade	infliximab		10 mg/kg	J1745	128 HCPCS units (10 mg per unit)
Inflectra	infliximab-dyyb		10 mg/kg	Q5103	128 HCPCS units (10 mg per unit)
Renflexis	infliximab-abda		10 mg/kg	Q5104	128 HCPCS units (10 mg per unit)
Rituxan	rituximab		1,225 mg total dose	J9312	123 HCPCS units (10 mg per unit)
Soliris	eculizumab	PNH	900 mg	J1300	90 HCPCS units (10 mg per unit)
		aHUS, MG	1200 mg	J1300	120 HCPCS units (10 mg per unit)
Stelara	ustekinumab		90 mg	J3357	90 HCPCS units (1 mg per unit)
		Crohn's Disease	520 mg	J3358	520 HCPCS units (1 mg per unit)
Xolair	omalizumab	Asthma	375 mg	J2357	90 HCPCS units (5 mg per unit)
		Chronic Urticaria	300 mg	J2357	60 HCPCS units (5 mg per unit)

Maximum Allowed Quantities for National Drug Code (NDC) Billing
The allowed quantities in this section are calculated based upon both the maximum dosage information supplied within this policy as well as the process by which NDC claims are billed. This list may not be inclusive of all available NDCs for each drug product and is subject to change.

Medication Name		Diagnosis	How Supplied	National Drug Code	Maximum Allowed
Brand	Generic				
Avastin	bevacizumab		100 mg/4 mL solution in vials	50242-0060-01	77 mL
			400 mg/16 mL solution in vials	50242-0061-01	77 mL
Entyvio	vedolizumab		300 mg powder for reconstitution	64764-0300-20	1 Vial
Herceptin	trastuzumab		440 mg powder for reconstitution	50242-0056-56	3 vials
				50242-0134-68	3 vials
			420 mg powder for reconstitution	50242-0333-01	3 vials
			150 mg powder for reconstitution	50242-0132-01	3 vials
Inflectra	infliximab-dyyb		100 mg powder for reconstitution	32228-0001-01	13 vials
Neulasta	pegfilgrastim		6 mg/0.6 mL prefilled syringe	54868-5229-00	0.6 mL
				55513-0190-01	0.6 mL
			6 mg/0.6 mL prefilled syringe with on-body Injector	55513-0190-01	0.6 mL

Medication Name		Diagnosis	How Supplied	National Drug Code	Maximum Allowed
Brand	Generic				
Fulphila	pegfilgrastim-jmdb		6 mg/0.6ml prefilled syringe	67457-0833-06	0.6 mL
Reclast	zoledronic acid		5 mg/100 mL solution in vials	00078-0435-61	100 mL
				35356-0351-01	100 mL
Remicade	infliximab		100 mg powder for reconstitution	57894-0030-01	13 vials
Renflexis	infliximab-abda		100 mg powder for reconstitution	00006-4305-02	13 vials
Rituxan	rituximab		100 mg/10 mL solution in vials	50242-0051-21	130 mL
			500 mg/50 mL solution in vials	50242-0053-06	130 mL
Soliris	eculizumab	PNH	300 mg/30 mL solution in vials	25682-0001-01	90 mL
		aHUS, MG	300 mg/30 mL solution in vials	25682-0001-01	120 mL
Stelara	ustekinumab		45 mg/0.5 mL prefilled syringe	57894-0060-03	0.5 mL
			45 mg/0.5 mL solution in vials	57894-0060-02	0.5 mL
			90 mg/1 mL prefilled syringe	57894-0061-03	1 mL
		Crohn's Disease	130 mg/26 mL solution in vials	57894-0054-27	104 mL
Xolair	omalizumab	Asthma	150 mg powder for reconstitution	50242-0040-62	3 vials
		Chronic Urticaria	150 mg powder for reconstitution	50242-0040-62	2 vials
zoledronic acid	zoledronic acid		5 mg/100 mL solution in vials	25021-0830-82	100 mL
				42023-0163-01	
				43598-0331-11	
				23155-0186-31	
				55111-0688-52	
			4 mg/5 mL solution in vials	00143-9642-01	5 mL
				47335-0035-40	
				25021-0801-66	
				42023-0151-01	
				43598-0330-11	
				53150-0871-01	
				23155-0170-31	
				55111-0685-07	
				60505-6110-00	
				45963-0440-55	
			4 mg/5 ml lyophilisate for solution for injection in vials	47335-0962-41	5 mL
			4 mg/100 mL solution in vials	25021-0826-82	100 mL
Zometa	zoledronic acid		4 mg/5 mL solution in vials	00078-0387-25	5 mL
			4 mg/100 mL solution in vials	00078-0590-61	100 mL

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

HCPCS Code	Description
J1300	Injection, eculizumab, 10 mg

HCPCS Code	Description
J1745	Injection, infliximab, excludes biosimilar, 10 mg
J2357	Injection, omalizumab, 5 mg
J2505	Injection, pegfilgrastim, 6 mg
J3357	Ustekinumab, for subcutaneous injection, 1mg
J3358	Ustekinumab, for intravenous injection, 1mg
J3380	Injection, vedolizumab, 1 mg
J3489	Injection, zoledronic acid, 1 mg
J9035	Injection, bevacizumab, 10 mg
J9312	Injection, rituximab, 10 mg
J9355	Injection, trastuzumab, 10 mg
Q5103	Injection, Infliximab-dyyb, biosimilar, (Inflectra), 10 mg
Q5104	Injection, Infliximab-abda, biosimilar, (Renflexis), 10 mg
Q5108	Injection, pegfilgrastim-jmdb, biosimilar, (Fulphila), 0.5 mg

National Drug Code	Description
50242-0060-01	Avastin 100 mg/4 mL solution in vials
50242-0061-01	Avastin 400 mg/16 mL solution in vials
64764-0300-20	Entyvio 300 mg powder for reconstitution
67457-0833-06	Fulphila 6 mg/0.6ml prefilled syringe
50242-0056-56	Herceptin 440 mg powder for reconstitution
50242-0134-68	Herceptin 440 mg powder for reconstitution
50242-0333-01	Herceptin 420 mg powder for reconstitution
50242-0132-01	Herceptin 150 mg powder for reconstitution
32228-0001-01	Inflectra 100 mg powder for reconstitution
55513-0190-01	Neulasta 6 mg/0.6 mL prefilled syringe
54868-5229-00	Neulasta 6 mg/0.6 mL prefilled syringe
00078-0435-61	Reclast 5 mg/100 mL solution in vials
35356-0351-01	Reclast 5 mg/100 mL solution in vials
57894-0030-01	Remicade 100 mg powder for reconstitution
00006-4305-02	Renflexis 100 mg powder for reconstitution
50242-0051-21	Rituxan 100 mg/10 mL solution in vials
50242-0053-06	Rituxan 500 mg/50 mL solution in vials
25682-0001-01	Soliris 300 mg/30 mL solution in vials
57894-0060-03	Stelara 45 mg/0.5 mL prefilled syringe
57894-0060-02	Stelara 45 mg/0.5 mL solution in vials
57894-0061-03	Stelara 90 mg/1 mL prefilled syringe
57894-0054-27	Stelara 130 mg/26 mL solution in vials
50242-0040-62	Xolair 150 mg powder for reconstitution
25021-0830-82	Zoledronic Acid 5 mg/100 mL solution in vials
42023-0163-01	Zoledronic Acid 5 mg/100 mL solution in vials
43598-0331-11	Zoledronic Acid 5 mg/100 mL solution in vials
23155-0186-31	Zoledronic Acid 5 mg/100 mL solution in vials
55111-0688-52	Zoledronic Acid 5 mg/100 mL solution in vials
00143-9642-01	Zoledronic Acid 4 mg/5 mL solution in vials
47335-0035-40	Zoledronic Acid 4 mg/5 mL solution in vials
25021-0801-66	Zoledronic Acid 4 mg/5 mL solution in vials
42023-0151-01	Zoledronic Acid 4 mg/5 mL solution in vials

National Drug Code	Description
43598-0330-11	Zoledronic Acid 4 mg/5 mL solution in vials
53150-0871-01	Zoledronic Acid 4 mg/5 mL solution in vials
23155-0170-31	Zoledronic Acid 4 mg/5 mL solution in vials
55111-0685-07	Zoledronic Acid 4 mg/5 mL solution in vials
60505-6110-00	Zoledronic Acid 4 mg/5 mL solution in vials
45963-0440-55	Zoledronic Acid 4 mg/5 mL solution in vials
47335-0962-41	Zoledronic Acid 4 mg/5 ml lyophilisate for solution for injection in vials
25021-0826-82	Zoledronic Acid 4 mg/100 mL solution in vials
00078-0387-25	Zometa 4 mg/5 mL solution in vials
00078-0590-61	Zometa 4 mg/100 mL solution in vials

BENEFIT CONSIDERATIONS

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

CLINICAL EVIDENCE

The aforementioned pharmaceuticals all have dosing parameters that support a maximum dosage per body weight or body surface area or a set maximal dosage independent of patient body size. These maximum doses are product-specific, and in some cases, disease state-specific and are defined in the U.S. Food and Drug Administration (FDA) approved product prescribing information and/or in national compendia and other peer reviewed resources. This policy creates an upper dose limit based on the clinical evidence and the 95th percentile for adult body weight (128 kg) and body surface area (2.59 meters^2) in the U.S. (adult male, 30 to 39 years, Fryar, 2016).
Clinical evidence supports the use of the medications listed in this policy up to maximum dosages based upon body surface area or patient weight, when used according to labeled indications or when otherwise supported by published clinical evidence.

Clinical evidence does not support the use of the medications listed in this policy beyond maximum dosages based upon body surface area or patient weight. Use of these agents beyond such established maximum dosages adds significantly to risk of adverse events without conferring additional clinical benefit.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) that addresses the maximum dosage for bevacizumab, eculizumab, infliximab, infliximab-abda, infliximab-dyyb, omalizumab, pegfilgrastim, pegfilgrastim-jmdb, rituximab, trastuzumab, ustekinumab, vedolizumab and zoledronic acid. Local Coverage Determinations (LCDs) exist for the drugs listed below. These LCDs are available at http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx. (Accessed October 26, 2018)

- Infliximab, infliximab-dyyb and infliximab-abda
  - Drugs and Biologicals, Coverage of, for Label and Off-Label Uses
  - Infliximab (Remicade™)
  - Infliximab
  - Drugs and Biologics (Non-chemotherapy)
- Rituximab
  - Drugs and Biologicals, Coverage of, for Label and Off-Label Uses
  - Rituximab (Rituxan®)
- Bevacizumab
  - Drugs and Biologicals, Coverage of, for Label and Off-Label Uses
  - Drugs and Biologics (Non-chemotherapy)
- Trastuzumab
  - Trastuzumab (Herceptin®)
- Zoledronic acid
  - Drugs and Biologicals, Coverage of, for Label and Off-Label Uses

- Pegfilgrastim
  - Pegfilgrastim (Neulasta®)
  - Drugs and Biologicals, Coverage of, for Label and Off-Label Uses
  - White Cell Colony Stimulating Factors
  - Human Granulocyte/Macrophage Colony Stimulating Factors
- Omalizumab
  - Omalizumab (Xolair®)
  - Drugs and Biologicals, Coverage of, for Label and Off-Label Uses
  - Drugs and Biologics (Non-chemotherapy)
- Eculizumab
  - Drugs and Biologics (Non-chemotherapy)

REFERENCES

1. Avastin [prescribing information]. South San Francisco, CA: Genentech, Inc.; June 2018.
2. Constantine S. Tam, Susan O'Brien, William Wierda, Hagop Kantarjian, Sijin Wen, Kim-Anh Do, Deborah A. Thomas, Jorge Cortes, Susan Lerner, and Michael J. Keating. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood 2008; 112: 975-980.
3. Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric Reference Data for Children and Adults: United States, 2011-2014. Vital Health Stat 3. 2016 Aug;(39):1-46..
4. Herceptin [prescribing information]. South San Francisco, CA: Genentech, Inc.; October 2018.
5. Neulasta [prescribing information]. Thousand Oaks, CA: Amgen Inc.; June 2018.
6. Reclast [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; July 2017.
7. Remicade [prescribing information]. Horsham, PA: Janssen Biotech Inc.; June 2018.
8. Rituxan [prescribing information]. South San Francisco, CA: Genentech, Inc.; October 2018.
9. Zometa [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; March 2016.
10. Reimbursement Codes [database online]. Rocky Hill, CT: RJ Health Systems International, LLC.; 2018.
11. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2018.
12. Inflectra [prescribing information]. New York, NY: Pfizer Labs; July 2018.
13. Stelara [prescribing information]. Horsham, PA: Janssen Biotech, Inc. June 2018.
14. Entyvio [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; February 2018.
15. Soliris [prescribing information]. Boston, MA: Alexion Pharmaceuticals, Inc.; July 2018.
16. Renflexis [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp; November 2017.
17. Xolair [prescribing information]. South San Francisco, CA: Genentech, Inc., September 2018.
18. Fulphila [prescribing information]. Rockford, IL: Mylan Institutional, LLC, June 2018.

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
03/01/2019	Reorganized policy template; simplified and relocated *Instructions for Use* and *Benefit Considerations* section. Archived previous policy version 2019D0034S.
01/01/2019	Annual review of the policy. Removed J9310 and associated maximum units. Added J9312 and applicable maximum units. Updated body weight and body surface area limits. Updated maximum dosages for bevacizumab, infliximab, trastuzumab. Updated CMS and references. Approved by the National Pharmacy & Therapeutics Committee on 12/19/2018. Policy 2018D0034R archived.
10/01/2018	Off cycle review. Added Q5108 and max dosage for Fulphila. Approved by the National Pharmacy & Therapeutics Committee on 09/19/2018. Policy 2018D0034Q archived.
04/01/2018	Off cycle review. Removed Q5102. Added Q5103, Q5104. Added new Herceptin vial sizes. Approved by National Pharmacy & Therapeutics Committee 03/21/2018. Policy 2018D0034P archived.
01/01/2018	Updated list of applicable HCPCS codes to reflect annual code edits: added J3358 and removed Q9989. Archived previous policy version 2017D0034O

Date	Action/Description
11/01/2017	Annual review of the policy. Added Entyvio, Renflexis, Soliris, Stelara, and Xolair to the policy. Approved by National Pharmacy & Therapeutics Committee 07/26/2017. Policy 2017D0034N archived.
02/01/2017	Annual review of the policy. Moved policy into new template. Added codes and quantity limit for Inflectra and Stelara. Approved by National Pharmacy & Therapeutics Committee 12/21/2016. Policy 2016D0034M archived.
01/01/2017	Policy revised. Updated description for J1745 Injection, infliximab, excludes biosimilar, 10mg. Policy 2016D0034L archived.
05/01/2016	Updated coverage rationale. Approved by National Pharmacy & Therapeutics Committee 02/26/2016. Policy 2015D0034K archived.
07/01/2015	Annual review of policy. Added codes for zoledronic acids. References updated. Approved by National Pharmacy & Therapeutics Committee 04/14/2015. Policy 2014D0034J archived.
06/01/2014	Annual review of policy. References updated. Approved by National Pharmacy & Therapeutics Committee 04/08/2014. Policy 2014D0034I archived.
01/01/2014	Policy updated with code J3489, effective on 01/01/2014. Removed inactive codes J3487 and J3488. Policy 2013D0034H archived.
07/01/2013	Policy updated. Added Reclast (zoledronic acid) to the policy. Added maximum allowed amounts for providers billing claims by NDC rather than J code. Added J3488 to policy. Approved by National Pharmacy & Therapeutics Committee 05/21/2013. Policy 2013D0034G archived.
06/01/2013	Policy revised. Increased 95th percentile for adult weight and BSA based upon NHANES 2007-2010 data, which resulted in revised upper dose limits for bevacizumab, infliximab, rituximab, and trastuzumab. Clinical evidence and references updated. Approved by National Pharmacy & Therapeutics Committee 04/09/2013. Policy 2013D0034F archived.
01/01/2013	Annual review of policy. References updated. Approved by National Pharmacy & Therapeutics Committee 11/13/2012. Policy 2012D0034E archived.
01/01/2012	Annual review of policy. Increased 95th percentile for adult weight and BSA based upon NHANES 2003-2006 data, which resulted in revised upper dose limits for infliximab, trastuzumab, bevacizumab, and rituximab. Approved by National Pharmacy & Therapeutics Committee 11/08/2011. Policy 2010D0034D archived.
11/24/2010	Annual review of policy with updates to CMS and Reference sections. Approved by National Pharmacy & Therapeutics Committee 11/09/2010. Policy 2009D0034C archived.
12/23/2009	Policy revised with changes in rituximab maximum dosage. Approved by National Pharmacy & Therapeutics Committee on 12/08/2009. Policy 2008D0034B archived.
04/07/2009	Policy revised with changes in bevacizumab maximum dosage. Policy 2008D0034A archived

INSTRUCTIONS FOR USE

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Drug Policies are intended to be used in connection with the

independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.