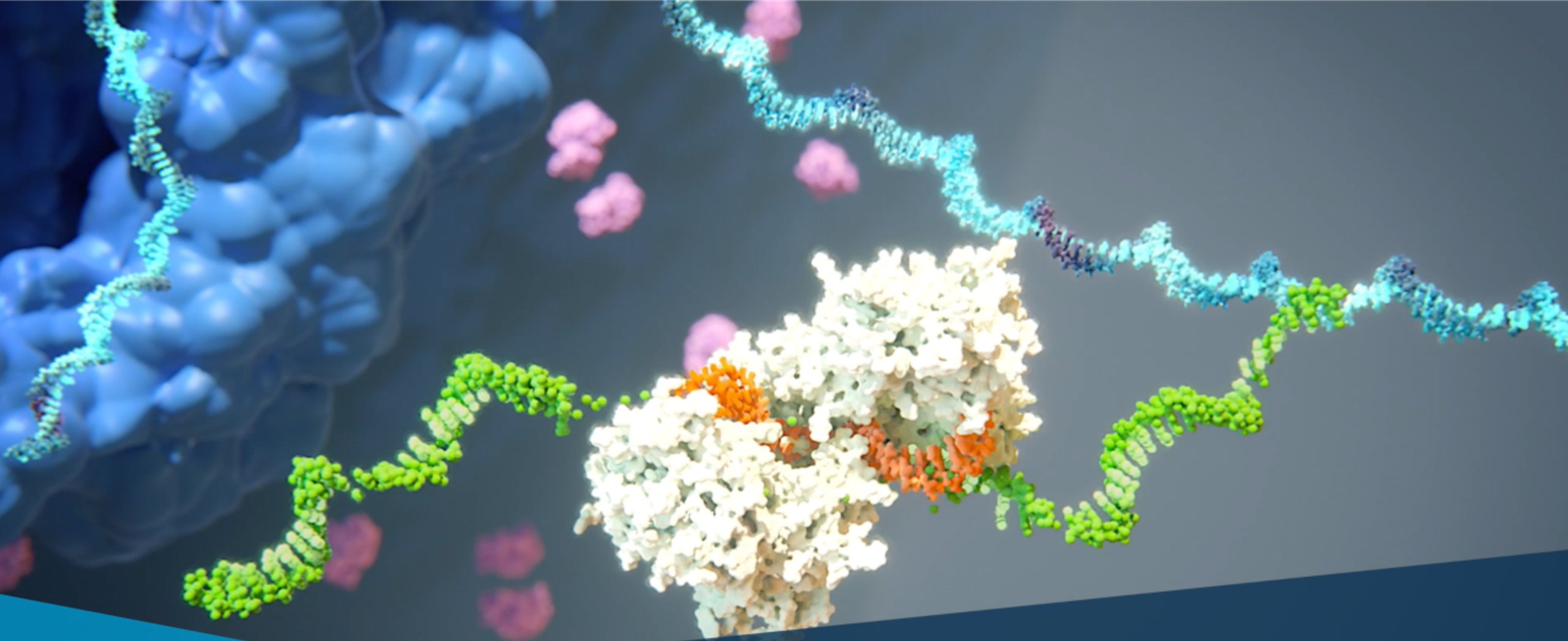


Medicare DME Coverage for ONPATTRO®

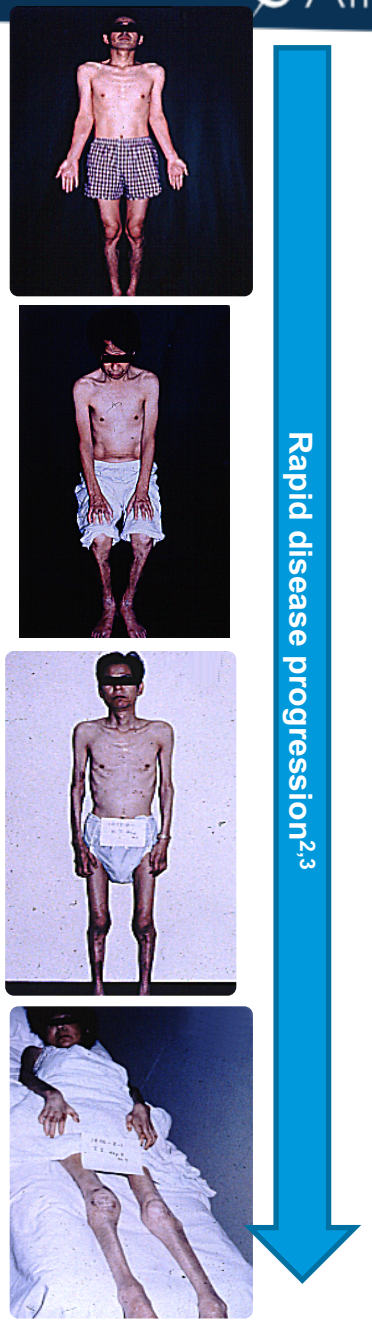
July 14, 2020

Alnylam® PHARMACEUTICALS

Hereditary ATTR (hATTR) Amyloidosis

Rare, Hereditary Progressively Debilitating, and Often Fatal Disease

- Caused by misfolded TTR protein that accumulates as amyloid deposits in multiple tissues including heart, nerves, and GI tract[1]
- Patients experience progressive symptoms which may include:
  - Peripheral neuropathy: Motor weakness, sensory loss, mobility challenges
  - Autonomic symptoms: orthostatic hypotension, persistent diarrhea, incontinence, falls, weight loss
  - Heart failure
- The median survival is 4.7 years following diagnosis[4]
- Rare orphan disease: hATTR polyneuropathy affects ~10,000-15,000[a] patients in the US with ~10-30%[a,2] diagnosed



TTR=transthyretin

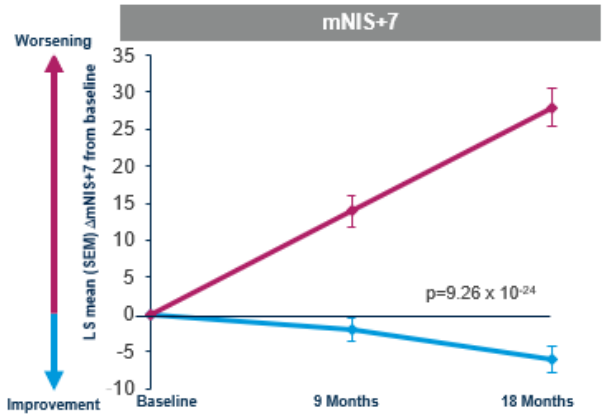
References: [1] Coelho T, et al. N Engl J Med. 2013;369(9):819-829; 2. Ando Y, et al. Orphanet J Rare Dis. 2013;8:31. 3. Conceição I, et al. J Peripher Nerv Syst. 2016;21(1):5-9. 4. Swiecicki PL, et al. Amyloid. 2015;22(2):123-131. 5. Ando, et al. Orphanet J Rare Dis, 2013; Ruberg, et al. Circulation, 2012.

a. Based on Alnylam estimates from interviews with key opinion leaders, THAOS registry, recent clinical trials and literature

Treatment with ONPATTRO®

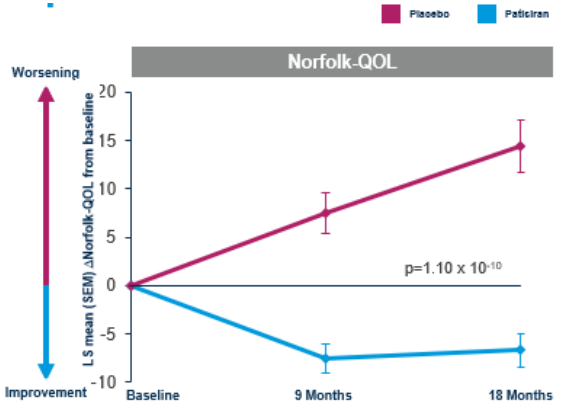
ONPATTRO® (patisiran) significantly improved polyneuropathy, and has shown reversal of disease in pivotal trials

- ONPATTRO® is the first treatment approved to treat hATTR polyneuropathy
  - A lipid nano-particle delivered siRNAi therapy that reduces TTR mRNA through RNA interference→ reducing serum TTR and TTR deposits in tissues
- Administered by a one-hour infusion every 3 weeks through an ambulatory infusion pump following premedication with corticosteroid, acetaminophen and IV H1 & H2 blockers
- All primary and secondary endpoints in pivotal APOLLO trial met including reversal of polyneuropathy from baseline in the majority of patients as measured by mNIS+7 and Norfolk QOL



At 18 months

- -6.0 point change relative to baseline
- 34.0 point difference relative to placebo
- 56.1% of patients improved*



At 18 months

- -6.7 point change relative to baseline
- 21.1 point difference relative to placebo
- 51.4% of patients improved*

References: 1. ONPATTRO [package insert]. Cambridge, MA: Alnylam Pharmaceuticals, Inc; 2018. 2. Adams et al. *N Engl J Med* 2018;379(1):11-21

Our Understanding of the Impediments

- Our understanding of CMS's objections to covering ONPATTRO under the DME benefit for home infusion are two-fold:

1. The definition of 'home infusion drugs' covered under DME benefit

→ MACs have interpreted this to limit coverage to only drugs that are self-administered; however, this interpretation has been inconsistently applied to add and cover drugs / indications under DME LCD L33794

Coverage "In the home" has never been defined

2. The cost of the pump and/or drug

→ CMS cannot deny coverage of an item or service based on cost alone

Net costs to CMS are minimal

MACs Have Inconsistently Applied Self-Administration Requirement Under DME LCD L33794

- DME MACs have limited coverage for home infusion to those drugs covered under DME LCD
- DME MACs have noted that certain characteristics of drugs would not be appropriate for coverage on DME LCD
  - Drugs requiring Healthcare Professional administration
  - Drugs not administered via a PICC line
  - Drugs requiring Premedications
- 13 of 37 drugs on LCD L33794 have FDA labels requiring HCP Administration, are not infused by a PICC line or require premedications
- Furthermore, few non-IVIG drugs added to L33794: only 2 non-IVIG drugs added since 2008

Drugs Requiring Healthcare Professional Administration[1]

- Epoprostenol
- Ganciclovir Sodium
- Morphine Sulfate
- Ziconotide
- Fentanyl Citrate
- Blinatumomab
- Cladribine
- Floxuridine
- Vinblastine Sulfate
- Vincristine Sulfate
- Hydromorphone
- Bleomycin Sulfate
- Amphotericin B Lipid Complex (Abelcet)

Drugs Not Administered via PICC Line

- Deferoxamine Mesylate
- Hydromorphone
- Gallium Nitrate
- Meperidine HCl
- Milroinone Sulfate
- Ziconotide
- Fentanyl Citrate
- Immune Globulin (multiple)
- Doxorubicin HCl
- Blinatumomab
- Bleomycin Sulfate
- Cladribine
- Cytarabine
- Fluorouracil
- Floxuridine
- Vinblastine Sulfate
- Vincristine Sulfate

Drugs Requiring Pre-medication(s)

- Blinatumomab

DME: Durable Medical Equipment; LCD: Local Coverage Determination; MAC: Medicare Administrative Contractor.

[1] Many drugs on DME LCD were approved prior to the 2006 revision of the FDA package insert format and therefore Boxed Warnings, Indications and Usage, Dosage and Administration terminology such as “required healthcare professional administration” are inconsistently documented. Other HCP-administered suggested drugs were left off this list foscarnet sodium, meperidine HCl, milrinone lactate, dopamine HCl, and cytarabine, but could be considered as requiring some HCP supervision and/or administration

We Seek Language in the DMEPOS Proposed Rule to Enable DME Coverage of ONPATTRO® for Home Infusion in Medicare Part B

- ONPATTRO (patisiran) was approved in August 2018; it remains the only drug infused through an ambulatory infusion pump approved by the FDA after the enactment of the Bipartisan Budget Act of 2018

- Our ask is to include language in the preamble to the DMEPOS proposed rule that adds HCPCS code J0222 to the temporary transitional home infusion payment, under payment category 1 and adds ONPATTRO to DME LCD L33794 (External Infusion Pump)
  - HCPCS code J0222 would therefore be added to the permanent home infusion benefit, consistent with CMS's existing policy of including all codes in the temporary transitional payment in the permanent benefit

- This change would lead to cost savings of ~45% per infusion on administration costs if infused at home compared to hospital outpatient department (HOPD)
  - Home infusion of a Medicare Part B patient on ONPATTRO translates into per beneficiary annual savings of $2,343.71 for Category 1 administration costs compared to HOPD administration (HOPD: $5,067.19; Home: $2,723.48)
  - Home infusion lead to beneficiary out-of-pocket savings of $469 per infusion and Medicare program savings of $1,875
  - Total annual home infusion costs per beneficiary are estimated at $6,331.21 (administration $2,723.48; supplies $434.69; pump rental $3,173.04): net cost is ~$1,270 for fewer than 500 Medicare patients

Draft Language to Provide Narrow Solution in DME Drug Coverage

Proposed Language for Preamble of DMEPOS Rule Regarding External Infusion Pumps Covered Under the DME Benefit Category and Associated Home Infusion Drugs

Section 1834(u)(7)(C)(iv) of the Social Security Act contemplates that new drugs will be added to the transitional payment for home infusion therapy services, if the codes describing the drugs are implemented after the Bipartisan Budget Act of 2018's (BBA's) enactment and the drugs meet the statutory definition of a home infusion drug. We have become aware of a drug code that satisfies these criteria: Healthcare Common Procedure Coding System (HCPCS) code J0222. We therefore propose to add HCPCS code J0222 to the temporary transitional payment, under payment category 1 (because that category includes similar intravenous, non-chemotherapy infusion drugs). Because J0222 describes a non-self-administered drug, we expect that this drug would be appropriate for use in the home when it can be furnished by a qualified home infusion therapy supplier in a safe and effective manner in the home. We propose to adopt this policy effective immediately on the date of publication of the final rule.[1] If this proposal is finalized, HCPCS code J0222 would also be added to the permanent home infusion benefit, consistent with our existing policy of including all codes in the temporary transitional payment in the permanent benefit.

[1]To the extent necessary, good cause supports waiver of any requirement to delay the effective date of this policy. The transitional payment expires on December 31, 2020. Delaying adoption of this policy until the effective date of the final rule would thus prevent HCPCS code J0222 from being added to the transitional payment, while the transitional payment is still in effect. We also believe that our proposal is in the public interest: Congress intended new codes to be added into the transitional payment expeditiously before its expiration, which is why Congress authorized home infusion drug codes to be added to the transitional payment through sub-regulatory guidance.

ONPATTRO Meets the Statutory and Regulatory Tests for Coverage As a "Home Infusion Drug"

SSA 1861(iii)(3)…

(C) "Home infusion drugs" are defined as "a parenteral drug or biological administered intravenously, or subcutaneously for an administration period of 15 minutes or more, in the home of an individual through a pump that is an item of durable medical equipment (as defined in subsection (n)). Such term does not include the following:

(i) Insulin pump systems

(ii) A self-administered drug or biological on a self-administered drug exclusion list" [1]

CY21 Home Infusion Proposed Rule

We stated that, consistent with the definition of "home infusion therapy," the home infusion therapy services payment explicitly and separately pays for the professional services related to the administration of the drugs identified on the DME LCD for External Infusion Pumps (L33794)13, when such services are furnished in the individual's home. For purposes of the temporary transitional payments for home infusion therapy services in CYs 2019 and 2020, the term "transitional home infusion drug" includes the HCPCS codes for the drugs and biologicals covered under the DME LCD for External Infusion Pumps (L33794)14.

Therefore, in the CY 2020 HH PPS final rule with comment period (84 FR 60618), we stated that this means that "home infusion drugs" are defined as parenteral drugs and biologicals administered intravenously, or subcutaneously for an administration period of 15 minutes or more, in the home of an individual through a pump that is an item of DME covered under the Medicare Part B DME benefit, pursuant to the statutory definition set out at section 1861(iii)(3)(C) of the Act, and incorporated by cross reference at section 1834(u)(7)(A)(iii) of the Act.

Note: Emphasis added in statutory references.

[1] SSA 1861(iii)(2)(C). This exclusion list is comprised of drugs identified by the MAC, which are "usually self-administered by the patients" and therefore not eligible for Part B. Pub. L. 114-225 Section 5012 21st Century Cures Ac; available at https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf

Back-Up

Medicare Part B Drug Infusion Reimbursement in Hospital Outpatient Department and Home Settings

Estimated Annual Category 1 Drug Infusion Costs for a Drug Administered Every 3 Weeks (Per Beneficiary)

	Hospital Outpatient Dept.[2]			Home Infusion[5]		
Category 1 Infusion[1]	**CPT® Code**	**Units**	**Unit Cost**	**CPT® Code**	**Units**	**Unit Cost**
First infusion						
Line 1	96365	1	$183.74	96365	1	$72.18
Line 2	96366	3[3]	$38.11	96366	4	$22.01
Calculation			(1 x $183.74) + (3 x $38.11)			160% x ((1 x $72.18) + (4 x $22.01))
First Infusion Total Cost			$298.07			$256.35
Subsequent infusion						
Line 1	96365	1	$183.74	96365	1	$72.18
Line 2	96366	3[3]	$38.11	96366	4	$22.01
Calculation			(1 x $183.74) + (3 x $38.11)			96.24% x ((1 x $72.18) + (4 x $22.01))
Subsequent Infusion Total Cost			$298.07			$154.20
Infusions Per Year[4]			17			17
Annualized Costs Formula			First infusion + (16 x subsequent infusion)			First infusion + (16 x subsequent infusion)
Calculation of Annual Costs			$298.07 + (16 x $298.07)			$256.35 + (16 x $154.20)
Total Annual Category 1 Costs			**$5,067.19**			**$2,723.48**

CPT: Current Procedural Terminology

[1]Per 2020 Home Infusion Final Rule, payment categories will be carried over from Temporary Transitional Home Infusion Benefit to Permanent Home Infusion Benefit. We assume drug to be covered under Category 1 payment category for modeling purposes. [2]Based on CY2020 Medicare Hospital Outpatient Prospective Payment System payment rates. [3]Assume a 4-hour infusion time is typically billed. [4]Assume drug is infused every 3 weeks, or approximately 17 times per year. [5]Payment rates based on 2020 Physician Fee Schedule. Estimates based on national payment amount. Weighting of first infusion and subsequent infusion based on 2020 Home Health / Home Infusion Final Rule. Per 2020 Home Health / Home Infusion Final Rule, payments will be made based on a 5-hour infusion regardless of the length of the visit.

Estimated Savings to Government and Beneficiaries for Home Infusion Compared to Hospital Outpatient Department-Based Drug Administration

Category 1 Infusion Cost Savings Estimates[1]	
HOPD Total Annual Costs[2,3]	$5,067.19
Home Infusion Total Annual Costs[3,4]	$2,723.48
Difference	**$2,343.71**
Savings (%)	**46.25%**
Savings per beneficiary per year	**$2,343.71**
Savings per 1,000 beneficiaries per year	**$2,343,710**
Savings per 1,000 beneficiaries over 10 years	**$23,437,100**

Cost Savings Estimates for Medicare and Beneficiaries

	Medicare Reimbursement	Beneficiary Liability
Medicare HOPD Annual Costs	$4,053.75	$1,013.44
Home Infusion Annual Costs	$2,178.78	$544.70
Difference	**$1,874.97**	**$468.74**
Savings (%)	**46.25%**	**46.25%**

Assumptions

- Assumes drug can be safely administered in the home setting
- Assumes majority of Medicare beneficiaries currently treated in hospital outpatient department setting
- Assumes patients adhere to treatment regimen with no change in compliance per prescribing information (e.g., infusion once every 3 weeks)
- Assumes Medicare beneficiaries liable for statutory cost sharing amount of 20%

HOPD: Hospital Outpatient Department.

[1]Per 2020 Home Infusion Final Rule, payment categories will be carried over from Temporary Transitional Home Infusion Benefit to Permanent Home Infusion Benefit. We assume drug to be covered under Category 1 payment category for modeling purposes. [2]Based on CY2020 Medicare Hospital Outpatient Prospective Payment System payment rates. [3]Drug is infused every 3 weeks, or approximately 17 times per year. [4]Payment rates based on 2020 Physician Fee Schedule. Estimates based on national payment amount. Weighting of first infusion and subsequent infusion based on 2020 Home Health / Home Infusion Final Rule.

A Hypothetical Example of Medicare Costs Under the Permanent Home Infusion Benefit

Product / Service	Relevant Codes	Payment Rate
Per Day Drug Payment Based on J-Code	**Category 1 Code**	**Note:** Assume infusions every 3 weeks = 17 infusions per year
First Infusion Per Day Payment for Home Infusion Administration for a Category 1 Therapy	**96365** – Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug) **96366x4** – Each additional hour, for a five-hour infusion	160% x ((1 x $72.18) + (4 x $22.01)) = $256.35
Subsequent Infusion Per Day Payment for Home Infusion Administration for a Category 1 Therapy	**96365** – Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug) **96366x4** – Each additional hour, for a five-hour infusion	96.24% x ((1 x $72.18) + (4 x $22.01)) = $154.20
Per Day Payment for Infusion Supplies	**A4221**- Supplies For Maintenance Of Drug Infusion Catheter, Per Week (List Drug Separately) **K0552-** Supplies For External Drug Infusion Pump, Syringe Type Cartridge, Sterile, Each	$22.70 + $2.87 = $25.57
	Total Costs (Without External Infusion Pump)	Administration **[$2,723.48]** + Per Day Infusion Supplies **[$434.69]** = **$3,158.17**
Monthly Payment for Rental of External Infusion Pump	**E0781** - Ambulatory Infusion Pump, Single Or Multiple Channels, Electric Or Battery Operated, With Administrative Equipment, Worn By Patient	$264.42 (monthly rental)[1]
	Total Annual Costs	$3,158.17 +(12 x $264.42) = **$6,331.21**

[1] Based on national average from DMEPOS Jul 2020 Fee Schedule

Assumptions:

- Four hour infusion
- Transitional payment is paid under paid under Part B therefore resulting in a 20% patient coinsurance
- Total reimbursement assumes the full cost of the monthly rental for the external infusion pump