AMYLOIDOSIS

CHI Formulary Indication Review

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Contents

Abbreviations

AL Amyloidosis	Light Chain Amyloidosis
ATTR-CM	Transthyretin Amyloidosis Cardiomyopathy
ATTR Amyloidosis	Transthyretin Amyloidosis
ATTRwt	Wild-Type Transthyretin Amyloidosis
ANC	Absolute neutrophil count
ASO	Antisense Oligonucleotide
CBC	Complete Blood Count
CrCl	Creatinine Clearance
CyBorD	Cyclophosphamide/Bortezomib/Dexamethasone
Dara-CyBorD	Daratumumab/Cyclophosphamide/Bortezomib/Dexamethasone
FLC	Free Light Chain
G-CSF	Granulocyte colony-stimulating factor
hATTR	Hereditary Transthyretin Amyloidosis
Hb	Hemoglobin
HCT	Hematopoietic Cell Transplantation
HF	Heart Failure
ICER	Incremental Cost Effectiveness Ratio
IMiD	Immunomodulatory Drug
KSA	Kingdom of Saudi Arabia
NCCN	National Comprehensive Cancer Network
NYHA	New York Heart Association
OS	Overall Survival
PD	Peritoneal Dialysis
PFS	Progression-Free Survival
PI	Proteasome Inhibitor
RBC	Red Blood Cells
SCT	Stem Cell Transplant
siRNA	Small Interfering RNA
TTR	Transthyretin

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Executive Summary

Amyloidosis is a heterogeneous disease that results from the extra-cellular deposition of insoluble beta-sheet fibrillar protein aggregates in different tissues[1]. Amyloidosis can be acquired or hereditary. The disease can be localized or systemic. Amyloid can accumulate in the liver, spleen, kidney, heart, nerves, and blood vessels, causing different clinical syndromes, including cardiomyopathy, hepatomegaly, proteinuria, macroglossia, autonomic dysfunction, ecchymoses, neuropathy, renal failure, hypertension, and corneal and vitreous abnormalities[1,2].

Amyloidosis is a rare disease, with an estimated incidence of 1 to 5 cases per 100,000 people[3]. It is estimated that about 4,000 people in the United States develop amyloid and light chain (AL) amyloidosis each year. The disease is typically diagnosed between the ages of 50 and 65. However, people as young as 20 have also been diagnosed with AL amyloidosis[4].

There are 18 different types of systemic and 22 localized forms of amyloidosis[5]. The principal systemic types seen in tertiary referral centers and inpatient medical services are:

- **Immunoglobulin light chain (AL amyloidosis):** AL amyloidosis is due to deposition of protein derived from immunoglobulin light chain fragments. It is a potential complication of any plasma cell dyscrasia that produces monoclonal immunoglobulin light chains. AL amyloidosis is a systemic disorder that can present with a variety of symptoms or signs, including heavy proteinuria (usually in the nephrotic range) and edema, hepatosplenomegaly, otherwise unexplained heart failure, and the carpal tunnel syndrome. This disorder has a poor long-term prognosis, with cardiac or hepatic failure, and infection being the major causes of death[5].

    - **Transthyretin (ATTR amyloidosis):** ATTR amyloidosis may occur as a **"wild-type" (ATTRwt)** associated with aging or as **mutant proteins** (**ATTRv** or **hATTR** [where v indicates a **variant** and h indicates **hereditary**; these were formerly termed ATTRm, to indicate a mutant protein]) associated with familial neuropathy and/or cardiomyopathy[5].

- **AA amyloidosis:** Also known as secondary amyloidosis, it is a potential complication of chronic diseases in which there is ongoing or recurring inflammation (such as chronic infections, rheumatoid arthritis, spondyloarthritis, or inflammatory bowel disease). The chronic inflammation results in sustained high-level production of serum amyloid A protein, an acute phase reactant, which can form amyloid deposits. It is the most common form in resource-limited countries[5].

Clinical manifestations vary depending upon the type of amyloid and the distribution of deposition. Some features that suggest amyloidosis include waxy skin and easy bruising, enlarged muscles (e.g., tongue, deltoids), carpal tunnel syndrome, heart failure, cardiac conduction abnormalities, hepatomegaly, heavy proteinuria or the nephrotic syndrome, peripheral and/or autonomic neuropathy, and impaired coagulation. The frequency of cardiac involvement varies among types of amyloidosis. The prognosis of **amyloid cardiomyopathy** also varies among types of amyloidosis, with high mortality rates particularly in light-chain (AL) amyloidosis[6].

Diagnosis is to be confirmed by **tissue biopsy** in all cases. Fat pad aspiration biopsy is the preferred initial biopsy technique for patients with other than single-organ involvement, because it is less likely to be complicated by serious bleeding than liver, renal, or rectal biopsy. In patients with single-organ involvement, biopsy of the clinically involved site is preferred[1,6].

Patients with biopsy-documented amyloidosis and a well-defined plasma cell dyscrasia (e.g., multiple myeloma or Waldenström macroglobulinemia) need not undergo further testing for an **underlying hematologic disorder**. Patients without a known plasma cell disorder should be tested to determine whether a **monoclonal protein** is present in serum, urine, or both using a combination of serum and urine protein electrophoresis, followed by immunofixation. Quantitation of serum free light chains (FLCs) is suggested for AL patients who do not have monoclonal proteins by immunofixation[1,6].

Data on the incidence of amyloidosis in Kingdom of Saudi Arabia (KSA) is scarce in the medical literature. Only one study was published examining transthyretin amyloidosis variants identified in the Saudi population[7]. An existing exome variant database of Saudi individuals, sequenced to globally investigate rare diseases in the population, was mined for *TTR* variants and filtered for missense mutations resulting in single amino acid changes. A total of 13,906 Saudi exomes from unrelated individuals were analyzed blindly. **Three *TTR* variants known to be associated with ATTR amyloidosis were identified**. Additionally, three novel *TTR* mutations were identified. Structural analysis of the three novel variants suggests that at least two could be amyloidogenic. **The most common variant associated with amyloidosis was p.Val142Ile** (allele frequency 0.001). Further investigation of these variants and their translation to clinical practice may help to diagnose, monitor, and manage patients with ATTR amyloidosis[7].

This report compiles all clinical and economic evidence related to amyloidosis and associated complications according to the relevant sources. The ultimate objective of issuing amyloidosis guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with **the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to amyloidosis patients in Saudi Arabia.** The main focus of the review was on Saudi, North American, and European guidelines issued within the last five years in addition to recent systematic reviews and Meta-Analysis.

Amyloidosis is linked to multiple complications; these include cardiomyopathy, arrhythmias, and gastrointestinal (GI) complications (nausea and vomiting, diarrhea, GI bleeding). **For a detailed review of these complications, please refer to the individual reports for each indication.**

Treatment of the different types of amyloidosis generally varies with the cause of fibril precursor production (e.g., treatment of the plasma cell dyscrasia in patients with immunoglobulin light chain [AL] amyloidosis, control of underlying inflammatory or infectious disease in AA amyloidosis)[8,9,10,11,12,13,14,15].

A. Management of AL amyloidosis

To best treat patients with AL amyloidosis, the initial evaluation must confirm the diagnosis, establish the extent and sites of the disease, and evaluate for comorbidities that are likely to have an impact on prognosis and treatment options. Simple staging systems that incorporate NT-proBNP and cardiac troponin are easily applied at the point of care. **In AL amyloidosis, treatment is directed primarily at suppressing the underlying plasma cell dyscrasia** [8,9,10,11,12,13,14,15].

The approach to the initial management of patients with AL amyloidosis varies depending on whether patients are eligible to pursue high dose melphalan followed by autologous hematopoietic cell transplantation (HCT). In general, patients with poor performance status, major comorbidities, involvement of three or more organs, and advanced cardiac amyloidosis are not considered transplant candidates [8,9,10,11,12,13,14,15].

A1. HCT-eligible patients

- **Induction therapy followed by high dose melphalan and autologous HCT** rather than chemotherapy alone is the preferred treatment approach (Recommendation Level A, Evidence Level II), provided that HCT can be performed in referral centers with adequate expertise in the procedure for this group of patients [8,9,10,11,12,13,14,15].
  - As induction therapy, **two to four cycles of a bortezomib-based regimen** are recommended. The preferred regimen is **daratumumab plus cyclophosphamide, bortezomib, and dexamethasone (Dara-CyBorD)** (Recommendation Level A, Evidence Level I) [8,12,13].
  - If daratumumab is not available, induction with CyBorD alone is an acceptable alternative (Recommendation Level A, Evidence Level II).
  - Other alternatives include Bortezomib ± Dexamethasone and Bortezomib/Lenalidomide/Dexamethasone (Recommendation Level A, Evidence Level II) [8,12,13].
  - Bortezomib and dexamethasone doses need to be adapted to cardiac stage, presence of autonomic/ peripheral neuropathy, fluid retention status and patient's functional status [8,12,13].

- Full high dose melphalan at 200 mg/m^2 is the preferred conditioning regimen prior to SCT and AMYLOID3 modified dose melphalan at 140 mg/m^2 should be used for patients with reduced renal function [8,12,13].
- Consolidation and maintenance therapy are not routinely recommended after SCT in AL amyloidosis [8,12,13].

A2. Patients not eligible for HCT

- For patients not eligible for HCT, a **bortezomib-based regimen** is recommended rather than melphalan plus dexamethasone (Recommendation Level A, Evidence Level II).
  - **Daratumumab plus CyBorD is the preferred regimen** (Recommendation Level A, Evidence Level I) [8,12,13].
  - If daratumumab is not available, acceptable alternatives are CyBorD alone or bortezomib, melphalan, and dexamethasone (VMDex) (Recommendation Level A, Evidence Level II) [8,12,13].
  - Bortezomib and dexamethasone doses need to be adapted to cardiac stage, presence of autonomic/ peripheral neuropathy, fluid retention status and patient's functional status.
  - Daratumumab is offered as a single agent or in combination with cyclophosphamide and dexamethasone to patients who are not candidates for bortezomib (i.e. patients with neuropathy) (Recommendation Level B, Evidence Level II) [8,12,13].
  - Lenalidomide/Dexamethasone or oral melphalan-dexamethasone or Carfilzomib/Dexamethasone or Venetoclax are all other alternatives in patients with neuropathy (Recommendation Level B, Evidence Level II) [8,12,13].

A3. Monitoring response

Patients are monitored to determine whether the disease is responding appropriately to therapy and whether a change in management is needed. In general, alternative systemic therapy is recommended if there is hematologic or organ progression at any time; if there is <50% reduction in the difference between the involved and uninvolved free light chain levels (dFLC) after two cycles of chemotherapy; or if dFLC is ≥40 mg/L after four to six cycles of chemotherapy or on day 100 after transplant [8,12,13].

A4. Relapsed or refractory disease

- For patients with relapsed or refractory disease, acceptable approaches include treatment with proteasome inhibitor-based regimens, immunomodulatory derivative-based regimens, daratumumab, or enrollment on a clinical trial [8,12,13].
- There are no sufficient data to determine which of these regimens will be of most benefit; the choice will be dictated by prior therapy, patient and

physician preferences, expected toxicity, drug availability, and insurance coverage.

- Patients Proteasome inhibitor (PI) Naïve or had a prolonged response to 1st line PI:
  - CyBorD/VMDex (Recommendation Level A, Evidence Level II); Ixazomib-Dex (Recommendation Level B, Evidence Level II); Dara-CyBorD (Recommendation Level C; Evidence Level III) [8,12,13].
- Proteasome inhibitor exposed Daratumumab Naïve:
  - Single agent daratumumab (Recommendation Level A; Evidence Level II), DaraCyBorD (Recommendation Level C; Evidence Level III), Dara-RD (Recommendation Level B; Evidence Level II), Isatuximab (Recommendation Level C; Evidence Level IV) [8,12,13].
- Proteasome inhibitor exposed IMiD Naïve:
  - Lenalidomide-Dexamethasone (±cyclophosphamide) (Recommendation Level A; Evidence Level II), Ixazomib-Lenalidomide dexamethasone (Recommendation Level A; Evidence Level II) [8,12,13].
- Lenalidomide Refractory:
  - Pomalidomide-Dexamethasone (Recommendation Level A; Evidence Level II), Bendamustine (Recommendation Level B; Evidence Level II) [8,12,13].
- Recommendation for patients with t(11;14) translocation:
  - Venetoclax (Recommendation Level B; Evidence Level II); Venetoclax-Bortezomib/Dexamethasone (Recommendation Level C; Evidence Level III), Melphalan Dexamethasone (Recommendation Level C; Evidence Level IV) [8,12,13].
- As an example, daratumumab may be preferred for patients with severe cardiac involvement while a lenalidomide-based regimen may be preferred for patients with peripheral neuropathy. Bendamustine-based regimens for patients who have received multiple prior regimens, or for those with toxicities that limit the use of other agents [8,12,13].

A5. Prognosis

- The prognosis of AL amyloidosis varies considerably depending on the nature, number, and extent of organ involvement. AL amyloidosis has a poor long-term prognosis when detected at an advanced stage. Earlier diagnosis is associated with lower early mortality and improved survival [8,12,13].

B. Management of Transthyretin amyloidosis

Several approaches have become available for the treatment of hereditary TTR amyloidosis (ATTR). These include the use of ribonucleic acid (RNA)-targeted therapies that interfere with hepatic TTR synthesis and other agents that reduce formation of TTR amyloid through stabilization of the tetramer configuration, preventing release of amyloidogenic monomers. Liver transplantation has also been used for the treatment of hereditary (variant or mutant) ATTR (ATTRv) as a

form of "surgical gene therapy." Liver transplantation is not applicable to wild-type ATTR (ATTRwt), and in most cases, access to heart transplantation is limited by the advanced age of the patient. Treatments for ATTR are discussed briefly below, particularly with a focus on amyloid heart disease [9,10,11,14,15].

B.1. RNA-targeted therapies

RNA-targeted therapies for ATTR amyloidosis-related cardiomyopathy and neuropathy have become available that interfere with hepatic TTR synthesis and the resultant availability of misfolded monomers to aggregate and form amyloid deposits; these include patisiran, inotersen, and vutrisiran [9,10,11,14,15].

a) Patisiran

- Patisiran is a TTR-specific small interfering RNA (siRNA) formulation in lipid nanoparticles, which has been shown to substantially reduce the production of both variant and wild-type forms of TTR in patients with hereditary ATTR and in healthy individuals[16,17,18].
- Benefit has been shown in clinical trials in patients with FAP due to ATTR[16] and for patients with amyloid cardiomyopathy due to ATTR.
- Patisiran is administered every three weeks by intravenous infusion [16,17,18].

b) Vutrisiran

- Vutrisiran is a transthyretin-directed siRNA for treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) in adults as an every-three-month subcutaneous injection.
- It is a chemically modified double-stranded siRNA that targets mutant and wild-type TTR messenger RNA (mRNA) and is covalently linked to a ligand containing three N-acetylgalactosamine (GalNAc) residues to enable delivery of the siRNA to hepatocytes, which causes degradation of mutant and wild-type TTR mRNA through RNA interference, resulting in a reduction of serum TTR protein and TTR protein deposits in tissues.
- Benefits have also been shown in patients with amyloid cardiomyopathy due to ATTR[19].

c) Inotersen

- Inotersen is an antisense oligonucleotide (ASO) construct that inhibits hepatic production of TTR, resulting in reduced levels of TTR in both healthy controls and in patients with hereditary ATTR with polyneuropathy[20,2122].
- Moderate to severe thrombocytopenia and bleeding complications have been reported with this agent. Benefits have also been shown for amyloid cardiomyopathy due to ATTR [20,2122].
- Inotersen is administered once weekly by subcutaneous injection [20,2122].

B.2 Stabilization of transthyretin tetramers

- **Tafamidis** and **diflunisal** each can reduce formation of TTR amyloid through stabilization of the TTR tetramer configuration, preventing release of amyloidogenic monomers [9,10,11,14,15].

B.3 Other agents

- Other agents under investigation for ATTR amyloidosis include AG10, a TTR stabilizer that mimics the effect of the protective TTR T119M variant[23]; tolcapone, a previously licensed drug for Parkinson disease, which was shown to be a potent stabilizer in preclinical studies; palindromic bivalent cross-linkers that deplete TTR; covalent stabilizers such as beta-aminoxypropionic acids; cyclic oligosaccharides (cyclodextrins); and polyamidoamine (PAMAM) dendrimers that inhibit formation and disrupt fibrils.

C. Specific organ involvement

C.1 Treatment of Amyloid cardiomyopathy:

- The treatment of symptomatic cardiac amyloidosis is twofold: **therapy for heart failure (HF) and treatment of the underlying disease** [9,10,11,14,15].
- Treatment of HF in patients with cardiac amyloidosis differs from the therapy generally recommended in patients with diastolic or systolic HF. While loop diuretics are a mainstay of treatment of cardiac amyloidosis, beta blockers and angiotensin-converting enzyme inhibitors are often not tolerated despite their efficacy in other types of systolic HF. Similarly, calcium channel blockers that may be useful in treatment of diastolic HF are contraindicated in amyloid cardiomyopathy [9,10,11,14,15].
- **Anticoagulation** is recommended in patients with amyloid cardiomyopathy with atrial fibrillation, intracardiac thrombi, or an embolic event.
- **Beta-blockers** should be used with caution and may worsen outcomes. **Angiotensin inhibitors** may be poorly tolerated due to orthostatic hypotension. Retrospective analysis of trials suggests a beneficial effect of spironolactone. There is no evidence to guide use of SGLT-2 inhibitors in amyloidosis [9,10,11,14,15].
- The efficacy of implantable cardioverter-defibrillator therapy in patients with severe cardiac amyloidosis is unclear [9,10,11,14,15].

- The main treatment option in patients with light-chain **(AL) amyloidosis is chemotherapy** (cf. section A). A variety of regimens are used, including high-dose melphalan with autologous hematopoietic stem cell transplantation. Bortezomib-based regimens are first-line therapy for most patients who are not candidates for hematopoietic stem cell transplantation, even in patients with advanced cardiac disease (New York Heart Association [NYHA] functional class III or IV) [8,12,13].

- For **transthyretin amyloidosis (ATTR) cardiomyopathy**, options include:
  - **For patients with ATTR cardiomyopathy with NYHA functional class I to III, treatment with tafamidis is recommended** (Recommendation level A, Evidence level II). In this population, a randomized trial found that tafamidis therapy reduced mortality as well as cardiovascular-related hospitalizations, and reduced declines in functional capacity and quality of life [9,10,11,14,15].
  - **Tafamidis is a TTR stabilizer and is the only Food and Drug Administration approved medication available for all ATTR-CM**. It delays disease progression but does not result in regression, and in trials, reduced all-cause mortality and cardiovascular hospitalizations. It has minimal side effects but has a high cost, needing copay assistance programs for patients [9,10,11,14,15].
    - The FDA-approved dosages are tafamidis 61 mg or tafamidis meglumine 80 mg.
    - In the **ATTR-ACT** study, **tafamidis compared with placebo demonstrated reductions in all-cause mortality and cardiovascular-related hospitalizations**. Benefits were consistent across pre-specified subgroups, including stratification by ATTRwt vs ATTRv status and NYHA functional class I or II vs III, **with the exception of higher cardiovascular hospitalization rates in NYHA functional class III participants who received tafamidis**[24].
    - The increased hospitalization rate was proposed to be driven by longer survival and expo-sure time in an advanced disease state, underscoring the importance of early diagnosis and treatment initiation [9,10,11,14,15].
    - A subsequent prespecified analysis from ATTR-ACT supported benefit from tafamidis, regardless of variant or wild-type status, with reductions in mortality and functional decline[24].
    - Additionally, **tafamidis slows the decline in patient-reported quality-of-life metrics**, and **the mortality benefit was evident up to 58 months** in the long-term extension of patients on continuous tafamidis compared with those initially on placebo who transitioned to tafamidis[24].
    - **The predominant barrier is risk for cost due to the high original list price of $225,000 annually. A cost-effectiveness analysis estimated a cost of $880,000 per quality-adjusted life-year gained** and that a 92.6% price reduction would be needed to make tafamidis meet established thresholds for cost-effectiveness [9].
    - Another barrier to prescribing tafamidis may be the **lack of data regarding the appropriate patient population who will benefit.**
      - Although not included in the approved labeling, uncertainty exists regarding the efficacy of tafamidis early along the

disease continuum, including **asymptomatic genetic carriers** without clinically –evident cardiac amyloidosis or those with **localized, non-cardiac disease**.

- Furthermore, some patients with **advanced disease** may not benefit from tafamidis, such as those excluded from the ATTR-ACT trial, including patients with NYHA functional class IV status and advanced HF, or those of advanced age (90 years or older), although use in such patients should be based on an individualized shared decision-making discussion [9,10,11,14,15].

- Although there are alternatives to tafamidis, they lack a similar evidence base and are not as well tolerated [9,10,11,14,15].

- **Alternatives to tafamidis include diflunisal**, also a TTR stabilizer, which is less effective but significantly cheaper. It is a nonsteroidal anti-inflammatory drug and should be avoided in chronic kidney disease, decompensated heart failure, and gastrointestinal (GI) bleeding.
  - Although tafamidis should remain the first-line agent in the treatment of ATTR-CM as the only available approved drug, the cost of diflunisal is approximately $25 to $50 per month, rendering it an alternative option for those who are "too well" or those patients who cannot afford tafamidis [9,10,11,14,15].
- In addition, patients diagnosed with familial ATTR (ATTRm) cardiomyopathy should undergo evaluation for liver transplantation, as this can be curative in selected patients with ATTRm but not in those with wild-type ATTR (ATTRwt) amyloidosis. However, cardiac disease has progressed after liver transplantation in some patients with ATTRm. Patients with advanced heart disease with ATTRm may be treated with combined heart and liver transplantation [9,10,11,14,15].

C.2 Treatment of Amyloid neuropathy:

- **TTR silencers such as patisiran, vutisiran, and inotersen are approved for hereditary (ATTRv) polyneuropathy**. These are currently only approved for amyloid polyneuropathy and not yet for cardiac amyloidosis[16,19,20].

  - Diflunisal and tafamidis are TTR stabilizers which also slow the progression of ATTRv polyneuropathy. However, **although approved for ATTR-CM, tafamidis does not have approval from the FDA for treatment of ATTRv polyneuropathy**.
  - Diflunisal was demonstrated effective in ATTRv polyneuropathy to slow disease progression but is not FDA approved for this indication [9,10,11,14,15].

- **Symptomatic management** includes treating sensory neuropathy with medications like pregabalin, gabapentin, duloxetine, or tricyclic

antidepressants, alongside the management of autonomic dysfunction with compression stockings, increased salt and fluids intake, etc[9].

C.3 Treatment of gastric amyloidosis

- Dietary modifications include dietary modifications (small evening meals, longer intervals between evening meals and laying down, calorie-dense supplements for malnutrition, FODMAP diet)
- For nausea and early satiety: Antiemetics: ondasetron, promethazine; Prokinetics: metoclopramide.
- For diarrhea: Opioid receptor agonists: loperamide, diphenoxylate/atropine; Antibiotics; Bile acid sequestrants; Octreotide
- For constipation: Laxatives: polyethylene glycol, magnesium-containing products, senna[9].

A **summary of the treatment strategies** for the management of amyloidosis is illustrated in Table 1 and Table 2.

Table 1. Management of Light Chain Amyloidosis

Management of Light Chain Amyloidosis (AL Amyloidosis) [8,12,13]				
Medication	**Indication**	**Line of Therapy**	**Recomen-dation**	**Evidence**
Daratumumab - CyBorD	Light chain amyloidosis, newly diagnosed	**1st (preferred)**	A	I
Bortezomib ± dexamethasone	Light chain amyloidosis, newly diagnosed, or relapsed/refractory	**1st** **2nd**	A	II
CyBorD	Light chain amyloidosis, newly diagnosed, or relapsed/refractory	**1st** **2nd**	A	II
Bortezomib/ lenalidomide/ dexamethasone	Light chain amyloidosis, newly diagnosed, or relapsed/refractory	**1st** **2nd**	A	II
Bortezomib/ melphalan/ dexamethasone (VMDex)	Light chain amyloidosis, newly diagnosed in patients not eligible for HCT, or relapsed/refractory	**1st** **2nd**	A	II
Melphalan/ dexamethasone	Light chain amyloidosis, newly diagnosed in	**1st** **2nd**	A	II

	patients not eligible for HCT, or relapsed/refractory			
High-dose melphalan with HCT	Light chain amyloidosis, newly diagnosed, or relapsed/refractory	**1st** **2nd**	A	II
Daratumumab	Light chain amyloidosis, relapsed/refractory	**2nd**	A	II
Ixazomib + dexamethasone	Light chain amyloidosis, relapsed/refractory	**2nd**	A	II
Ixazomib/ lenalidomide/ dexamethasone	Light chain amyloidosis, relapsed/refractory	**2nd**	A	II
Lenalidomide/ cyclophosphamide / dexamethasone	Light chain amyloidosis, relapsed/refractory	**2nd**	A	II
Lenalidomide/ dexamethasone	Light chain amyloidosis, relapsed/refractory	**2nd**	A	II
Daratumumab/ Lenalidomide/ dexamethasone	Light chain amyloidosis, relapsed/refractory	**2nd**	B	II
Pomalidomide/ dexamethasone	Light chain amyloidosis, relapsed/refractory	**2nd** **3rd**	A	II
Bendamustine/ dexamethasone	Light chain amyloidosis, relapsed/refractory	**2nd** **3rd**	B	II
Carfilzomib for non-cardiac amyloidosis ± dexamethasone	Light chain amyloidosis, relapsed/refractory	**2nd**	B	II
Venetoclax ± dexamethasone	Light chain amyloidosis, relapsed/refractory in patients with t(11;14)	**2nd**	B	II
Isatuximab	Light chain amyloidosis, relapsed/refractory	**2nd** **3rd**	B	II

Table 2. Management of Transthyretin Amyloidosis (ATTR Amyloidosis)

Management of Transthyretin Amyloidosis (ATTR Amyloidosis) [9,10,11,14,15]				
Medication	**Indication**	**Line of Therapy**	**Recomen-dation**	**Evidence**
Tafamidis	Amyloid cardiomyopathy (ATTRwt-CM and ATTRv-CM)	**1st**	A	II
TTR silencers (Patisiran Inotersen Vutrisiran)	Polyneuropathy caused by hereditary transthyretin-mediated amyloidosis (hATTR)	**1st**	A	II

All the medications in the standard of care therapy are available in the Saudi Market, except the TTR silencers (Patisiran, Inotersen, Vutrisiran) and diflunisal (used off-label in amyloisodis). Section 3 provides a full description of each treatment protocol with a final statement on the place in therapy. All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA), reflecting specific drug class role in the MDS therapeutic landscape.

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in sickle cell disease were reviewed and summarized. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health, Haute Autorite de Sante (HAS), Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC). A summary of these recommendations are shown in Section 3.

Daratumumab had a favorable opinion for reimbursement in combination with CyBorD protocol in newly diagnosed systemic light chain (AL) amyloidosis from the HTA bodies (HAS, CADTH, IQWIG, PBAC) due to a substantial clinical benefit with an acceptable financial analysis. Tafamidis had a favorable opinion for reimbursement in adult patients with wild-type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM) from the majority of the HTA bodies, except PBAC and NICE that didn't approve the reimbursement of the drug within its marketing authorization. The cost-effectiveness estimates were higher than what NICE and PBAC normally considers an acceptable use of healthcare resources. However, since there is an unmet clinical need in the management of ATTR cardiomyopathy due to the absence of effective alternative treatments, and since tafamidis has a clinical added value as per the majority of the HTA bodies, we consider that Tafamidis should be covered for patients with wild-type or hereditary ATTR-CM with a NYHA classification of I to III and a history of heart failure.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

1.1 KSA Guidelines

To date, there are no published KSA guidelines for the management of amyloidosis.

1.2 North American Guidelines

1.2.1 National Comprehensive Cancer Network (NCCN)

The National Comprehensive Cancer Network (NCCN) published its updated recommendations for the management of primary systemic light chain amyloidosis (SLCA) in November 2022, including recommendations for the diagnosis, evaluation, and treatment of SLCA[8].

a) Overview

- Primary systemic light chain amyloidosis in contrast to multiple myeloma is typically characterized by low burden of monoclonal plasma cells in the bone marrow.
- The abnormal plasma cells yield light chains that get transformed to amyloid fibrils that have an affinity for visceral organs (such as the kidney, heart, gastrointestinal tract, liver, spleen, and nervous system) and cause related end-organ dysfunction.
- The therapy for SLCA is directed to recovering the function of the affected organs by targeting the abnormal plasma cell clone and slowing deposition of harmful amyloid fibrils [8].

b) Initial Diagnostic Workup

- The workup of patients with suspected amyloidosis is aimed towards demonstration of the amyloid protein in tissue, identification of the protein of origin, and in the setting of light chain amyloidosis demonstration of the monoclonal plasma cell disorder.
- Subsequent workup is aimed towards identifying the organs involved and the severity of organ involvement and assessment of the feasibility and safety of different treatment approaches [8].
- The initial evaluation and diagnostic workup of patients with suspected SLCA according to the NCCN guidelines is summarized in Table 3 [8].

Table 3. Initial Evaluation and Diagnostic Workup (NCCN Guidelines)

Initial Diagnostic Workup
Clinical and amyloid-related assessment
▪ History and physical (H&P) ▪ Orthostatic vital signs ▪ Whole-body low-dose CT scan or FDG PET/CT ▪ ECG
Laboratory evaluation (directed toward commonly affected organ systems)
▪ CBC, differential, platelet count ▪ Peripheral blood smear ▪ Prothrombin time (PT), partial thromboplastin time (PTT), and Factor X ▪ Serum BUN/creatinine, electrolytes, albumin, calcium, serum uric acid, serum LDH, and beta-2 microglobulin ▪ Creatinine clearance (calculated or measured directly) ▪ Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), and serum immunofixation electrophoresis (SIFE) ▪ 24-h urine for total protein, urine protein electrophoresis (UPEP), and urine immunofixation electrophoresis (UIFE) ▪ Serum free light chain (FLC) assay ▪ NT-proBNP,c troponin T (TnT) ▪ Alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin ▪ Coagulation studies as clinically indicated
Pathologic evaluation
▪ Unilateral bone marrow aspirate + biopsy ▪ Plasma cell fluorescence in situ hybridization (FISH) on bone marrow ▪ Abdominal fat pad sampling and/or involved organ biopsy as clinically indicated ▪ Amyloid tissue subtyping with mass spectrometry
Special testing based on organ system involvement
▪ Cardiac - Echocardiogram with strain assessment to examine longitudinal strain - Cardiac MRI (in certain circumstances) ▪ Liver and GI tract - Gastric emptying scan (if gastroparesis present) - Abdominal ultrasound or abdominal CT scan to document craniocaudal liver span as clinically indicated ▪ Peripheral nervous system - Electromyography (if clinically significant peripheral neuropathy)/nerve conduction studies ▪ Other - Endocrine testing: Thyroid-stimulating hormone (TSH), cortisol - Pulmonary testing: Pulmonary function tests - Chest CT without contrast as indicated

- The diagnosis of amyloidosis requires the identification of amyloid deposits in tissues either by aspiration of abdominal subcutaneous fat and/or biopsy of the organs involved.
- Characterization of amyloidosis as a systemic light chain type requires the demonstration of the underlying plasma cell clone. Therefore, identification of FLCs in the serum or urine must be followed by confirmation of amyloid in the tissue by pathologic evaluation [8].

c) Staging

- While multiple prognostic models have been proposed for patients with amyloidosis, the NCCN panel recommends use of a staging system that incorporates NT-proBNP ≥1800 ng/L (or BNP ≥400 ng/L), cTnT ≥0.025 μ/L (or cardiac troponin I [cTnI] ≥ 0.1 μ/L), and the difference between involved and uninvolved serum free light chains (dFLC) ≥18 mg/dL as risk factors.
- Patients with no risk factors are classified as stage I, those with one elevated risk factor as stage II, those with two elevated risk factors as stage III, and those with three elevated risk factors as stage IV. For patients classified as having stage I, II, III, or IV disease, the median overall survival (OS) from diagnosis is 94, 40, 14, and 6 months, respectively [8].

d) Treatment of Newly Diagnosed SLCA

All patients with newly diagnosed SLCA should be assessed for autologous HCT eligibility. Those with low tumor burden can proceed to receive HCT immediately. Those who are not eligible for HCT due to high tumor burden may receive systemic therapy first, and their eligibility for transplant may be assessed after initiating systemic therapy based on improvements in functional status and/or organ response. The NCCN panel members recommend that treatment of SLCA should be in the context of a clinical trial when possible [8].

d.1) Primary Therapy for SLCA

- **The preferred regimen for primary treatment of SLCA is Daratumumab and Hyaluronidase in Combination with Bortezomib/ Cyclophosphamide/ Dexamethasone (CyBorD) (Category 1)** [8].
- This is based on the results of the ANDROMEDA trial in which patients (n = 388) with newly diagnosed amyloidosis were randomized to receive six cycles of cyclophosphamide, bortezomib, and dexamethasone (CyBorD) with or without subcutaneous daratumumab (daratumumab and hyaluronidase). Those receiving subcutaneous daratumumab as part of their regimen received

single-agent daratumumab monthly as maintenance therapy for up to 2 years[25,26]

- After a median follow-up of 11.4 months, the addition of daratumumab to CyBorD resulted in higher rates of hematologic CR (53% vs. 18%), cardiac response (42% vs. 22%), and renal response (53% vs. 24%). The addition of daratumumab also delayed major organ deterioration, hematologic progression, and death (hazard ratio [HR], 0.58; 95% CI, 0.36–0.93)[25].
- The most common grade 3 or 4 adverse events in the daratumumab arm compared with the control arm were lymphopenia (13.0% vs. 10.1%), pneumonia (7.8% vs. 4.3%), cardiac failure (6.2% vs. 4.8%), and diarrhea (5.7% vs. 3.7%) [25].
- The U.S. Food and Drug Administration (FDA) has approved this regimen for patients with SLCA.
- Primary therapy recommendations for transplant and non-transplant eligible patients according to NCCN guidelines are outlined in Table 4 [8].

Table 4. Primary Therapy for Transplant and Non-Transplant Candidates (NCCN Guidelines)

Primary Therapy for Transplant and Non-Transplant Candidates	
Preferred Regimens	▪ Daratumumab and hyaluronidase-fihj/ bortezomib/cyclophosphamide/dexamethasone (category 1)
Other Recommended Regimens	▪ Bortezomib ± dexamethasone ▪ Bortezomib/cyclophosphamide/dexamethasone ▪ Bortezomib/lenalidomide/dexamethasone ▪ Bortezomib/melphalan/dexamethasone (if ineligible for HCT)
Useful in Certain Circumstances	▪ Melphalan/dexamethasone (if ineligible for HCT)

All recommendations are Category 2A, unless otherwise specified
If not a candidate for HCT at initial diagnosis, reassess after initiating systemic therapy based on improvements in functional status and/or organ response.

d.2) Therapy for Previously Treated SLCA

- There are no clinical trial data to determine the appropriate regimens for previously treated SLCA. The treatment would depend on prior therapy received, patient preferences, and toxicity profile. The NCCN panel recommends considering repeating the initial therapy, especially if the patient has no relapse of disease for several years [8].

- The NCCN panel notes that patients on regimens containing bortezomib are associated with a higher risk of treatment-related peripheral and autonomic neuropathy, especially in those with disease-related baseline neuropathy. Therefore, close monitoring, judicious dosing, or alternative therapies should be considered in some patients [8].
- Daratumumab may be administered subcutaneously (daratumumab 1800 mg with hyaluronidase 30,000 units) or intravenously (daratumumab 16 mg/kg). Subcutaneous administration has fewer infusion-related reactions and a faster administration time [8].
- Therapy recommendations for previously treated patients according to NCCN guidelines are outlined in Table 5 [8].

Table 5. Therapy for Previously Treated Patients (NCCN Guidelines)

Therapy for Previously Treated Disease	
Consider repeating initial therapy, especially if relapse-free for several years ▪ Bortezomib ± dexamethasone ▪ Bortezomib/cyclophosphamide/dexamethasone ▪ Bortezomib/melphalan/dexamethasone ▪ Daratumumab ▪ Ixazomib + dexamethasone ▪ Ixazomib/lenalidomide/dexamethasone ▪ Lenalidomide/cyclophosphamide/dexamethasone ▪ Lenalidomide/dexamethasone ▪ High-dose melphalan with HCT ▪ Melphalan/dexamethasone ▪ Pomalidomide/dexamethasone	
Useful in Certain Circumstances	▪ Bendamustine/dexamethasone ▪ Carfilzomib for non-cardiac amyloidosis ± dexamethasone ▪ Venetoclax t(11;14) ± dexamethasone

All recommendations are Category 2A, unless otherwise specified

1.2.2 American College of Cardiology (ACC)

The American College of Cardiology (ACC) released in 2023 an expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis[9]. The following key points are a summary of the expert's report:

a) Definition and diagnosis:

- Amyloid cardiomyopathy is caused by misfolding of:
  - Monoclonal immunoglobulin light chain produced in bone marrow plasma cell disorders called AL, or
  - Transthyretin (TTR) protein called ATTR. ATTR-cardiomyopathy (ATTR-CM) can occur in the context of genetically normal protein (wild type or ATTRwt-CM) or due to genetic mutations (most commonly isoleucine substitution for valine at position 122), rendering the protein abnormal (ATTRv-CM)[9].
- Multidisciplinary care is required since amyloid fibrils can deposit in multiple organs[9].
- **Cardiac clues** to diagnosis of amyloidosis includes increased left ventricular hypertrophy in the absence of hypertension or valvular heart disease, heart failure symptoms, diastolic dysfunction, atrial fibrillation, conduction system disease, and elevated cardiac biomarkers. **Extracardiac manifestations** include carpal tunnel syndrome, spinal stenosis, hip or knee replacement, prior shoulder surgery, proteinuria, and peripheral or autonomic neuropathy causing orthostatic hypotension. Pathognomonic extracardiac findings for AL include macroglossia, periorbital purpura, and acquired factor X deficiency. Findings unique to ATTR are spontaneous biceps rupture and spinal stenosis[9].
- Low voltage electrocardiography and presence of hypertrophy on echocardiography is only present in 30% of amyloid patients. Other echo findings include left ventricular hypertrophy, atrioventricular valve/right ventricular free wall/interatrial septum thickening, diastolic dysfunction, biatrial enlargement, and decreased global longitudinal strain with apical sparing[9].
- **Cardiac magnetic resonance** imaging can help differentiate amyloidosis from other infiltrative diseases. Findings include extracellular volume expansion and diffuse late gadolinium enhancement[9].
- The first step in identifying type of amyloidosis is a **monoclonal protein screen** involving: serum free light chain assay, serum and urine immunofixation electrophoresis. If all are negative, AL has been ruled out. If any are positive, the next step is **biopsy** of the involved organ with mass spectrometry to confirm AL deposition. A negative fat pad biopsy does not rule out AL or ATTR, and biopsy of the involved organ (heart or kidneys) should be considered[9].
- A serum/urine protein electrophoresis should not be used to rule out monoclonal protein due to lower accuracy relative to immunofixation. In chronic kidney disease, elevated serum free light chain ratios of K/L are

common but with a normal serum and urine immunofixation electrophoresis [9].

- If AL has been ruled out, a **technetium pyrophosphate scan** can be used to diagnose ATTR-CM. **Genetic testing** is warranted to distinguish between ATTRwt-CM or ATTRv-CM [9].
- The diagnostic algorithm for cardiac amyloidosis according to the ACC consensus is illustrated in Figure 1 [9].

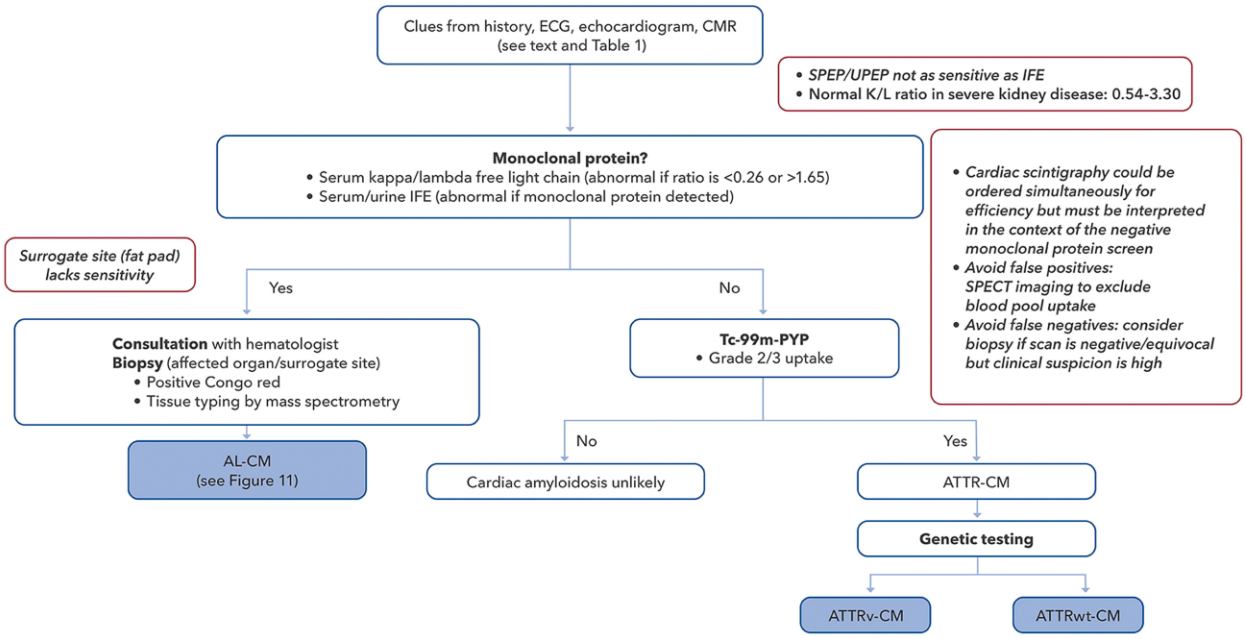

Figure 1. *Diagnostic Algorithm for Cardiac Amyloidosis. Adapted from Kittleson MM, Ruberg FL, Ambardekar A V., et al. 2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With Cardiac Amyloidosis. J Am Coll Cardiol. 2023;81(11):1076-1126. doi:10.1016/j.jacc.2022.11.022*

b) Treatment of cardiac amyloidosis

- The treatment algorithm for patients with cardiac amyloidosis according to the American college of Cardiology is illustrated in Figure 2 [9].

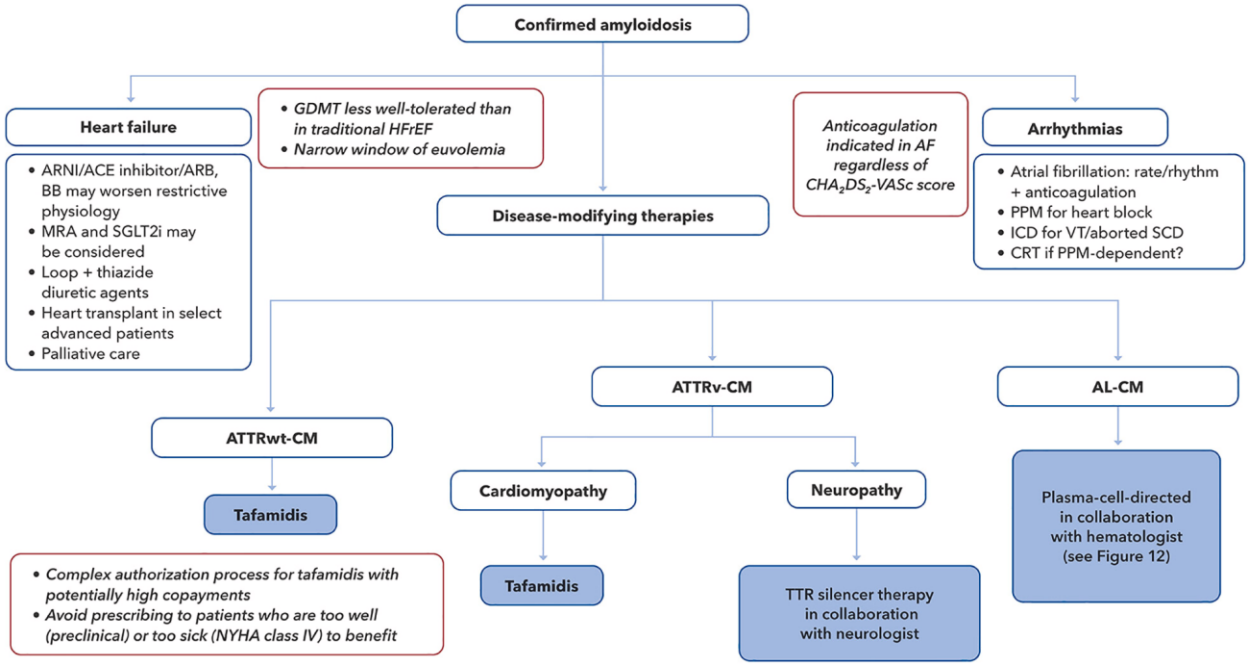

Figure 2. *Overview of Management of Cardiac Amyloidosis. Adapted from Kittleson MM, Ruberg FL, Ambardekar A V., et al. 2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With Cardiac Amyloidosis.* J Am Coll Cardiol. *2023;81(11):1076-1126. doi:10.1016/j.jacc.2022.11.022*

- **Tafamidis is a TTR stabilizer and is the only Food and Drug Administration approved medication available for all ATTR-CM**. It delays disease progression but does not result in regression, and in trials, reduced all-cause mortality and cardiovascular hospitalizations. It has minimal side effects but has a high cost, needing copay assistance programs for patients[9].
  - The FDA-approved dosages are tafamidis 61 mg or tafamidis meglumine 80 mg.
  - In the **ATTR-ACT** (Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy) study, **tafamidis compared with placebo demonstrated reductions in all-cause mortality and cardiovascular-related hospitalizations**. Benefits were consistent across pre-specified subgroups, including stratification by ATTRwt vs ATTRv status and NYHA functional class I or II vs III, **with the exception of higher cardiovascular hospitalization rates in NYHA functional class III participants who received tafamidis**.
  - The increased hospitalization rate was proposed to be driven by longer survival and expo-sure time in an advanced disease state, underscoring the importance of early diagnosis and treatment initiation.
  - A subsequent prespecified analysis from ATTR-ACT supported benefit from tafamidis, regardless of variant or wild-type status, with reductions in mortality and functional decline.

- Additionally, **tafamidis slows the decline in patient-reported quality-of-life metrics**, and **the mortality benefit was evident up to 58 months** in the long-term extension of patients on continuous tafamidis compared with those initially on placebo who transitioned to tafamidis.
- **The predominant barrier is risk for cost due to the high original list price of $225,000 annually. A cost-effectiveness analysis estimated a cost of $880,000 per quality-adjusted life-year gained** and that a 92.6% price reduction would be needed to make tafamidis meet established thresholds for cost-effectiveness.
- Another barrier to prescribing tafamidis may be the **lack of data regarding the appropriate patient population who will benefit.**
    - Although not included in the approved labeling, uncertainty exists regarding the efficacy of tafamidis early along the disease continuum, including **asymptomatic genetic carriers** without clinically –evident cardiac amyloidosis or those with **localized, non-cardiac disease**.
    - Furthermore, some patients with **advanced disease** may not benefit from tafamidis, such as those excluded from the ATTR-ACT trial, including patients with NYHA functional class IV status and advanced HF, or those of advanced age (90 years or older), although use in such patients should be based on an individualized shared decision-making discussion.
- Although there are alternatives to tafamidis, they lack a similar evidence base and are not as well tolerated [9].

o Alternatives to tafamidis include **diflunisal**, also a TTR stabilizer, which is less effective but significantly cheaper. It is a nonsteroidal anti-inflammatory drug and **should be avoided in chronic kidney disease, decompensated heart failure, and gastrointestinal (GI) bleeding** [9].

- Although **tafamidis should remain the first-line agent in the treatment of ATTR-CM** as the only available approved drug, **the cost of diflunisal is approximately $25 to $50 per month**, rendering it an alternative option for those who are “too well” or those patients who cannot afford tafamidis.
- Whereas diflunisal was superior to placebo in slowing neurologic disease progression in the randomized, placebo-controlled trial of ATTR polyneuropathy, only **limited retrospective data inform its use in ATTR-CM** [9].

o **Beta-blockers** should be used with caution and may worsen outcomes. Angiotensin inhibitors may be poorly tolerated due to orthostatic hypotension. Retrospective analysis of trials suggests a beneficial effect of spironolactone. There is no evidence to guide use of SGLT-2 inhibitors in amyloidosis [9].

- **If atrial fibrillation is present, anticoagulation is recommended** regardless of CHA_2DS_2-VASc score, and prior to cardioversion, a transesophageal echocardiogram should always be performed regardless of anticoagulation status due to high risk for intracardiac thrombus [9].
- There should be **close monitoring for conduction disease and ventricular arrhythmias**, both being very common in amyloid cardiomyopathy. However, defibrillators have not consistently demonstrated improved survival for amyloidosis and hence should be considered based on standard heart failure guidelines for amyloid patients [9].
- If aortic stenosis is present with cardiac amyloidosis, aortic valve replacement (AVR) may help improve symptoms and referral for transcatheter AVR (TAVR) should be considered [9].
- The consensus continues with the multidisciplinary care of cardiac amyloidosis, including the management of neurological, gastro-intestinal, hematologic, and renal manifestations.

c) Neurology

- **Emerging therapies** not yet approved for cardiac amyloidosis include **TTR silencers such as patisiran or vutisiran (approved for ATTRv polyneuropathy) and inotersen**. These are currently only approved for amyloid polyneuropathy. Data on green tea derivatives are lacking and not recommended [9].
  - Diflunisal and tafamidis are TTR stabilizers which also slow the progression of ATTRv polyneuropathy. However, **although approved for ATTR-CM, tafamidis does not have approval from the FDA for treatment of ATTRv polyneuropathy**.
  - Diflunisal was demonstrated effective in ATTRv polyneuropathy to slow disease progression but is not FDA approved for this indication [9].
- The recommended approach for the management of amyloid neuropathy is illustrated in Figure 3[9].

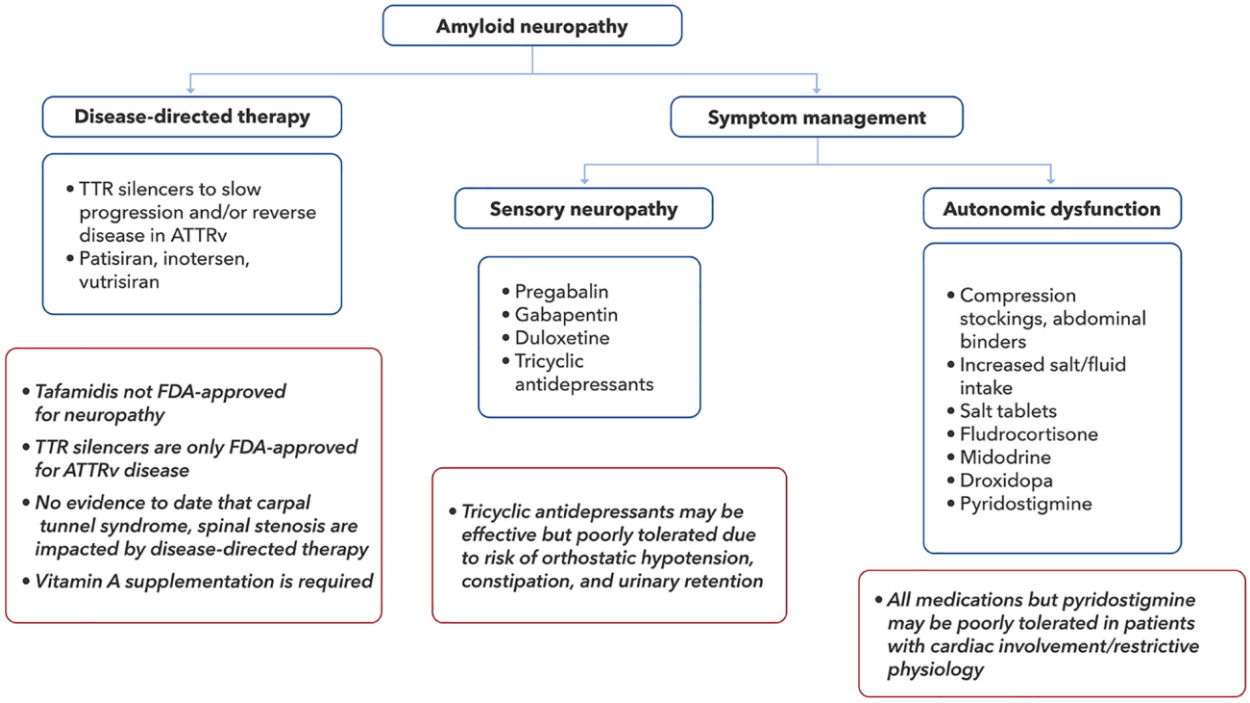

Figure 3. *Management of Amyloid Neuropathy. Adapted from Kittleson MM, Ruberg FL, Ambardekar A V., et al. 2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With Cardiac Amyloidosis.* J Am Coll Cardiol. *2023;81(11):1076-1126. doi:10.1016/j.jacc.2022.11.022*

d) Gastro-enterology

- GI mucosa involvement can cause protein losing enteropathy, GI dysmotility, abdominal pain, constipation, or diarrhea and bleeding. Treatment is supportive and should include collaboration with a GI specialist.
- Dietary modifications include dietary modifications (small evening meals, longer intervals between evening meals and laying down, calorie-dense supplements for malnutrition, FODMAP diet), alongside medications:
  - For nausea and early satiety: Antiemetics: ondasetron, promethazine; Prokinetics: metoclopramide.
  - For diarrhea: Opioid receptor agonists: loperamide, diphenoxylate/atropine; Antibiotics; Bile acid sequestrants; Octreotide.
  - For constipation: Laxatives: polyethylene glycol, magnesium-containing products, senna [9].

e) Hematologic manifestations and management

- Because AL amyloidosis most commonly results from a clonal plasma cell disorder, the primary treatment uses chemotherapy and/or immunotherapy to target the aberrant plasma cells, eradicate the underlying clone, and decrease amyloid precursor protein production, there by limiting further organ damage and allowing for regression of tissue amyloid deposits [9].
- Treatment for multiple myeloma with AL amyloidosis includes either **high-dose melphalan (HDM) with stem cell transplant and daratumumab with cyclophosphamide, bortezomib, and dexamethasone** (Daratumumab-CyBorD) [9].
- **Daratumumab-CyBorD has now emerged as the standard of care for newly diagnosed AL amyloidosis**. It may become the preferred induction therapy before HDM/SCT and offers great promise to the majority of patients who may not be candidates for SCT [9].
  - The landmark study **ANDROMEDA** was a phase 3 trial of daratumumab (ananti-CD38 monoclonal antibody) in combination with cyclophosphamide, bortezomib, and dexamethasone (CyBorD) in patients with newly-diagnosed AL amyloidosis.
  - **There was an unprecedented high rate of deep hematologic responses with very good partial responses or better in 78.5% of patients who received daratumumab plus CyBorD vs 49.2% of patients who received CyBorD alone.**
  - Based on this, daratumumab was approved by the FDA and the European Medicines Agency for treatment of newly-diagnosed AL amyloidosis. **Daratumumab remains the only agent approved for treatment of AL amyloidosis** [9].
- For **AL-CM, a stem cell transplant followed by cardiac transplant would be ideal**, but in some cases, sequential heart transplant followed by stem cell transplantation may be considered [9].

f) Nephrology

- Kidney involvement is very common with AL and ATTR amyloidosis. Treatment is **supportive** and includes low salt diet, use of diuretics for fluid overload, and angiotensin antagonists for proteinuria [9].

1.2.3 Canadian Cardiovascular Society (CCS)-Canadian Heart Failure Society (CFHS)

The Canadian Cardiovascular Society (CCS) in association with the Canadian Heart Failure Society (CFHS) released in 2020 a joint position statement on the evaluation and management of patients with cardiac amyloidosis[10]. They also released the same year recommendations on the use of tafamidis in amyloidosis in heart failure patients[27]. The following key points are a summary of the recommendations:

a) CCS-CFHS Joint position statement on the evaluation and management of patients with cardiac amyloidosis

a.1) Evaluation:

- A diagnostic workup for cardiac amyloidosis is recommended for patients who present with signs and symptoms of HF who have one or more of the following features: (1) unexplained increased LV wall thickness; (2) older than 60 years of age with low-flow low-gradient AS and LVEF > 40%; (3) unexplained peripheral sensorimotor neuropathy and/or dysautonomia; (4) history of bilateral carpal tunnel syndrome; and (5) established AL or ATTR amyloidosis (Strong Recommendation, Moderate-Quality Evidence) [10].
- Performance of routine investigations for the evaluation of HF in patients who present with suspected cardiac amyloidosis is recommended, including 12-lead ECG, troponin, and BNP/NTproBNP (Strong Recommendation, Moderate-Quality Evidence).
- Serum and urine protein electrophoresis with immunofixation and sFLC assay should be performed in all patients with suspected cardiac amyloidosis to evaluate for possible AL amyloidosis or other plasma cell dyscrasia (Strong Recommendation, Moderate-Quality Evidence).
- Echocardiography with longitudinal LV strain measurement, or CMR with LGE and T1 mapping imaging should be performed in all patients with suspected cardiac amyloidosis to evaluate for characteristic features of cardiac amyloidosis or alternative causes of HF (Strong Recommendation, Moderate-Quality Evidence).
- Performance of nuclear scintigraphy with bone-seeking radiotracer (if available) is recommended to evaluate for cardiac involvement when ATTR cardiac amyloidosis is suspected after exclusion of AL (Strong Recommendation, Moderate-Quality Evidence).
- The performance of endomyocardial biopsy is recommended for diagnosis and subtyping with mass spectrometry or immunohistochemistry/immunofluorescence (if available) when the existing diagnostic workup for cardiac amyloidosis is equivocal or

discordant with clinical suspicion (Strong Recommendation, Low Quality Evidence).

- For patients with a diagnosis of ATTR cardiac amyloidosis, we recommend the performance of genetic testing to differentiate hATTR from wtATTR (Strong Recommendation, Moderate-Quality Evidence) [10].

a.2) Management:

- Heart transplantation is to be considered for select patients with advanced HF due to cardiac amyloidosis, in whom significant extracardiac manifestations are absent and the risk of disease progression is considered low and/or amenable to disease modifying therapy (Strong Recommendation, Moderate-Quality Evidence) [10].
- In the absence of contraindications, we recommend **therapeutic anticoagulation** in patients with cardiac amyloidosis and AF, regardless of calculated risk of stroke or systemic embolism (Strong Recommendation, Low-Quality Evidence) [10].
- **Tafamidis (if available) is recommended for patients with ATTR cardiac amyloidosis and NYHA class I-III symptoms** (Strong Recommendation, High-Quality Evidence)[10].
  - Tafamidis is an oral TTR stabilizer that binds to TTR tetramers in circulation and prevents their breakdown into unstable amyloidogenic monomers.
  - In the Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT), 441 patients with ATTR cardiomyopathy (76% wtATTR, 24% hATTR) and NYHA functional class I-III symptoms were randomized to tafamidis or placebo.
  - Over 30 months, tafamidis was associated with a 32% reduction in mortality and a 30% reduction in cardiovascular hospitalization.
  - Tafamidis was well tolerated, and was also associated with improved quality of life and 6-minute walk distance scores compared with placebo.
  - The ATTR-ACT trial included patients with NTproBNP levels > 600 pg/mL and excluded patients with NYHA class IV symptoms or severe functional disability, measured using a 6-minute walk distance < 100 m, representing criteria that should be considered when determining eligibility for treatment.
  - Subgroup analysis from the ATTR-ACT trial suggested that the reduction in cardiovascular hospitalization associated with tafamidis is greatest for patients with NYHA class I-II symptoms.

- **Treatment with a TTR RNA silencing agent (patisiran or inotersen) is recommended for patients with hATTR amyloidosis with ambulatory polyneuropathy** (Strong Recommendation, High-Quality Evidence)[10].
    - Inotersen and patisiran are TTR RNA silencing agents that prevent the hepatic production of TTR protein. Inotersen is an antisense oligonucleotide and patisiran is a small interfering RNA molecule.
    - Both agents have been studied in phase III clinical trials involving ambulatory patients with hATTR and polyneuropathy symptoms.
    - In the Efficacy and Safety of Inotersen in Familial Amyloid Polyneuropathy (NEUROTTR) trial, 172 patients were randomized to subcutaneous inotersen or placebo. After 15 months, patients randomized to inotersen had significantly better neurologic function and quality of life compared with placebo.
    - In the A Phase 3 Multicenter, Multinational, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Patisiran (ALN-TTR02) in Transthyretin (TTR)-Mediated Polyneuropathy (APOLLO) trial, 225 patients were randomized to intravenous patisiran or placebo. Over 18 months, neurologic function and quality of life for patients in the patisiran arm were improved compared with placebo.
    - Neither of these agents has been tested in patients with wtATTR, and neither trial confirmed the presence of cardiac involvement with biopsy or scintigraphy.
    - A prespecified subgroup analysis of 126 APOLLO patients with unexplained LV wall thickening suggestive of cardiac amyloidosis showed reductions in mean LV wall thickness, global longitudinal strain, and NTproBNP, and a trend toward lower rates of mortality and cardiac hospitalizations among patients randomized to patisiran compared with placebo.
    - In hATTR patients with a mixed phenotype (polyneuropathy and cardiomyopathy), the decision to use tafamidis or a TTR silencer should be individualized and is best undertaken by a multidisciplinary team. The efficacy and safety of combination therapy with tafamidis and TTR silencing therapy has not been evaluated.
- Other potentially disease-modifying agents that have been examined in limited off-label studies in patients with cardiac amyloidosis include: diflunisal, combination doxycycline and either tauroursodeoxycholic acid (TUDCA) or ursodeoxycholic acid (ursodiol), and epigallocatechin 3-gallate (EGCG; green tea extract)[10].
    - Diflunisal is a nonsteroidal anti-inflammatory drug that stabilizes TTR, has shown benefit for treatment of hATTR polyneuropathy, and is generally well tolerated except in patients with significant renal insufficiency or those at high risk for decompensated HF.

- The latter 2 therapies have shown amyloid fibril inhibition or degradation properties in vivo and might have efficacy for patients with either AL or ATTR.
- Although none of these therapies have been rigorously tested, they might represent a therapeutic alternative for patients for whom approved therapies are not available.
- The safety and efficacy of combination therapies involving these agents have not been evaluated.

- Serial imaging with echocardiography or CMR is recommended in addition to measuring BNP/ NTproBNP levels be used to monitor cardiac disease progression and/or response to therapy in patients with cardiac amyloidosis[10].
- Comprehensive interdisciplinary management is to be offered to patients with established cardiac amyloidosis (Strong Recommendation, Very Low-Quality Evidence)[10].

b) CCS-CFHS Practical Tips on the Use of Tafamidis

- Patient selection for tafamidis should reflect the inclusion criteria for the major randomized controlled clinical trial that showed clinical benefits of tafamidis over placebo with respect to mortality and cardiovascular hospitalization, including established ATTR-CA and objective evidence of HF (with elevated natriuretic peptides where available)[27].
- Patients with NYHA class IV symptoms or severe functional disability, measured using a 6-minute walk test < 100 m, were excluded from ATTR-ACT and should not routinely be considered for treatment with tafamidis [27].
- Subgroup analysis from the ATTR-ACT trial suggested that the reduction in cardiovascular hospitalizations seen with tafamidis might be limited to patients with less severe symptoms (NYHA class I or II) [27].
- Because of the complexity in diagnosing CA and the potential for offering advanced or experimental treatment options, consideration should be given to referring patients with CA to experienced centers [27].
- Other agents are currently under investigation, which might modify current treatment recommendations [27].

1.2.4 American Heart Association (AHA)

The American Heart Association (AHA) released in 2020 a scientific statement on cardiac amyloidosis, including a discussion on its evolving management[11]. The following key points are a summary of the statement:

a) Overview of Disease-Modifying Therapies for ATTR-CM

Targets for disease-modifying therapies in cardiac amyloidosis include TTR silencing, TTR stabilization, and TTR disruption. TTR stabilizers bind to the TTR tetramer and prevent misfolding and thus deposition of amyloid fibrils. TTR silencers target TTR hepatic synthesis. TTR disruptors target the clearance of amyloid fibrils from tissues [11].

A summary of the disease-modifying therapies for ATTR-CM is shown in Table 6[11].

Table 6. Disease-Modifying Therapies for ATTR-CM (AHA Guideline)

Drug	Indication/ Approval	Dose/Delivery	Clinical Trial Key Inclusion/Exclusion	Potential Side Effects
TTR stabilizers				
Tafamidis	FDA approved for ATTRwt-CM and ATTRv-CM	20, 61, or 80 mg once daily	ATTR-ACT trial Inclusion: End-diastolic septal thickness >12 mm History of heart failure NT-proBNP ≥600 pg/mL Exclusion: 6MWT <100 m NYHA class IV symptoms Liver or heart transplantation eGFR <25 mL·min^{-1}·1.73 m^{-2}	None
Diflunisal	FDA approved as NSAID	Diflunisal	FDA approved as NSAID	Diflunisal
TTR silencers				
Patisiran	FDA approved for ATTRv with neuropathy	0.3 mg/kg intravenously every 3 wk Premedication with intravenous corticosteroids, intravenous H1 blocker, H2 blocker Daily vitamin A supplement	APOLLO Trial Inclusion: Documented *TTR* mutation Confirmed ATTRv with polyneuropathy (familial amyloid polyneuropathy) NIS score 5–130 PND score ≤3b Exclusion: NYHA class III–IV symptoms Liver transplantation	Infusion-related reactions Vitamin A deficiency
Inotersen	FDA approved for ATTRv with neuropathy	284 mg/wk subcutaneousl	NEURO-TTR Trial Inclusion: ATTRv with	Thrombocytopenia Glomerulon

		y Daily vitamin A supplement	polyneuropathy (familial amyloid polyneuropathy) stage 1 and 2 familial amyloid polyneuropathy NIS ≥10 and ≤130 Documented TTR mutation Documented amyloid deposit on biopsy Exclusion: Platelets <125×10^9/L Creatinine clearance <60 mL·min^{-1}·1.73 m^{-2} NYHA class III symptoms Liver transplantation	ephritis Infusion-related reactions Vitamin A deficiency

b) Approach to treatment in cardiac amyloidosis

Treatment of cardiac amyloidosis focuses on 3 areas: management of heart failure, management of arrhythmias, and initiation of disease-modifying agents[11].

b.1) Management of heart failure:

- There are no data supporting the use of standard guideline-directed medical therapy for heart failure with reduced ejection fraction or HFpEF in ATTR-CM, including angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, or angiotensin receptors blockers–neprilysin inhibitors.
- Furthermore, these therapies may exacerbate hypotension when amyloid-associated autonomic dysfunction is present.
- β-Blockers and nondihydropyridine calcium channel blockers are often poorly tolerated, even at low doses, because patients with ATTR-CM rely on heart rate response to maintain cardiac output given a fixed stroke volume.
- In AL amyloidosis, nondihydropyridine calcium channel blockers also bind amyloid fibrils and can result in heart block or shock[11].

b.2) Management of arrhythmias:

- As a result of atrial dysfunction in ATTR-CM, anticoagulation is indicated for atrial fibrillation/flutter regardless of CHA2 DS2 -VASc score.
- Digoxin may be used cautiously for rate control, although there is concern about potential digoxin toxicity caused by binding of digoxin to amyloid fibrils.

- Amiodarone is the agent of choice for both rhythm and rate control, particularly in cases in which β-blockade is not tolerated; cardioversion and ablation should also be considered in selected cases.
- Because of the high incidence of conduction system disease from amyloid infiltration, ambulatory electrocardiographic monitoring is part of the syncope evaluation, and pacemakers are indicated per Heart Rhythm Society consensus guidelines.
- Implantable cardioverter defibrillators (ICDs) are recommended in cases of aborted sudden cardiac death with expected survival >1 year or significant ventricular arrhythmias [11].

b.3) Implementation of Disease-Modifying Therapies in ATTR-CM:

- The use of US Food and Drug Administration–approved disease-modifying therapy is based on the presence of cardiomyopathy and polyneuropathy and the distinction between ATTRv and ATTRwt amyloidosis.
- **In patients with predominantly cardiac disease resulting from ATTRv or ATTRwt, tafamidis is indicated in those with NYHA class I to III symptoms, and early initiation appears to slow disease progression** [11].
- The **benefit of tafamidis has not been observed in patients with class IV symptoms**, severe aortic stenosis, or impaired renal function (glomerular filtration rate <25 mL·min−1·1.73 m^2 body surface area) [11].
- **Patients with ATTRv and polyneuropathy should be considered for TTR silencing therapy with patisiran or inotersen**; currently, neither is indicated for ATTRv-CM without polyneuropathy or in ATTRwt-CM [11].
- In patients with ATTRv-CM with polyneuropathy, the choice between therapeutic agents is based on accessibility and side-effect profile.
- The use of combination therapies is appealing to synergistically target both TTR silencing and stabilization of the remaining synthesized protein, but this approach lacks data and may be cost-prohibitive.
- **Diflusinal (250 mg orally twice daily) may be considered with caution for off-label therapy for asymptomatic ATTR carriers**, **for patients with ATTR-CM who are not eligible for TTR silencers, or for patients with ATTR-CM who are intolerant of or cannot afford tafamidis** [11].
- Because of the nonsteroidal anti-inflammatory properties, close monitoring is needed, and diflunisal is contraindicated in patients with significant thrombocytopenia and renal dysfunction and should be used cautiously in patients on anticoagulation or with a history of gastrointestinal bleeding [11].

b.4) Advanced Heart Failure Therapies in ATTR-CM:

- For patients with ATTR-CM with stage D heart failure, use of an LV assist device is challenging because of the small LV cavity size and concomitant right ventricular dysfunction.
- Heart transplantation may be considered in patients with stage D heart failure.
- Generally, heart-liver transplantation is performed in patients with ATTRv-CM at risk for neuropathy because neuropathy may progress with heart transplantation alone, although the criteria for heart alone versus heart-liver transplantation are not well defined [11].

1.3 European Guidelines

1.3.1 European Hematology Association (EHA)-International Society of Amyloidosis (ISA)

1.3.1.1 EHA-ISA Guidelines for Non-Transplant Chemotherapy for Treatment of Systemic AL Amyloidosis

The European Hematology Association (EHA) in association with the International Society of Amyloidosis (ISA) released in 2022 guidelines for non-transplant chemotherapy for the treatment of systemic AL amyloidosis[12]. The key recommendations of the guideline are outlined in the following sections:

a) Goals of treatment, assessing and monitoring treatment response

- Goal of treatment is to achieve a complete haematologic response (Grade B, Level IIb) with iFLC <20 mg/L or dFLC <10 mg/L (Grade B; Level III) [12].
- Patients achieving less than a very good partial response by cycle 3 or less than a partial response by cycle 2 should be considered for treatment modification (Grade C; Level IV) [12].

b) Treatment of newly diagnosed patients with AL amyloidosis

- The primary decision is whether a patient is a candidate for an autologous stem cell transplant (ASCT) as part of the upfront therapy, or combination chemotherapy without ASCT.
- For patients who are ineligible for high dose therapy and no available option of a clinical trial, **a combination of daratumumab-CyBorD is the preferred regimen**, if daratumumab is available [12].
- If **daratumumab is not available, then a bortezomib-based triplet combination, either CyBorD or VMDex, are primary options** [12].

- By expert consensus, CyBorD is the preferred regimen in most patients because it is easy to administer on an outpatient basis, with either oral or IV cyclophosphamide; may be preferable in patients with moderate or severe reduction of eGFR and/or heavy hypoalbuminemia and in those with potentially reversible contraindications to stem cell transplant.
- Bortezomib and dexamethasone doses need to be adapted to cardiac stage, presence of autonomic/ peripheral neuropathy, fluid retention status and patient's functional status.
- Optimal duration of therapy has not been evaluated formally. Expert consensus suggests treatment is given for at least two cycles beyond best response. For patients with at least very good partial response (VGPR) after 3 cycles, depending on the treatment tolerance, it is reasonable to continue for a total of 6–8 treatment cycles as depth of response can improve.
- Recommendations for upfront treatment: Patients without significant neuropathy:
  - Cardiac Stage I-IIIa: Dara-CyBorD (preferred)(Grade A; Level 1a); alternative CyBorD (Grade B; Level IIa) or VMDex (Grade A; Level 1a) [12].
  - Cardiac Stage IIIb: Dose modified Dara-CyBorD (Grade C; Level IV) or single agent daratumumab (Grade B; Level III); alternative dose modified CyBorD or VMDex (Grade C; Level IV) [12].

c) Maintenance therapy

- Routine maintenance not recommended (Grade C; Level IV) [12].

d) Consolidation therapy

- For eligible patients, high dose melphalan may be used as consolidation after less than a complete response to chemotherapy, considering that complete responses are often very long lasting in AL amyloidosis and that high dose melphalan only obtains 16% of complete response in patients refractory to induction treatment [12].
- However, in non-ASCT eligible patients, there is limited data regarding the role of consolidation.
- Recommendations:
  - Routine consolidation not recommended (Grade C; Level IV) [12].
  - Consolidation treatment may be considered patients with VGPR or CR with persistent MRD and no organ response (Grade C; Level IV) [12].

e) Special populations

- Cardiac Stage IIIB patients:
  - Dose modified Dara-CyBorD (Grade C; Level IV) or single agent daratumumab (Grade B; Level III); alternative dose modified CyBorD or VMDex (Grade C; Level IV) [12].
- Patients with neuropathy
  - Single agent daratumumab or Lenalidomide/Dexamethasone or oral melphalan-dexamethasone or Carfilzomib/Dex or Venetoclax are all possible options (Grade C; Level IV) [12].
  - Single agent daratumumab is the preferred option (Grade C; Level IV) [12].
- IgM related amyloidosis
  - Preferred treatment: Rituximab-Bendamustine (Grade B; Level IIb) or ASCT (Grade B, Level IIb) [12].
  - Alternatives: Rituximab-bortezomib-Dex or RituximabCyclo-Dex or CyBorD or Ibrutinib(±Rituximab) (Level C; Grade IV) [12].

f) Treatment of relapsed disease

- Proteasome inhibitor (PI) Naïve or prolonged response to 1st line PI:
  - CyBorD/VMDex B (Level B; Grade III); Ixazomib-Dex (Grade A; Level Ib); Dara-V(C)D (Level C; Grade IV) [12].
- Proteasome inhibitor exposed Daratumumab Naïve:
  - Single agent daratumumab (Level B; Grade IIb), DaraV(C)D (Level C; Grade IV), Dara-RD (Level B; Grade III), Isatuximab (Level C; Grade IV) [12].
- Proteasome inhibitor exposed IMiD Naïve:
  - Lenalidomide-Dexamethasone (±cyclophosphamide) (Level B; Grade IIa), Ixazomib-Lenalidomide dexamethasone (Grade B; Level IIb) [12].
- Lenalidomide Refractory:
  - Pomalidomide-Dexamethasone (Level B; Grade IIa), Bendamustine (Level B; Grade IIa) [12].
- Recommendation for patients with t(11;14) translocation:
  - Venetoclax (Grade B; Level III); Venetoclax-BortezomibDexamethasone (Grade C; Level III), Melphalan Dexamethasone (Grade C; Level IV) [12].

g) BCMA targeting agents

- The B-cell maturation antigen (BCMA) is another cell surface molecule ubiquitously expressed on plasma cell as well as their B-cell progenitors. There have been several unique targeting strategies demonstrating clear anti-plasma cell activity in multiple myeloma [12].
- To date, however, the experience specifically in AL amyloidosis is limited.

- A novel antibody-drug conjugate, Belantamab mafodotin, combines the potent mafodotin toxin with plasma cell targeting antiBCMA monoclonal antibody.
- A prospective EMN study (NCT04617925) is examining Belantamab in relapsed AL amyloidosis. An important consideration with this agent is the unique ocular toxicity in the form of keratopathy which has proven to be a challenge in the delivery of this agent.
- In AL amyloidosis, with the often-lower clonal burden, less frequent and finite dosing strategies built around response adapted approaches may help limit this issue without compromising efficacy.
- Recommendations:
  - Belantamab Mafodotin (Grade B; Level III) [12].
  - CAR-T cell or Bispecific antibodies are not recommended outside of clinical trials [12].

h) Treatment of localized AL amyloidosis

- Local treatment (surgical, laser or cytotherapeutic debulking) (Grade B; Level III) [12].
- Chemotherapy is not generally recommended [12].

i) Anti-amyloid fibril treatments

- The antibiotic doxycycline can inhibit amyloid fibril formation in vivo and abrogate light chain toxicity.
- A couple of small retrospective studies showed that doxycycline may reduce early mortality in cardiac patients when used as antibiotic prophylaxis along with effective chemotherapy, and a controlled study is underway (NCT03474458).
- A recent randomized study from China failed to show benefit of doxycycline added to standard of care.
- At present, the use of amyloid-targeting agents cannot be recommended outside clinical trials.
- Recommendation: Doxycycline (Grade C; Level IV); Antifebrile antibodies are not recommended outside of clinical trials [12].

1.3.1.2 EHA-ISA Guidelines for High Dose Chemotherapy and Stem Cell Transplantation for Systemic AL Amyloidosis

EHA in association with the ISA released in 2022 guidelines for high dose chemotherapy and stem cell transplantation for systemic AL amyloidosis[13]. The key recommendations of the guideline are outlined in the following sections:

a) Eligibility criteria

- Careful patient selection is critical for the success of SCT in AL amyloidosis.
- Broad eligibility criteria for SCT in AL amyloidosis are as follows: Confirmed tissue diagnosis of amyloidosis and accurate typing proving AL amyloidosis; Clear evidence of a clonal plasma cell dyscrasia; Age>18 years and<70 years (Patients older than70 years of age should be discussed in a multidisciplinary setting and evaluated for eligibility for SCT in a center of excellence with experience); At least one major vital organ involvement (soft tissues involvement alone or amyloid deposition in bone mar-row alone are not considered to be vital organ involvement); Left ventricular ejection fraction; 40%,NYHAclass<III; Oxygen saturation 95% on room air, DLCO>50%; Supine systolic blood pressure; 90 mm Hg; ECOG performance status score; 2 unless limited by peripheral neuropathy; Direct Bilirubin<2 mg/dL; NTproBNP<5,000 pg/mL; Troponin I<0.1 ng/mL and Troponin T<60 ng/L and hs-Troponin T<75 ng/mL; eGFR>30 mL/min/m^2; Patients on chronic and stable schedule of dialysis for ESRD should not be excluded if other eligibility criteria met [13].

b) Induction therapy prior to SCT:

- Induction therapy with bortezomib based regimen ± daratumumab for 2–4 cycles should be considered if bone marrow plasmacytosis>10% and defer SCT if hematologic CR achieved with induction therapy [13].

c) Stem cell mobilization and collection

- G-CSF at 10–16 mcg/kg/day, either as single or split dose and plerixafor (on demand or planned) for patients with cardiac involvement should be used for stem cell mobilization. Close monitoring of electrolytes and volume status should be performed during stem cell collection [13].

d) Conditioning regimen

- Full high dose melphalan at 200 mg/m^2 is the preferred conditioning regimen prior to SCT and AMYLOID3 modified dose melphalan at 140 mg/m^2 should be used for patients with reduced renal function [13].

e) Consolidation and maintenance therapy following SCT

- Consolidation and maintenance therapy are not routinely recommended after SCT in AL amyloidosis [13].

f) Supportive care

- Stem cell mobilization and collection phase:
  - Stem cell mobilization should be performed preferably with GCSF ±plerixafor
  - Patients with significant cardiac involvement and CHF should undergo stem cell mobilization with GCSF and planned plerixafor to avoid excessive fluid retention.
  - Patients should be assessed daily (before and after stem cell collection) during this phase and volume overload should be managed with intravenous loop diuretics.
  - Use of cardiac monitoring/telemetry is recommended inpatients with cardiac involvement and CHF, hypotension, presyncope or arrhythmia.
  - Hypotension from autonomic neuropathy should be man-aged with midodrine, compression stockings, prevention of intravascular volume depletion and droxidopa[13].

- Peri-stem cell transplantation phase:
  - G-CSF post SCT should be given till neutrophil engraftment
  - Antimicrobial prophylaxis–fluoroquinolone, acyclovir or valcyclovir, fluconazole, if allergic to fluoroquinolone, consider penicillin or doxycycline in consultation with infectious disease based on antibiogram for the institution
  - GI prophylaxis with proton pump inhibitor
  - Transfusion parameters, Hemoglobin of<8 g/dL for blood transfusion, Platelet count of<10 k or<20 k if bleeding and with fever for platelet transfusion, Platelet count of<50 k if factor X level 25%–50%, spleen and/or liver involvement, GI bleeding or severe mucositis for platelet transfusion
  - Febrile neutropenia: follow institutional guidelines, avoid aminoglycosides for the risk of nephrotoxicity
  - Special circumstances: Albumin infusion if serum albumin<2 g/dL due to advanced nephrotic syndrome, can be repeated daily or few times a week[13].

- Post-stem cell transplantation phase
  - Antimicrobial prophylaxis for VZV to be continued for12 months post SCT
  - Prophylaxis for pneumocystis pneumonia to be continued for 3 months post SCT
  - Immunization schedule per institution policy[13].

1.3.2 European Society of Cardiology (ESC)

The European Society of Cardiology (ESC) released in 2021 a position statement for the diagnosis and treatment of cardiac amyloidosis[14]. The essential concept of the statement are outlines in the following sections:

a) Definition and Classification

- Although nine types of cardiac amyloidosis are known, AL and ATTR currently account for the vast majority of cardiac amyloidosis.
- Both invasive and non-invasive diagnostic criteria are accepted to diagnose cardiac amyloidosis. While invasive diagnostic criteria apply to all forms of cardiac amyloidosis, non-invasive criteria are accepted only for ATTR[14].

b) Diagnosis of cardiac amyloidosis

- Cardiac amyloidosis should be considered in patients with increased wall thickness in the presence of cardiac or extracardiac red flags and/or in specific clinical situations.
- A diagnostic algorithm based initially on the use of bone scintigraphy coupled to assessment for monoclonal proteins allows appropriate diagnosis in patients with suggestive signs/symptoms[14].
- The diagnosis algorithm of cardiac amyloidosis is illustrated in Figure 4[14].

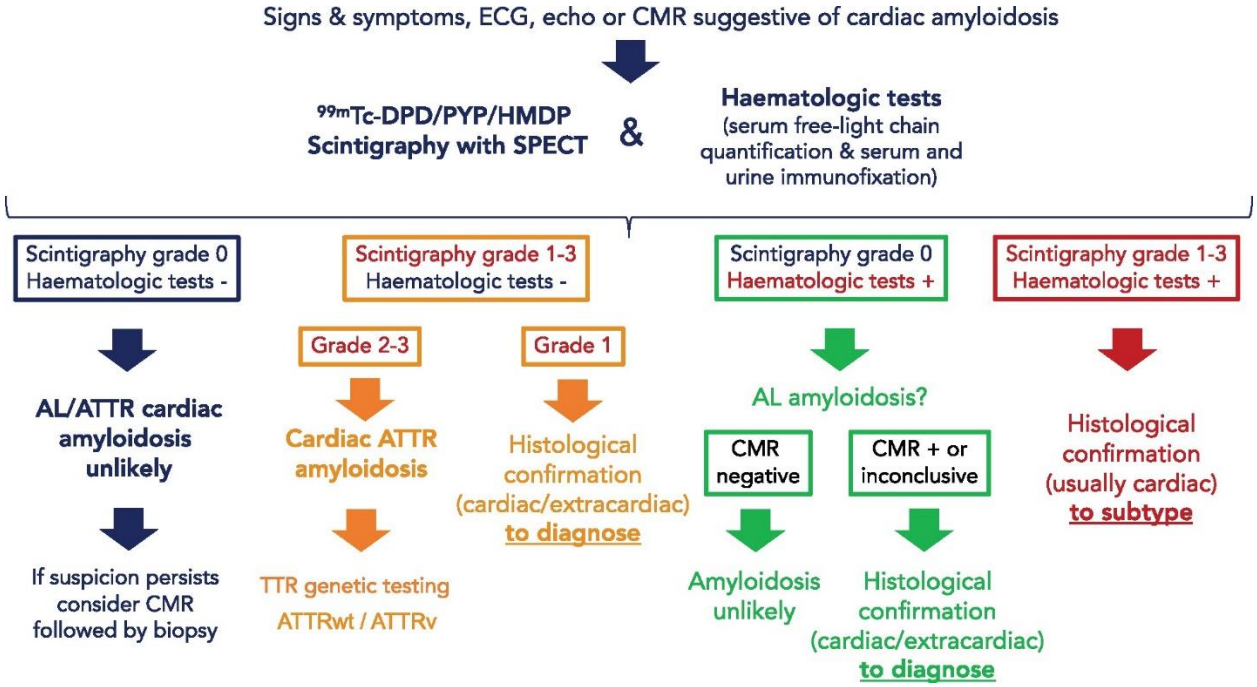

Figure 4. *Diagnostic algorithm for cardiac amyloidosis (ESC guideline). Adapted from Garcia-Pavia P, Rapezzi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis: a*

position statement of the ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J. *2021;42(16):1554-1568. doi:10.1093/eurheartj/ehab072*.

c) Outcome and prognosis

- While several staging systems are available to facilitate prognosis, there are limited data on how to assess progression. In the era of emerging effective specific therapies, this is a major unmet need.
- Follow-up of patients with cardiac amyloidosis and mutation carriers should be conducted following a structured protocol [14].

d) Treatment

Treatment of cardiac amyloidosis involves two areas: (i) treatment and prevention of complications and (ii) stopping or delaying amyloid deposition by specific treatment [14].

d.1) Treatment of complications and comorbidities

- Supportive care of patients with cardiac amyloidosis according to the ESC guideline is shown in Figure 5 [14].
- It encompasses different clinical aspects including treatment of heart failure, arrhythmias, conduction disturbances, thromboembolism, and concomitant presence of severe aortic stenosis.

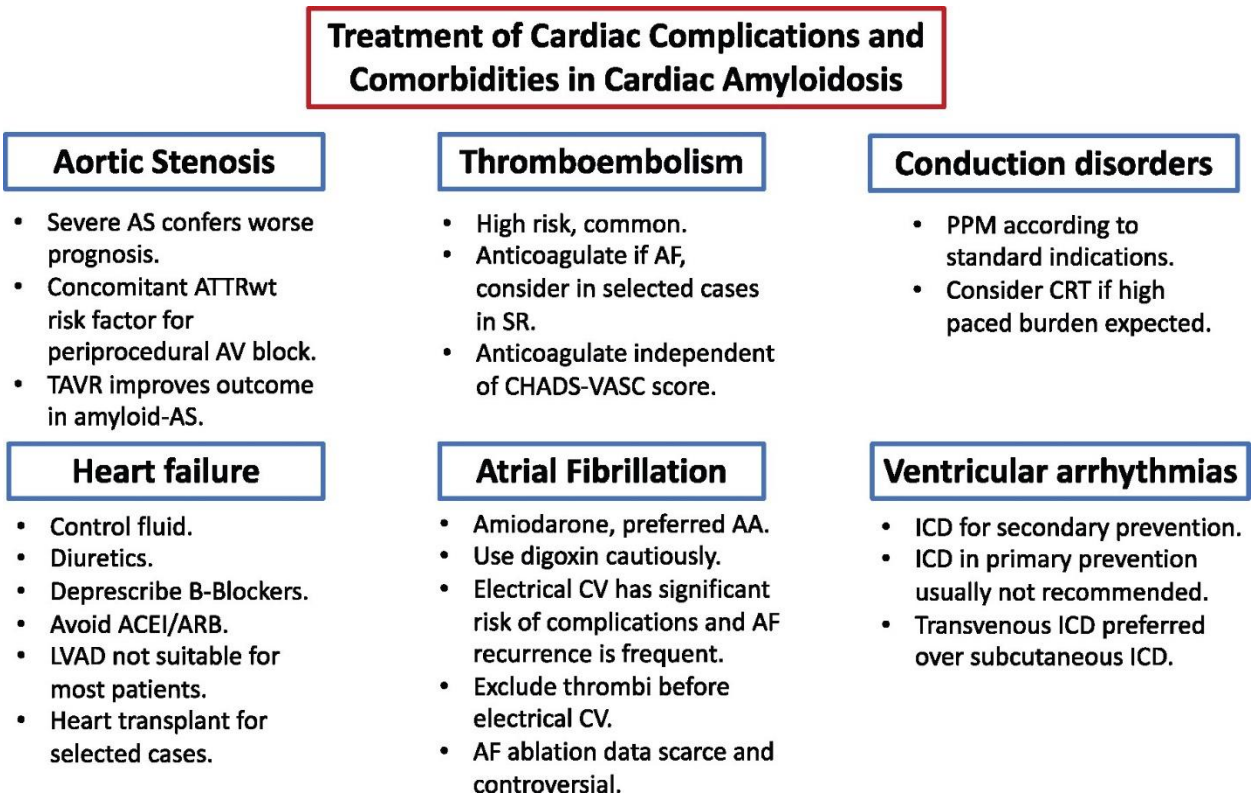

Figure 5. *Treatment of cardiac complications and comorbidities in cardiac amyloidosis (ESC guideline). Adapted from Garcia-Pavia P, Rapezzi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases.* Eur Heart J. *2021;42(16):1554-1568. doi:10.1093/eurheartj/ehab072.*

d.2) Specific (disease-modifying) treatment

- Patients with **AL amyloidosis** not only have a hematologic malignancy, but also their multiorgan involvement makes them particularly fragile and susceptible to treatment toxicity. Therapeutic approaches depend on risk assessment that is defined in many circumstances by the degree of cardiac involvement and cardiac response depends also on hematological response [14].
- Specific pharmacologic treatments available for **ATTR amyloidosis** include stabilizing molecules (tafamidis) and genetic silencers (patisiran and inotersen) [14].
- Current therapeutic alternatives distinguish between **ATTRv** and **ATTRwt** and, in the case of ATTRv, according to the presence of **cardiomyopathy**, **polyneuropathy**, **or both**. The therapeutic alternatives for ATTR amyloidosis are shown in Figure 6 [14].

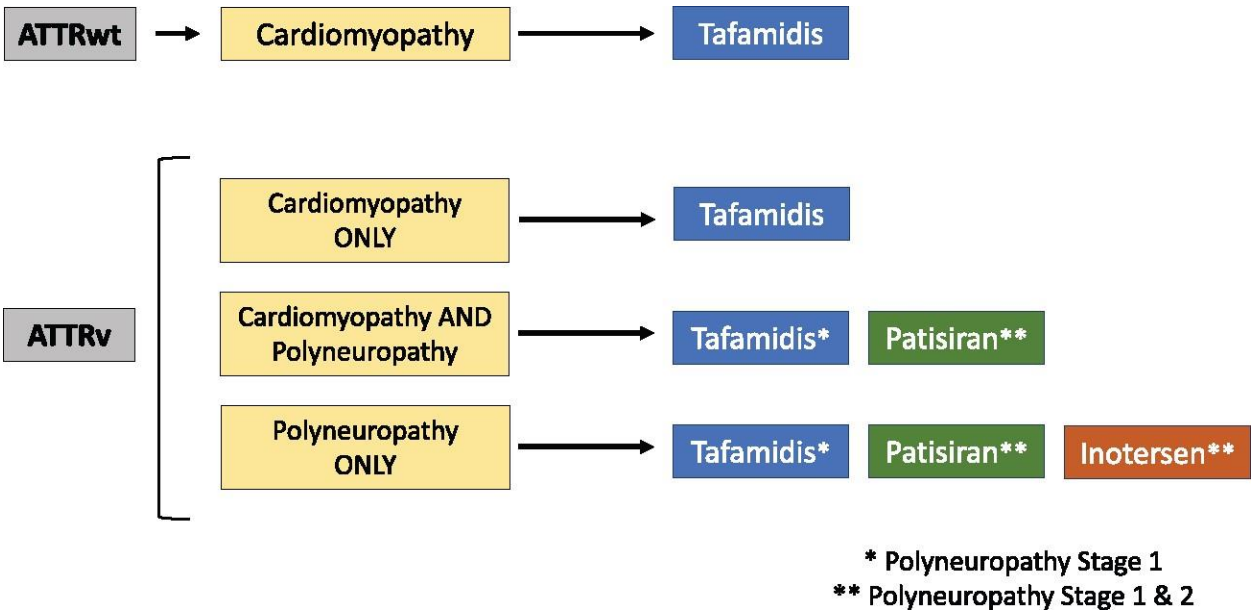

Figure 6. *Proposed therapeutic alternatives in transthyretin amyloidosis patients (ESC guideline). Adapted from Garcia-Pavia P, Rapezzi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases.* Eur Heart J. *2021;42(16):1554-1568. doi:10.1093/eurheartj/ehab072.*

- **Tafamidis** is currently the only drug that has shown efficacy in a randomized trial in patients with **ATTRwt and ATTRv with cardiomyopathy**, and **should be considered in patients with reasonable expected survival** [14].
- **Patisiran** could be considered in **ATTRv patients with cardiac involvement in whom gene silencers are prescribed due to symptomatic neurological disease** [14].

1.4 Other International Guidelines

1.4.1 Japanese Circulation Society (JCS) Guideline on Diagnosis and Treatment of Cardiac Amyloidosis

The Japanese Circulation Society (JCS) released in 2020 their guidelines on the diagnosis and treatment of cardiac amyloidosis[15]. The key recommendations with their level of evidence are summarized in the following sections.

a) Diagnosis:

Diagnosis recommendations from the 2020 JCS guideline with their level of evidence are shown in Table 7[15].

Table 7. Diagnosis Recommendations for Patients with Suspected Cardiac Amyloidosis (JCS Guideline)

Recommendations	*Class, LOE*
Blood Sampling	
▪ Measurement of high-sensitivity cardiac troponin to aid the diagnosis of amyloidosis ▪ Measurement of BNP/NT-proBNP to aid the diagnosis of amyloidosis ▪ Measurement of high-sensitivity cardiac troponin to assess prognosis in ATTRwt amyloidosis ▪ Measurement of BNP/NT-proBNP to assess prognosis in ATTRwt amyloidosis ▪ Measurement of serum immunoglobulin to diagnose AL amyloidosis ▪ Serum and urine immunofixation (or electrophoresis) to diagnose AL amyloidosis ▪ Measurement of serum free-light chains to diagnose AL amyloidosis	IIa, C IIa, C IIa, C IIa, C I, A I, A I, A
Cardiac CT	
▪ Myocardial late enhancement/ECV assessment with cardiac CT as an alternative to CMR	IIa, C
Nuclear Imaging	
▪ Diagnosis of ATTR cardiac amyloidosis with 99mTc-PYP scintigraphy ▪ Assessment of myocardial sympathetic nerve function with 123I-MIBG scintigraphy ▪ Diagnosis of cardiac amyloidosis using amyloid PET	I, C IIa, C IIb, C
Biopsy (Other Than the Heart)	
▪ Perform abdominal fat pad biopsy as a means of detecting amyloid other than myocardial biopsy when cardiac amyloidosis is suspected ▪ Perform lip salivary gland biopsy, skin biopsy, and gastrointestinal tract biopsy as a means of detecting and typing other than myocardial biopsy when cardiac amyloidosis is suspected ▪ Repeat biopsies from other sites (abdominal fat, skin, digestive tract, labial salivary glands) when single biopsy failed to detect amyloid deposits	I, C I, C IIa, C III, C

▪ Perform abdominal fat pad biopsy, skin biopsy, gastrointestinal biopsy, and labial salivary gland biopsy as a means of assessing the severity and prognosis of cardiac amyloidosis	
Genetic Testing for the Definitive Diagnosis of ATTR-Type Cardiac Amyloidosis	
▪ Detection of TTR variant	I, C

b) Treatment:

Treatment recommendations from the 2020 JCS guideline with their level of evidence are summarized in Table 8[15].

Table 8. Treatment Recommendations for Patients with Cardiac Amyloidosis (JCS Guideline)

Recommendations	*Class, LOE*
Genetic Counseling for Patients and Relatives of ATTRv Amyloidosis	
▪ Genetic counseling for patients with ATTRv amyloidosis ▪ Genetic counseling for asymptomatic relatives of ATTRv amyloidosis patients	I, C I, C
Drug Therapy in Patients With Cardiac Amyloidosis	
▪ Diuretics for fluid retention ▪ Nitrates or carperitide for pulmonary congestion in acute settings ▪ Catecholamines or phosphodiesterase inhibitors in pump failure with low output ▪ Tolerated dosing of ACE inhibitors, β-blockers and aldosterone antagonists to reduce clinical events ▪ Direct Oral Anticoagulant (DOAC) for atrial fibrillation (AF) ▪ DOAC for AT with LV dysfunction ▪ β-blocker for AF tachycardia ▪ NonDPH Ca antagonist for ATTR amyloidosis with preserved systolic function ▪ NonDPH Ca antagonist for ATTR amyloidosis with impaired systolic function ▪ NonDPH Ca antagonist for AL amyroidosis ▪ Digitalis for AF	I, C IIa, C IIa, C IIb, C I, C IIa, C II, C IIb, C III, C III, C III, C
Palliative Care	
▪ Conduct advance care planning in which physicians share decisions with the patient and his/her family members about treatment and care before the patient becomes difficult to make his or her own decisions ▪ Continued treatment to manage heart failure and complications and relieve symptoms ▪ Multidisciplinary team-based frequent assessment for the patient's physical, mental and spiritual needs	I, B I, C II, C
Disease Modifying Therapies for ATTRv Neuropathy and Cardiomyopathy	

▪ Liver transplantation ▪ Tafamidis for neuropathy ▪ Patisiran for neuropathy ▪ Tafamidsis for patients with NYHA Class I/II and satisfy patient requirements in the statement of the Japanese Circulation Society ▪ Tafamidsis for patients with NYHA Class III and satisfy patient requirements in the statement of the Japanese Circulation Society	I, C I, B I, B IIa, B IIb, B

Tafamidis should be administered with a dosage of 20mg for neuropathy and 80mg for cardiomyopathy (dosage of tafamidis can be reduced in the case of intolerance to 80mg).

1.5 Systematic Reviews/Meta-Analyses

A detailed search of PubMed and Cochrane databases for systematic reviews and meta-analysis on amyloidosis didn't yield to any result more recent than the detailed previous guidelines. This is probably due to the fact that the treatment guidelines for amyloidosis are constantly being updated with the many clinical trials and treatment alternatives emerging in the market.

Section 2.0 Drug Therapy

2.1 Alkylating Agents

2.1.1 Bendamustine

Table 9. Bendamustine Drug Information

Scientific Name Bendamustine	
Trade Name(s) on Saudi Market	Ribomustine; Squadaion; Bendokey
SFDA Classification	Prescription
SFDA approved Indication	Yes, used off-label in amyloidosis
FDA approved / off label	Yes, used off-label in amyloidosis
EMEA approved / off label	Yes, used off-label in amyloidosis
MHRA approved / off label	Yes, used off-label in amyloidosis
PMDA approved / off label	Yes, used off-label in amyloidosis
Indication (ICD-10)	E85. 81
Drug Class	Antineoplastic agent
Drug Sub-class	Alkylating agent
SFDA Registration Number (New)	Ribomustine: 1808222507 (100 mg); 1808222508 (100 mg); 1808222506 (25 mg) Squadaion: 0411211258 (25 mg); 0411211259 (100 mg) Bendokey: 1503233373
ATC Code	L01AA09
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Powder for concentrate for solution for infusion
Route of Administration	Intravenous
Dose (Adult) [DDD]*	60 to 100 mg/m^2 on days 1 and 2 of a 28-day treatment cycle (in combination with dexamethasone)
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): CrCl <30 mL/minute: Use is not recommended. Hepatic Impairment (Adult): - Moderate impairment (AST or ALT 2.5 to 10 times ULN and total

	bilirubin 1.5 to 3 times ULN): Use is not recommended. - Severe impairment (total bilirubin >3 times ULN): Use is not recommended.
Prescribing edits*	AGE, MD, ST, CU, PE
AGE (Age Edit)	Not used in the pediatric population
CU (Concurrent Use)	Used with dexamethasone; Used with anti-emetics
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	Second and later-line treatment of relapsed/refractory AL amyloidosis
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol (Bendamustine/dexamethasone)
Maximum Daily Dose Adults*	N/A
Maximum Daily Dose Pediatrics*	N/A
Safety	High alert medication
Main Adverse Drug Reactions (most common and most serious)	- Most common: Peripheral edema, Skin rash, Dehydration, weight loss, abdominal pain, anorexia, constipation, decreased appetite, diarrhea, stomatitis, vomiting, bone marrow depression, decreased hemoglobin, decreased neutrophils decreased platelet count, leukopenia, lymphocytopenia, Increased serum bilirubin, Asthenia, chills, dizziness, fatigue, headache, insomnia, back pain, cough, dyspnea, fever - Most serious: Bone marrow depression,
Drug Interactions*	- Risk X: BCG Intravesical, Cladribine, Dipyrone, Fexinidazole - Risk D: CYP1A2 Inhibitors, CYP1A2 Inducers, Lenograstim,

	Lipegfilgrastim, Palifermin, Ropeginterferon Alfa-2b
Special Population	N/A
Pregnancy	Pregnancy Category D
Lactation	It is not known if bendamustine is present in breast milk. Breastfeeding is not recommended by the manufacturer during treatment or for 1 week after the last bendamustine dose.
Contraindications	Known hypersensitivity (eg, anaphylactic or anaphylactoid reactions) to bendamustine or any component of the formulation.
Monitoring Requirements	- CBC with differential and platelets - Serum creatinine; LFTs - Potassium and uric acid levels in patients at risk for tumor lysis syndrome. - Pregnancy status - Monitor for signs/symptoms of infusion reactions, anaphylaxis, infection, dermatologic toxicity, progressive multifocal leukoencephalopathy, and tumor lysis syndrome. - Monitor for development of secondary malignancies, including dermatologic evaluations, during and after treatment.
Precautions	- Bone marrow suppression - Dermatologic toxicity - Extravasation - Hepatotoxicity - Hypersensitivity/infusion reaction - Infection - Progressive multifocal leukoencephalopathy - Secondary malignancy - Tumor lysis syndrome

Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the HTA instances: National Institute for Health and Care Excellence (NICE), Haute Autorité de Santé (HAS), Canadian Agency for Drugs and Technologies in Health (CADTH), Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC) didn't yield any recent result for bendamustine in amyloidosis.

Conclusion Statement – Bendamustine

In amyloidosis, bendamustine is recommended as a second- and later line agent in combination with dexamethasone in patients with relapsed/refractory non-cardiac light chain amyloidosis. There is no data issued by HTA bodies regarding its use.

2.1.2 Cyclophosphamide

Table 10. Cyclophosphamide Drug Information

Scientific Name Cyclophosphamide[30]	
Trade Name(s) on Saudi Market	Endoxan
SFDA Classification	Prescription
SFDA approved Indication	Yes, 1981
FDA approved / off label	Yes, 1959
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2005
Indication (ICD-10)	E85. 81
Drug Class	Antineoplastic agent
Drug Sub-class	Alkylating agent
SFDA Registration Number (New)	Endoxan: 14-16-81 (Sugarcoated Tablets 50mg) 17-16-81 (200mg vial) 18-16-81 (500mg vial) 19-16-81 (1g vial)
ATC Code	L01AA01
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Powder for Injectable Solution, Tablet
Route of Administration	Intravenous, Oral
Dose (Adult) [DDD]*	CyBorD regimen: **Oral or IV:** 300 mg/m^2 once weekly (in combination with bortezomib and

	dexamethasone) **or** 350 mg/m^2 on days 1, 8, and 15 (in combination with bortezomib and dexamethasone) for up to 8 cycles.
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): - CrCl ≥30 mL/min: No adjustment. - CrCl 10 to 29 mL/minute: Administer 75% or 100% of normal dose. - CrCl <10 mL/minute: Administer 50% (Ref), 75%, or 100% of normal dose. - Hemodialysis, intermittent (thrice weekly): Moderately dialyzable. Administer 50% or 75% of the normal dose. On dialysis days, administer after hemodialysis, allowing at least 12 hours before the next hemodialysis session. - Peritoneal dialysis: Administer 75% of the normal dose. If possible, allow at least 12 hours before next peritoneal dialysis exchange. - CRRT: 100% of the normal dose Hepatic Impairment (Adult): - Serum bilirubin 3.1 to 5 mg/dL or transaminases >3 times ULN: Administer 75% of dose. - Serum bilirubin >5 mg/dL: Avoid use.
Prescribing edits*	MD, ST, PE
AGE (Age Edit)	N/A
CU (Concurrent Use)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	First and second-line treatment of AL amyloidosis
EU (Emergency Use Only)	N/A

PE (Protocol Edit)	Dara-CyborD; CyBorD; Lenalidomide/ Cyclophosphamide/ Dexamethasone
Maximum Daily Dose Adults*	N/A
Maximum Daily Dose Pediatrics*	N/A
Safety	High alert medication
Main Adverse Drug Reactions (most common and most serious)	- Most common/serious: Bone marrow suppression, infection, hemorrhagic cystitits, cardiotoxicity, hepatotoxicity, pulmonary toxicity, secondary malignancies
Drug Interactions*	- Risk X: Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Dipyrone, Etanercept, Fexinidazole, Filgotinib, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Lenograstim, Lipegfilgrastim, Palifermin, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Succinylcholine, Vaccines (Inactivated/Non-Replicating)
Special Population	N/A
Pregnancy	Pregnancy Category D
Lactation	Cyclophosphamide and its metabolites are present in breast milk. Breastfeeding is not recommended by the manufacturer during therapy and for 1 week after the last cyclophosphamide dose. Others recommend breastfeeding be

	avoided for at least 6 weeks after the last dose of cyclophosphamide.
Contraindications	History of severe hypersensitivity to cyclophosphamide, its metabolites, or any component of the formulation; urinary outflow obstruction.
Monitoring Requirements	- CBC with differential and platelets, BUN, serum electrolytes, serum creatinine, urinalysis. - Pregnancy status - Assess risk for opportunistic infections - Monitor for signs/symptoms of hemorrhagic cystitis or other urinary/renal toxicity, pulmonary toxicity, cardiac toxicity, hepatic toxicity, secondary malignancies, and/or wound healing impairment. - Monitor adherence (for oral dosing).
Precautions	- Hypersensitivity - Hepatic/Renal impairment patients
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the HTA instances: National Institute for Health and Care Excellence (NICE), Haute Autorité de Santé (HAS), Canadian Agency for Drugs and Technologies in Health (CADTH), Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC) didn't yield any recent result for cyclophosphamide in amyloidosis. Only guidance on daratumumab reimbursement in combination with bortezomib/cyclophosphamide/ dexamethasone (Dara-CyBorD) was found. This is probably due to the fact that cyclophosphamide is an old drug, with many affordable generics available on the market.

Conclusion Statement – Cyclophosphamide

In amyloidosis, cyclophosphamide is recommended as a first-line agent in combination with bortezomib, dexamethasone, and daratumumab (Dara-CyBorD

protocol; preferred regiment) in the management of systemic light chain amyloidosis as an induction therapy for 2-4 cycles prior to stem cell transplant. It is also a first and second-line agent in combination with bortezomib and dexamethasone (CyBorD protocol) and a second-line agent in combination with dexamethasone and lenalidomide in patients with relapsed or refractory systemic light chain amyloidosis IMiD-treatment naïve and exposed to PI drugs. There is no data issued by HTA bodies regarding its use.

2.1.3 Melphalan

Table 11. Melphalan Drug Information

Scientific Name **Melphalan**[38]	
Trade Name(s) on Saudi Market	Alkeran (tablets) ; Megval (injection)
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2016 (Alkeran); 2021 (Megval)
FDA approved / off label	Yes, 1964
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2015
Indication (ICD-10)	E85. 81
Drug Class	Antineoplastic agent
Drug Sub-class	Alkylating Agent
SFDA Registration Number (New)	0512211427 (Megval 50mg injection) 0512211427 (Alkeran 2mg tabs)
ATC Code	L01AA03
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Tablet; Powder and solvent for solution for injection
Route of Administration	Oral; Intravenous
Dose (Adult) [DDD]*	**Amyloidosis, light chain (off-label use): Oral:** 0.22 mg/kg/day for 4 days every 28 days (in combination with bortezomib and oral dexamethasone) for up to 6 to 8 cycles; refer to protocol for further information. **Amyloidosis, light chain, conditioning regimen for ASCT: IV:** 200 mg/m^2 (or 140 mg/m^2 if >65 years of age, left ventricular ejection fraction 40% to 45%, or stem cell collection ≥2 to <2.5 × 10^6 cells/kg) as a one-time dose prior to stem cell infusion;

	some patients received a further reduced dose of 100 mg/m^2. **MM, previously untreated; transplant ineligible: Oral:** 9 mg/m^2/day for 4 days (days 1 to 4) every 6 weeks for 9 cycles
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): Oral: Moderate to severe renal impairment: Consider a reduced dose initially. IV: Conditioning regimen for MM: No dosage adjustment is necessary. HD: Not removed by HD
Prescribing edits*	MD, ST, PE
AGE (Age Edit)	N/A
CU (Concurrent Use)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	First and second-line treatment of AL amyloidosis
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Bortezomib/Melphalan/Dexamethasone ; High-dose Melphalan with HCT; Melphalan/ Dexamethasone
Maximum Daily Dose Adults*	N/A
Maximum Daily Dose Pediatrics*	N/A
Safety	High alert medication
Main Adverse Drug Reactions (most common and most serious)	- Most common: Peripheral edema, hypokalemia, hypophosphatemia, abdominal pain, constipation, decreased appetite, diarrhea, dysgeusia, dyspepsia, nausea, stomatitis, vomiting, anemia, decreased neutrophils, platelet count, white blood cell count, febrile neutropenia, lymphocytopenia, dizziness, fatigue, fever - Most serious: Bone marrow depression, bone marrow failure (can

	be irreversible), renal failure, hepatic sinusoidal obstruction syndrome, pulmonary fibrosis, secondary malignancy
Drug Interactions*	- Risk X: Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating)
Special Population	Older adults
Pregnancy	Pregnancy category D
Lactation	It is not known if melphalan is present in breast milk. Breastfeeding is not recommended during treatment and for 1 week after the last melphalan dose.
Contraindications	Hypersensitivity to melphalan or any component of the formulation
Monitoring Requirements	CBC with differential and platelet count, serum electrolytes, renal/liver function tests, serum uric acid. Monitor for signs/symptoms of hypersensitivity reaction, pulmonary toxicity, and GI toxicity; monitor infusion site. Monitor adherence (oral melphalan).
Precautions	- Bone marrow suppression - Extravasation - GI toxicity - Hepatotoxicity

	- Hypersensititvity - Pulmonary toxicity - Secondary malignancy - Renal impairment (prolonged mucositis in HD melphalan regimens for ASCT)
Black Box Warning	- Bone marrow suppression - Secondary malignancy - Hypersensitivity - Experienced physician
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the HTA instances: National Institute for Health and Care Excellence (NICE), Haute Autorité de Santé (HAS), Canadian Agency for Drugs and Technologies in Health (CADTH), Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC) didn't yield any recent result for melphalan in amyloidosis. This is probably due to the fact that high-dose melphalan is an old well established standard of care with a proven record of efficacy in conditioning regimens for ASTC.

Conclusion Statement – Melphalan

In amyloidosis, high dose melphalan followed by hematopoietic stem cell transplant is recommended as a first-line treatment for systemic light chain amyloidosis as well as a second-line treatment in patients with relapsed/refractory disease. Melphalan oral is also a first-line treatment option in combination with dexamethasone ± bortezomib (MDex or VMDex protocols) in newly diagnosed patients with systemic light chain amyloidosis not eligible for stem cell transplant, as well as a second-line option in patients with relapsed/refractory disease in these combinations. There is no data issued by HTA bodies regarding its use.

2.2 Angiogenesis Inhibitors

2.2.1 Lenalidomide

Table 12. Lenalidomide Drug Information

Scientific Name Lenalidomide[37]	
Trade Name(s) on Saudi Market	Lenalidomide SPC, Sotira, Lidova, Lenamide, Lenalidomide BOS
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2018

FDA approved / off label	Yes, 2005
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2010
Indication (ICD-10)	E85. 81
Drug Class	Antineoplastic agent
Drug Sub-class	Angiogenesis Inhibitor
SFDA Registration Number (New)	Lenalidomide SPC: 9-5171-18 (5mg); 10-5171-18 (10mg); 11-5171-18 (25mg); 0810200199 (15mg); 0810200193 (20mg) Sotira: 326-334-20 (5mg); 327-334-20 (10mg); 328-334-20 (15mg); 329-334-20 (25mg) Lidova: 111-370-20 (5mg); 112-370-20 (10mg); 113-370-20 (25mg) Lenamide: 1008210918 (5mg); 1008210920 (10mg); 1008210921 (25mg) Lenalidomide BOS: 1008210921 (25mg); 0603233331 (15mg); 0603233328 (10mg); 0603233329 (5mg)
ATC Code	L04AX04
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Capsule
Route of Administration	Oral
Dose (Adult) [DDD]*	15 mg once daily for 21 days of a 28-day cycle (in combination with dexamethasone)
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): - CrCl ≥60 mL/mine: No adjustment - CrCl 30 to <60 mL/min: 10 mg once daily; may increase to 15 mg once daily after 2 cycles - CrCl 15 to <30 mL/minute: 15 mg every other day; may increase dose to 10 mg once daily - CrCl <15 mL/minute: 5 mg once daily - Hemodialysis/PD: 5 mg once daily (after dialysis) - CRRT/PIRRT: No data; dosing as for patients with CrCl 15 to <30 mL/minute is suggested

	- Non PIRRT days: 5 mg once daily
Prescribing edits*	AGE, MD, ST, PE
AGE (Age Edit)	Not used in children below 12 years of age
CU (Concurrent Use)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	First and second-line treatment of AL amyloidosis
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Bortezomib/Lenalidomide/Dexamethasone ; Ixazomib/ lenalidomide/ dexamethasone; Lenalidomide/Cyclophosphamide/ Dexamethasone ; Lenalidomide/ dexamethasone; Daratumumab/ Lenalidomide/ dexamethasone
Maximum Daily Dose Adults*	N/A
Maximum Daily Dose Pediatrics*	N/A
Safety	High alert medication
Main Adverse Drug Reactions (most common and most serious)	- Most common: Skin rash, xeroderma, diarrhea, gastro-enteritis, nausea, anemia, leukopenia, neutropenia, thrombocytopenia, influenza, asthenia, headache, paresthesia, muscle spasms, bronchitis, dyspnea, nasopharyngitis, rhinitis - Most serious: Hematologic toxicity and infection, hepatic toxicity, hypersensitivity, secondary malignancies, thromboembolic events (deep vein thrombosis, pulmonary embolism)
Drug Interactions*	- Risk X: Abrocitinib, Anakinra, Baricitinib, BCG Products, Brivudine, Canakinumab, Certolizumab Pegol, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Nadofaragene Firadenovec, Natalizumab, Pembrolizumab, Pimecrolimus, Rilonacept, Ruxolitinib

	(Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tocilizumab, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T
Special Population	Older adults, pediatric patients
Pregnancy	Use is contraindicated in pregnancy (US Boxed Warning).
Lactation	It is not known if lenalidomide is present in breast milk. Breastfeeding is not recommended by the manufacturer.
Contraindications	Severe hypersensitivity to lenalidomide or any component of the formulation Pregnancy
Monitoring Requirements	CBC with differential, serum creatinine, LFTs, thyroid function tests, ECG when clinically indicated. Monitor for signs and symptoms of infection, bleeding or bruising, hepatotoxicity, secondary malignancies, thromboembolism.
Precautions	- CNS effects - Tumor flare - Tumor lysis syndrome - Heart failure - Renal impairment - Stem cell mobilization (decrease CD34+ counts)
Black Box Warning	- Embryo-fetal toxicity - Hematologic toxicity - Venous and arterial thromboembolism
REMS*	Yes (Lenalidomide REMS program)

Health Technology Assessment (HTA)

The table below lists the National Institute for Health and Care Excellence (NICE), Haute Autorité de Santé (HAS), Canadian Agency for Drugs and Technologies in Health (CADTH), Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC) HTA review and recommendations of lenalidomide in amyloidosis treatment options.

Table 13. Lenalidomide HTA Analysis

Medication	Agency	Date – HTA Recommendation
Ixazomib/ Lenalidomide/ Dexamethasone	NICE	2/2023: **Ixazomib, with lenalidomide and dexamethasone, is recommended as an option for treating multiple myeloma in adults, only if they have had 2 or 3 lines of therapy**. - Without ixazomib combination, there would be an unmet need for an oral triplet therapy for people who have had 2 or 3 previous therapies - Lenalidomide plus dexamethasone remains the only relevant comparator - Ixazomib combination improves progression-free survival after 2 or 3 lines of therapy o The median PFS for ixazomib combination after 2 or 3 previous lines of treatment was 22 months compared with 13 months for lenalidomide and dexamethasone. The stratified hazard ratio was 0.62 (95% confidence interval [CI] 0.45 to 0.86, p=0.0033). - Ixazomib likely improves overall survival - Ixazomib combination does not meet the end of life criteria - The most likely cost-effectiveness estimates is below £30,000 per QALY gained - The committee noted that there was a high level of unmet need for people

		with relapsed or refractory MM at this line of treatment. They noted that people would welcome a new oral triplet therapy option at the third and fourth-line treatment setting, which led to the conclusion that it was appropriate to recommend ixazomib combination for treating multiple myeloma after 2 or 3 therapies.
Lenalidomide	NICE	3/2021: **Lenalidomide is recommended as maintenance treatment after an ASCT for newly diagnosed multiple myeloma in adults, only if the dosage schedule is 10 mg per day on days 1 to 21 of a 28-day cycle**. - Lenalidomide is an effective maintenance treatment for people who have had an autologous stem cell transplant. - The main clinical evidence for lenalidomide maintenance treatment came from Myeloma XI (n=1971). - The safety profile of lenalidomide as a maintenance treatment compared with monitoring alone is likely to be acceptable. - Maintenance therapy with lenalidomide is likely to be a cost-effective use of NHS resources when given on days 1 to 21 of each 28-day cycle.
Lenalidomide	HAS	4/20: **Unfavorable opinion for reimbursement as combination therapy with bortezomib and dexamethasone for the treatment of adult patients with previously untreated MM who are not eligible for transplant.** 3/17: **Favorable opinion for reimbursement as monotherapy in the**

		maintenance treatment of adult patients with previously untreated MM who have undergone ASCT (CAV V compared to no treatment).
Bortezomib/ Lenalidomide/ Dexamethasone (VRd)	CADTH	1/22: **The clinical effectiveness regarding response, relapse, PFS and OS broadly favored VRd over VCd,** although the magnitude and direction of association was not always consistent. Limited evidence on the safety of VRd relative to VCd. No evidence on the cost-effectiveness of VRd as induction therapy before ASCT for MM was found. Among the 5 included guidelines, 3 specifically recommend VRd as a first option for induction therapy among transplant-eligible newly diagnosed patients, and 2 recommend more broadly defined 3-drug induction regimens that include VRd.
Daratumumab/ Lenalidomide**/ Dexamethasone**	CADTH	3/20: **pERC conditionally recommends to reimburse daratumumab in combination with lenalidomide and dexamethasone (DRd) for patients with newly diagnosed MM who are not suitable for ASCT** if the following conditions are met: Cost-effectiveness being improved to an acceptable level, feasibility of adoption (budget impact) being addressed. - There is a net clinical benefit of DRd compared with Rd based on a statistically significant and clinically meaningful improvement in PFS. - DRd could not be considered cost-effective compared with Rd
Lenalidomide	CADTH	6/19: **pERC conditionally recommends the reimbursement of lenalidomie with low dose dexamethasone in patients with newly diagnosed MM in whom HCT is not intended**, if the following

		conditions are met: feasibility of adoption (budget impact) being addressed.
Lenalidomide	PBAC	7/19: **Use is recommended**

Conclusion Statement – Lenalidomide

In amyloidosis, lenalidomide in combination with bortezomib/dexamethasone (VRD protocol) is mostly recommended as a second-line treatment option for systemic light chain amyloidosis. Lenalidomide is also a second-line treatment option for patient with relapsed/refractory light chain amyloidosis that are IMiD-treatment naïve in the following combinations: Ixazomib/ lenalidomide/ dexamethasone and Lenalidomide/ dexamethasone ± cyclophosphamide/ (in patients already exposed to treatment with a PI). There is no data issued by HTA bodies regarding its use.

2.2.2 Pomalidomide

Table 14. Pomalidomide Drug Information

Scientific Name Pomalidomide[39]	
Trade Name(s) on Saudi Market	Pomalidomide SPC, Imnovid
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2020
FDA approved / off label	Yes, 2013
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2015
Indication (ICD-10)	E85. 81
Drug Class	Antineoplastic agent
Drug Sub-class	Angiogenesis Inhibitor
SFDA Registration Number (New)	Pomalidomide SPC 0810200192 (1mg); 0810200197 (4mg); 0810200198 (3mg); 0810200202 (1mg); 0810200203 (2mg); 0810200204 (2mg); 0810200205 (4mg); 0810200207 (3mg); Imnovid 3107222371 (1mg); 3107222370 (2mg); 3107222366 (3mg); 3107222365 (4mg)
ATC Code	L04AX06
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Capsule
Route of Administration	Oral

Dose (Adult) [DDD]*	4 mg once daily on days 1 to 21 of 28-day cycles (in combination with dexamethasone); until disease progression or unacceptable toxicity
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): *CrCl ≥15 to <60 mL/minute:* No dosage adjustments provided in the manufacturer's labeling. HD: *Hemodialysis:* 3 mg once daily after dialysis on dialysis days. Hepatic Impairment (Adult): Mild or moderate impairment (Child-Pugh class A or B): Initial: 3 mg once daily. Severe impairment (Child-Pugh class C): Initial: 2 mg once daily.
Prescribing edits*	AGE, MD, ST, PE
AGE (Age Edit)	Not used in pediatric patients
CU (Concurrent Use)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	Second and later line treatment of AL amyloidosis
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Pomalidomide/Dexamethasone
Maximum Daily Dose Adults*	N/A
Maximum Daily Dose Pediatrics*	N/A
Safety	High alert medication
Main Adverse Drug Reactions (most common and most serious)	- Most common: Peripheral edema, skin rash, pruritus, hypercalcemia, hyperglycemia, hypokalemia, hyponatremia, weight loss, constipation, decreased appetite, diarrhea, nausea, vomiting, anemia, leukopenia, neutropenia, thrombocytopenia anxiety, confusion, dizziness, fatigue, headache, myasthenia, peripheral

	neuropathy, arthralgia, asthenia, back pain, muscle spasm, musculoskeletal chest pain, musculoskeletal pain, ostealgia, increased serum creatinine cough, dyspnea, epistaxis, pneumonia, upper respiratory tract infection, fever - Most serious: Acute myocardial infarction, angina pectoris, arterial thromboembolism, atrial fibrillation, cardiac failure, cerebrovascular accident, deep vein thrombosis, hypotension, ischemic heart disease, pulmonary embolism, septic shock, syncope, venous thromboembolism
Drug Interactions*	- Risk X: Abatacept, Abrocitinib, Anakinra, Baricitinib, BCG Products, Brivudine, Bromperidol, Canakinumab, Certolizumab Pegol, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Flunarizine, Nadofaragene Firadenovec, Natalizumb, Orphenadrine, Oxomemazine, Pembrolizumab, Pimecrolimus, Talimogene Laherparepvec, Tertomotide, Tocilizumab, Tofacitinib, Upadacitinib, Vaccines (Live), Vedolizumab - Risk D: COVID-19 Vaccine, CYP1A2 Inhibitors (Strong), Deferiprone, Denosumab, DexmedeTOMIDine, Droperidol, Flunitrazepam, HydrOXYzine, Influenza Vaccine, Leflunomide, Lemborexant, Opioid Agonists, Oxycodone, Polymethylmethacrylate, Ropeginterferon Alfa-2a/b,

	Sipuleucel-T, Suvorexant, Vaccines (Inactivated), Zolpidem
Special Population	Hepatic impairment, cigarette smokers
Pregnancy	[US Boxed Warning]: Pomalidomide is contraindicated in pregnancy. Pomalidomide is a thalidomide analogue. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death.
Lactation	It is not known if pomalidomide is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer.
Contraindications	Severe hypersensitivity to pomalidomide or any component of the formulation Pregnancy
Monitoring Requirements	CBC with differential and platelets (weekly for the first 8 weeks and then monthly) Renal function, LFTs (monthly). Monitor for signs/symptoms of thromboembolism, neuropathy, tumor lysis syndrome, hypersensitivity, dermatologic reactions, and interstitial lung disease. Consider thyroid function tests Monitor adherence. Pregnancy testing
Precautions	- Bone marrow suppression - CNS effects - Dermatologic reactions - Hepatotoxicity - Hypersensitivity - Interstitial lung disease - Neuropathy - Secondary malignancy

	- Thromboembolic events - Tumor lysis syndrome
Black Box Warning	- Pregnancy - Thromboembolic events
REMS*	Yes (Pomalidomide REMS program)

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the HTA instances: National Institute for Health and Care Excellence (NICE), Haute Autorité de Santé (HAS), Canadian Agency for Drugs and Technologies in Health (CADTH), Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC) didn't yield any recent result for pomalidomide in amyloidosis. This is probably due to the fact that pomalidomide's use in amyloidosis is limited to later-lines treatment. HTA recommendations are available for pomalidomide in multiple myeloma which is a growing indication for the drug.

Conclusion Statement – Pomalidomide

In amyloidosis, pomalidomide in combination with dexamethasone is recommended as a second or later-line treatment option for systemic light chain amyloidosis in patients who are refractory to lenalidomide. There is no data issued by HTA bodies regarding its use.

2.3 Anti-CD38 Monoclonal Antibodies

2.3.1 Daratumumab

Table 15. Daratumumab Drug Information

Scientific Name Daratumumab (IV) /Daratumumab and Hylaluronidase (SC)[31]	
Trade Name(s) on Saudi Market	Darzalex
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2017
FDA approved / off label	Yes, 2015
EMEA approved / off label	Yes, 2017
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2017
Indication (ICD-10)	E85. 81
Drug Class	Antineoplastic agent
Drug Sub-class	Anti-CD38 Monoclonal Antibody
SFDA Registration Number (New)	Darzalex: 0602233214 (400mg/20mL IV) 0602233215 (100mg/5mL IV)

	1208210930 (1800mg/15mL SC)
ATC Code	L01XC24
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	**Subcutaneous**: *In combination with bortezomib, cyclophosphamide and dexamethasone (Dh-CyBorD):* *Weeks 1 to 8*: **SC:** Daratumumab 1,800 mg/hyaluronidase 30,000 units once weekly for a total of 8 doses. *Weeks 9 to 24*: **SC:** Daratumumab 1,800 mg/hyaluronidase 30,000 units once every 2 weeks (beginning week 9) for a total of 8 doses. *Weeks 25 and beyond*: **SC:** Daratumumab 1,800 mg/hyaluronidase 30,000 units once every 4 weeks (beginning week 25) until disease progression or unacceptable toxicity or a maximum of 2 years. **IV (off label use):** *Weeks 1 to 8:* 16 mg/kg once weekly for 8 doses. *Weeks 9 to 24:* 16 mg/kg once every 2 weeks for 8 doses. *Weeks 25 and beyond:* 16 mg/kg once every 4 weeks until disease progression.
Dose (Pediatrics)	N/A
Adjustment	N/A
Prescribing edits*	AGE, MD, ST, PE
AGE (Age Edit)	Not used in children
CU (Concurrent Use)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A

ST (Step Therapy)	First and second-line treatment of AL amyloidosis
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Daratumumab-CyBorD Daratumumab single-agent Daratumumab/Lenalidomide/ Dexamethasone
Maximum Daily Dose Adults*	N/A
Maximum Daily Dose Pediatrics*	N/A
Safety	High alert medication
Main Adverse Drug Reactions (most common and most serious)	- Most common: Constipation, decreased appetite, diarrhea, nausea, vomiting, anemia, lymphocytopenia, neutropenia, thrombocytopenia, fatigue, headache, arthralgia, back pain, limb pain, chest pain, cough, dyspnea, nasal congestion, nasopharyngitis, pneumonia, upper respiratory tract infection , fever, infusion related reactions - Most serious: Severe infusion related reaction
Drug Interactions*	- Risk X: Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Fexinidazole, Filgotinib, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating)

Special Population	Older adults
Pregnancy	Pregnancy Category C
Lactation	It is not known if daratumumab is present in breast milk. Monoclonal antibodies can be detected in breast milk and are not expected to enter the neonatal or infant circulation in substantial amounts.
Contraindications	History of severe hypersensitivity (e.g., anaphylactic reactions) to daratumumab or any component of the formulation.
Monitoring Requirements	CBCs periodically; type and screen (blood type) prior to initiating therapy. Monitor for signs/symptoms of hepatitis B virus reactivation, infection, ocular adverse reactions, and bleeding.
Precautions	- Bone marrow suppression - Hepatitis B virus reactivation - Infusion reactions
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

The table below lists the Haute Autorité de Santé (**HAS)**, Canadian Agency for Drugs and Technologies in Health (**CADTH**), Institute for Quality and Efficiency in Health Care (**IQWIG**), and the Pharmaceutical Benefits Advisory Committee (**PBAC**) HTA review and recommendations of daratumumab in amyloidosis treatment options.

Table 16. Daratumumab HTA Analysis

Medication	Agency	Date – HTA Recommendation
Daratumumab	HAS[32]	02/22: **Favorable opinion for reimbursement in newly diagnosed systemic light chain (AL) amyloidosis.** - **Substantial clinical benefit** in the treatment of adult patients with newly diagnosed AL amyloidosis, in combination with CyBorD.

		- Daratumumab, in combination with bortezomib + cyclophosphamide + dexamethasone (CyBorD), provides a **minor clinical added value (CAV IV)** compared to the CyBorD alone, in the treatment of adult patients with newly diagnosed AL amyloidosis: • Demonstration of the **superiority** of the addition of daratumumab to the CyBorD protocol in terms of complete hematological response (a relevant primary endpoint), compared to CyBorD protocol alone with 53% versus 18% respectively, i.e. an OR=5.13, 95% CI [3.22; 8.18], p<0.0001) in a phase 3, randomized open-label study having included newly diagnosed patients with at least one organ involved. • However, absence of demonstration of a statistically significant difference between the D-CyBorD protocol and the CyBorD protocol for the risk of onset of a major organ deterioration progression-free survival (MOD-PFS) event (first ranked secondary endpoint). • Absence of robust data for overall survival (second ranked secondary endpoint), with the ranked analysis having been stopped before this endpoint. • Absence of robust data on quality of life, which was an exploratory endpoint.
Daratumumab	CADTH[33]	05/22: pERC recommends that subcutaneous daratumumab in combination with cyclophosphamide, bortezomib, and dexamethasone (DCyBorD) be **reimbursed** for the treatment of adult patients with newly diagnosed light chain (AL) amyloidosis only if the following conditions are met: 1. Histopathologic diagnosis of systemic AL amyloidosis based on detection by IHC and polarizing light microscopy of green birefringent in Congo red-stained tissue specimens or characteristic electron microscopy appearance

		2. Measurable disease by serum M protein ≥ 0.5 g/ dL or abnormal serum free light chain ratio or a difference between involved and uninvolved free light chains (dFLC) ≥ 50 mg/L 3. Involvement of at least 1 organ system 4. Adequate hematologic, hepatic, and renal function (eGFR ≥ 20 mL/min/1.73 m^2) 5. Patients should have good performance status - The ANDROMEDA trial (N = 386) demonstrated that DCyBorD was associated with a higher hematologic complete response (CR) rate compared with cyclophosphamide, bortezomib, and dexamethasone (CyBorD) that was statistically significant (53.3% versus 18.1%; relative risk ratio = 2.9; 95% confidence interval [CI], 2.1 to 4.1, P < 0.001) - The ICER for DCyBorD is $67,484 compared with CyBorD. A price reduction of at least 21% would be required for DCyBorD to be associated with an ICER of $50,000 per QALY compared with CyBorD. Because of uncertain evidence surrounding treatment duration and end-stage organ failure management costs, additional price reduction may be warranted.
Daratumumab	IQWIG[34]	11/21: Patients for whom bortezomib + cyclophosphamide + dexamethasone is the best individual choice: **hint of minor added benefit**. Patients for whom a therapy other than bortezomib + cyclophosphamide + dexamethasone is the best individual choice: **added benefit not proven**.
Daratumumab	PBAC[35]	05/22: **Recommended** the listing of daratumumab subcutaneous (SC), for use in combination with cyclophosphamide, bortezomib and dexamethasone (CyBorD), for the treatment of patients with newly diagnosed systemic light-chain AL amyloidosis. - The PBAC recognized that there are no treatments on the PBS available specifically for this condition, and it considered that the

		addition of daratumumab SC plus CyBorD offered a high added therapeutic value. - The PBAC considered that the revised economic analysis, based on reduced financial estimates which also accounted for the overlap between patients with AL amyloidosis and multiple myeloma (MM), were acceptable. - ICER of $75,000 to < $95,000 per QALY

Conclusion Statement – Daratumumab

In amyloidosis, daratumumab in combination with bortezomib, cyclophosphamide, and dexamethasone (Dara-CyBorD) is recommended as a first-line treatment for patients with systemic-light chain amyloidosis (as an induction therapy for 2-4 cycles in patients eligible for HCT). Daratumumab is also approved as a single-agent or in combination with lenalidomide/dexamethasone (Dara-RD) as a second-line agent for patients with relapsed/refractory amyloidosis in patients already exposed to proteasome inhibitors.

Daratumumab had a favorable opinion for reimbursement in combination with CyBorD protocol in newly diagnosed systemic light chain (AL) amyloidosis from the HTA bodies (HAS, CADTH, IQWIG, PBAC) due to a substantial clinical benefit with an acceptable financial analysis.

2.3.2 Isatuximab

Table 17. Isatuximab Drug Information

Scientific Name Isatuximab	
Trade Name(s) on Saudi Market	Sarclisa
SFDA Classification	Prescription
SFDA approved Indication	Yes, used off-label in amyloidosis
FDA approved / off label	Yes, used off-label in amyloidosis
EMEA approved / off label	Yes, used off-label in amyloidosis
MHRA approved / off label	Yes, used off-label in amyloidosis
PMDA approved / off label	Yes, used off-label in amyloidosis
Indication (ICD-10)	E85. 81
Drug Class	Antineoplastic agent
Drug Sub-class	Anti-CD38 Monoclonal Antibody
SFDA Registration Number (New)	2403210642 (100mg) 2403210643 (500mg)
ATC Code	N/A
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	

Dosage Form	Concentrate for solution for infusion
Route of Administration	Intravenous
Dose (Adult) [DDD]*	*Cycle 1:* 10 mg/kg on days 1, 8, 15, and 22 of a 28-day cycle (in combination with pomalidomide and dexamethasone **or** in combination with carfilzomib and dexamethasone). *Cycle 2 and beyond:* 10 mg/kg on days 1 and 15 of a 28-day cycle (in combination with pomalidomide and dexamethasone **or** in combination with carfilzomib and dexamethasone), continue until disease progression or unacceptable toxicity.
Dose (Pediatrics)	N/ A
Adjustment	N/A
Prescribing edits*	AGE, MD, ST, CU, PE
AGE (Age Edit)	Not used in the pediatric population
CU (Concurrent Use)	Used with dexamethasone
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	Second and later-line treatment of relapsed/refractory AL amyloidosis
EU (Emergency Use Only)	N/A
Maximum Daily Dose Adults*	10 mg/Kg
Maximum Daily Dose Pediatrics*	N/A
Safety	High alert medication
Main Adverse Drug Reactions (most common and most serious)	- Most common: Hypertension, diarrhea, nausea, vomiting, anemia, febrile neutropenia, lymphocytopenia, neutropenia, thromobocytopenia, infusion-related reactions, infections, fatigue, bronchitis - Most serious: Severe infusion-related reactions, heart failure,

	secondary malignancies, cytokine release syndrom
Drug Interactions*	- Risk X: Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Dipyrone, Fexinidazole, Filgotinib, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: COVID-19 Vaccine, Deferiprone, Denosumab, Influenza Virus Vaccines, Leflunomide, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated/Non-Replicating)
Special Population	N/A
Pregnancy	Based on the mechanism of action, in utero exposure to isatuximab may cause fetal harm, including depletion of fetal CD38-positive immune cells and decreased bone density.
Lactation	It is not known if isatuximab is present in breast milk. However, isatuximab is a monoclonal antibody (IgG_1) and maternal IgG is known to be present in breast milk. Breastfeeding is not recommended.
Contraindications	Severe hypersensitivity to isatuximab or any component of the formulation
Monitoring Requirements	Blood type and screening prior to the first isatuximab infusion CBC periodically Pregnancy status Monitor vital signs frequently during entire infusion; monitor for

	signs/symptoms of infusion reaction; monitor patients with neutropenia for signs of infection Monitor for the development of second primary malignancies.
Precautions	- Polysorbate 80 (allergic reactions)
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the HTA instances: National Institute for Health and Care Excellence (NICE), Haute Autorité de Santé (HAS), Canadian Agency for Drugs and Technologies in Health (CADTH), Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC) didn't yield any recent result for bendamustine in amyloidosis.

Conclusion Statement – Isatuximab

In amyloidosis, isatuximab is recommended as a second- and later line agent in combination with dexamethasone in patients with relapsed/refractory non-cardiac light chain amyloidosis. Its use in this indication is off-label based on phase II data. There is no data issued by HTA bodies regarding its use.

2.4 BCL-2 Inhibitors

2.4.1 Venetoclax

Table 18. Venetoclax Drug Information

Scientific Name Venetoclax	
Trade Name(s) on Saudi Market	Venclexta
SFDA Classification	Prescription
SFDA approved Indication	Yes, used off-label in amyloidosis
FDA approved / off label	Yes, used off-label in amyloidosis
EMEA approved / off label	Yes, used off-label in amyloidosis
MHRA approved / off label	Yes, used off-label in amyloidosis
PMDA approved / off label	Yes, used off-label in amyloidosis
Indication (ICD-10)	E85. 81
Drug Class	Antineoplastic agent
Drug Sub-class	BCL-2 Inhibitor
SFDA Registration Number (New)	2707222354 2707222353
ATC Code	L01XX52

Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	*Venetoclax in combination with dexamethasone:* **Oral:** 800 mg once daily; continue until disease progression or unacceptable toxicity. **Note:** A venetoclax dose ramp-up phase has been described in some studies.
Dose (Pediatrics)	N/A
Adjustment	Renal Impairment (Adult): - No dosage adjustment likely to be necessary for any degree of kidney impairment. - Hemodialysis, intermittent (thrice weekly): Unlikely to be dialyzed (highly protein bound): Safety and efficacy data are currently limited to case reports. - Peritoneal dialysis/CRRT: Unlikely to be dialyzed (highly protein bound): No safety or efficacy data currently exist. However, no dosage adjustment likely to be necessary based on pharmacokinetic characteristics of venetoclax Hepatic Impairment (Adult): - Mild or moderate impairment (Child-Pugh classes A or B): No dosage adjustment necessary. - Severe impairment (Child-Pugh class C): Reduce the daily venetoclax dose by 50%; monitor closely for adverse reactions.
Prescribing edits*	AGE, MD, ST, CU, PE, PA
AGE (Age Edit)	Not used in the pediatric population
CU (Concurrent Use)	Used with dexamethasone
G (Gender Edit)	N/A

MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	To be used in patient with t(11;4)
QL (Quantity Limit)	N/A
ST (Step Therapy)	Second and later-line treatment of relapsed/refractory AL amyloidosis in patient with t(11;4)
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Part of a treatment protocol
Maximum Daily Dose Adults*	800 mg
Maximum Daily Dose Pediatrics*	N/A
Safety	High alert medication
Main Adverse Drug Reactions (most common and most serious)	- Most common: edema, hyperglycemia, hyperkalemia, nausea - Most serious: anemia, leukopenia, lymphocytopenia, neutropenia, thrombocytopenia
Drug Interactions*	- Risk X: Abrocitinib, Baricitinib, Brivudine, Cenobamate, Cladribine, Dabrafenib, Efavirenz, Grapefruit juice, Lorlatinib, Modafinil, Natalizumab, Phenytoin, Primidone, Rifampin, St John's wort., Tacrolimus - Risk D: Amiodarone, Carvedilol, Conivaptan, Digoxin, Diltiazem, Dronedarone, Fluconazole, Indinavir, Leflunomide, Lopinavir, Propafenone, Voriconazole
Special Population	N/A
Pregnancy	Pregnancy Category D
Lactation	It is not known if venetoclax is present in breast milk. Breastfeeding is not recommended by the manufacturer during treatment or for 1 week after the last venetoclax dose.
Contraindications	Concomitant use with strong CYP3A inhibitors at initiation and during ramp-up phase in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) due to the potential for increased risk

	of tumor lysis syndrome. Hypersensitivity to venetoclax or any component of the formulation.
Monitoring Requirements	- CBC with differential - Blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine). - Pregnancy status - Assess tumor burden, including radiographic evaluation (e.g., CT scan), for tumor lysis syndrome (TLS) risk evaluation. - Monitor for signs/symptoms of infection. - Monitor for adverse reactions in patients with hepatic impairment. - Monitor adherence.
Precautions	- Bone marrow suppression - Infection - Tumor lysis syndrome - Immunizations with live vaccines
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the HTA instances: National Institute for Health and Care Excellence (NICE), Haute Autorité de Santé (HAS), Canadian Agency for Drugs and Technologies in Health (CADTH), Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC) didn't yield any recent result for venetoclax in amyloidosis.

Conclusion Statement – Venetoclax

In amyloidosis, venetoclax is recommended as a second- and later line agent in combination with dexamethasone in patients with relapsed/refractory non-cardiac light chain amyloidosis and with t(11;4). There is no data issued by HTA bodies regarding its use.

2.5 Proteasome Inhibitors

2.5.1 Bortezomib

Table 19. Bortezomib Drug Information

Scientific Name Bortezomib[28]	
Trade Name(s) on Saudi Market	Velcade, Bortezomib SPC, Veelbore, Bortezomib BOS, Bortezon, Imozet, Borvix, Valtroza, Bortada, Proteomib, Veltero, Bortezomib EPC
SFDA Classification	Prescription
SFDA approved Indication	Yes, Velcade (2006)
FDA approved / off label	Yes, 2003
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2006
Indication (ICD-10)	E85. 81
Drug Class	Antineoplastic agent
Drug Sub-class	Proteasome Inhibitor
SFDA Registration Number (New)	89-6-06 (Velcade); 4-5171-18 (Bortezomib SPC); 278-334-18 (Veelbore); 0410200180 (Bortezomib BOS); 25-305-20 (Bortezon); 1-5579-21 (Imozet); 2412200362 (Borvix); 1407210866 (Valtroza); 0707210852 (Bortada); 1710211184 (Proteomib); 1111211297 (Veltero); 2401233151 (Bortezomib EPC IV); 1004233513 (Bortezomib EPC IV/SC)
ATC Code	L01XX32
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Powder for Solution
Route of Administration	Intravenous, Subcutaneous
Dose (Adult) [DDD]*	1.3 mg/m^2 days 1, 4, 8, and 11 of a 21-day treatment cycle
Dose (Pediatrics)	N/ A
Adjustment	Hepatic Impairment (Adult): - Mild impairment (bilirubin ≤1 times ULN and AST >ULN or bilirubin >1 to 1.5 times ULN and any AST): No initial dose adjustment is necessary.

	- Moderate (bilirubin >1.5 to 3 times ULN and any AST) and severe impairment (bilirubin >3 times ULN and any AST): Reduce initial dose to 0.7 mg/m^2 in the first cycle; based on patient tolerance, may consider dose escalation to 1 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles.
Prescribing edits*	AGE, MD, ST, PE
AGE (Age Edit)	Not used in children
CU (Concurrent Use)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	First and second-line treatment of AL amyloidosis
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	CyBorD; Dara-CyBorD; VMDex; Bortezomib/ Dexamethasone; Bortezomib/ lenalidomide/ dexamethasone
Maximum Daily Dose Adults*	N/A
Maximum Daily Dose Pediatrics*	N/A
Safety	High alert medication: This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.
Main Adverse Drug Reactions (most common and most serious)	- Most common: Skin rash, abdominal pain, anorexia, constipation, decreased appetite, diarrhea, nausea and vomiting, herpes zoster infection, dizziness, fatigue , malaise, headache, neuralgia, paresthesia, peripheral

	neuropathy, asthenia, dyspnea, fever - Most serious: Peripheral neuropathy, cardiac disorder (cardiogenic shock, heart failure, hypotension)
Drug Interactions*	- Risk X: BCG Products, Bromperidol, Cladribine, CYP3A4 inducers, Dipyrone, Fexinidazole, Fusidic acid (systemic) - Risk D: Amifostine, Deferipone, Green Tea, Multivitamins/Fluoride, Multivitamins/Minerals, Obinutuzumab, Ropeginterferon Alfa-2b
Special Population	N/A
Pregnancy	Pregnancy Category D: Not used in pregnancy Causes harm to fetus, advice women on this treatment on the potential risks
Lactation	Not known if bortezomib is present in breast milk. Avoid breastfeeding during and for 2 months following bortezomib treatment.
Contraindications	Hypersensitivity to bortezomib, boron, boric acid (generic product), glycine (some generics), mannitol (Velcade, some generics), or any component of the formulations; administration via the intrathecal route.
Monitoring Requirements	- CBC with differential and platelets - Liver function tests, renal function - Blood glucose (in patients with diabetes) - Pregnancy status prior to therapy initiation - BP - Signs/symptoms of peripheral neuropathy, dehydration,

	hypotension, posterior reversible leukoencephalopathy syndrome, progressive multifocal leukoencephalopathy, tumor lysis syndrome, or hyper-/hypoglycemia. - Baseline chest x-ray and then periodic pulmonary function testing
Precautions	- Bone marrow suppression - Cardiovascular effects - GI effects - Hepatotoxicity - Herpes reactivation - Hypersensitivity - Hypotension - Peripheral neuropathy - Posterior reversible leukoencephalopathy syndrome - Progressive multifocal leukoencephalopathy - Pulmonary toxicity - Thrombotic microangiopathy - Tumor lysis syndrome - Diabetes
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the HTA instances: National Institute for Health and Care Excellence (NICE), Haute Autorité de Santé (HAS), Canadian Agency for Drugs and Technologies in Health (CADTH), Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC) didn't yield to any specific guidance for bortezomib in amyloidosis. Only guidance on daratumumab reimbursement in combination with bortezomib/cyclophosphamide/ dexamethasone (Dara-CyBorD) was found. This is probably due to the fact that bortezomib combinations has long been the standard of care in AL amyloidosis, with a proven record of efficacy and safety. Moreover, bortezomib and its generics are available in international markets, making it an affordable treatment option.

Conclusion Statement – Bortezomib

In amyloidosis, bortezomib is recommended as a first-line agent in combination with cyclophosphamide, dexamethasone, and daratumumab (Dara-CyBorD protocol; preferred regiment) in the management of systemic light chain amyloidosis as an induction therapy for 2-4 cycles prior to stem cell transplant. It is also a first and second-line agent in combination with cyclophosphamide and dexamethasone (CyBorD protocol) or with dexamethasone or as a single agent. Bortezomib is also a first or second-line treatment option in combination with Melphalan/Dexamethasone (VMDex) in patients not eligible for HCT, and a first or second-line agent in combination with dexamethasone and lenalidomide (VRD protocol) in patients with relapsed or refractory systemic light chain amyloidosis IMiD-treatment naïve. There is no data issued by HTA bodies regarding its use.

2.5.2 Carfilzomib

Table 20. Carfilzomib Drug Information

Scientific Name Carfilzomib[29]	
Trade Name(s) on Saudi Market	Kyprolis; Carfilzomib SPC
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2019
FDA approved / off label	Yes, 2012
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2017
Indication (ICD-10)	E85. 81
Drug Class	Antineoplastic agent
Drug Sub-class	Proteasome Inhibitor
SFDA Registration Number (New)	2201233141 (Kyprolis) 3112200377 (Carfilzomib SPC)
ATC Code	L01XX45
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Powder for Solution
Route of Administration	Intravenous
Dose (Adult) [DDD]*	Cycle 1: 20 mg/m^2 on days 1 and 2, and 36 mg/m^2 (up to 45 mg/m^2) over 30 minutes on days 8, 9, 15, and 16 of a 28-day treatment cycle Cycles 2 to 8: 36 mg/m^2 (up to 45 mg/m^2) over 30 minutes on days 1, 2,

	8, 9, 15, and 16 of a 28-day treatment cycle
Dose (Pediatrics)	N/ A
Adjustment	Renal Impairment (Adult): - Preexisting renal impairment: No initial dosage adjustment necessary - Renal toxicity during treatment: SrCr ≥2 times baseline, CrCl <15 mL/minute or CrCl decreases to ≤50% of baseline, or patient requires hemodialysis: Withhold dose and monitor kidney function. Hepatic Impairment (Adult): - Mild (total bilirubin 1 to 1.5 times ULN and any AST or total bilirubin ≤ULN and AST >ULN) or moderate (total bilirubin >1.5 to 3 times ULN and any AST): Reduce carfilzomib dose by 25%. - Severe (bilirubin > 3 times ULN): No dosage adjustments provided in the manufacturer's labeling (a recommended dose has not been in established).
Prescribing edits*	AGE, MD, ST, PE
AGE (Age Edit)	Not used in children
CU (Concurrent Use)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	Second-line treatment of AL amyloidosis
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Carfilzomib ± Dexamethasone
Maximum Daily Dose Adults*	N/A
Maximum Daily Dose Pediatrics*	N/A
Safety	High alert medication:

Main Adverse Drug Reactions (most common and most serious)	- Most common: Cardiovascular (Cardiac arrhythmia, chest pain, hypertension, peripheral edema), hypokaliemia, hypomagnesemia, constipation, nausea, anemia, leukopenia, lymphocytopenia, neutropenia, chills, dizziness, fatigue, headache, peripheral neuropathy, back pain, increased creatinine, cough, dyspnea - Most serious: Cardiomyopathy, heart failure, ischemic heart disease, venous thromboembolism, cardiac arrhythmia, hypertensive crisis, peripheral neuropathy
Drug Interactions*	- Risk X: Abrocitinib, Baricitinib, BCG Products, Brivudine, Cladribine, Deucravacitinib, Filgotinib, Nadofaragene Firadenovec, Natalizumab, Pimecrolimus, Ruxolitinib (Topical), Tacrolimus (Topical), Talimogene Laherparepvec, Tertomotide, Tofacitinib, Upadacitinib, Vaccines (Live) - Risk D: COVID-19 Vaccine, Deferiprone, Denosumab, Hormonal Contraceptives, Influenza Virus Vaccines, Leflunomide, Polymethylmethacrylate, Rabies Vaccine, Ropeginterferon Alfa-2b, Sipuleucel-T, Vaccines (Inactivated)
Special Population	Older adults
Pregnancy	Based on the mechanism of action and findings from animal reproduction studies, carfilzomib may cause fetal harm if administered to a pregnant patient.

Lactation	Not known if carfilzomib is present in breast milk. Avoid breastfeeding during and for 2 months following bortezomib treatment.
Contraindications	N/A
Monitoring Requirements	- CBC with differential and platelets - Serum potassium levels regularly - Liver function tests, renal function, pulmonary function - Pregnancy status prior to therapy initiation - BP - Signs/symptoms of congestive heart failure, hemorrhage, peripheral neuropathy, posterior reversible leukoencephalopathy syndrome, progressive multifocal leukoencephalopathy, tumor lysis syndrome, thromboembolic events.
Precautions	- Bone marrow suppression - Cardiovascular effects - Hemorrhage - Hepatotoxicity - Hypertension - Infusion-related reactions - Infusion-related reactions - Posterior reversible leukoencephalopathy syndrome - Progressive multifocal leukoencephalopathy - Pulmonary toxicity - Renal toxicity - Thrombotic microangiopathy - Thromboembolic events - Tumor lysis syndrome
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the HTA instances: National Institute for Health and Care Excellence (NICE), Haute Autorité de Santé (HAS), Canadian Agency for Drugs and Technologies in Health (CADTH), Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC) didn't yield to any specific guidance for carfilzomib in amyloidosis. This is probably due to the fact that carfilzomib's use is limited in amyloidsis; it is a later-line treatment option that is also not recommended in patients with cardiac amyloidsis.

Conclusion Statement – Carfilzomib

In amyloidosis, calrilzomib is recommended as a second-line agent in combination with dexamethasone in patients with relapsed/refractory non-cardiac light chain amyloidosis. There is no data issued by HTA bodies regarding its use.

2.5.3 Ixazomib

Table 21. Ixazomib Drug Information

Scientific Name **Ixazomib Citrate**[36]	
Trade Name(s) on Saudi Market	Ninlaro
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2018
FDA approved / off label	Yes, 2015
EMEA approved / off label	Yes, not mentioned
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2017
Indication (ICD-10)	E85. 81
Drug Class	Antineoplastic agent
Drug Sub-class	Proteasome Inhibitor
SFDA Registration Number (New)	1-5600-21 (2.3mg); 2-5600-21 (3mg); 3-5600-21 (4mg)
ATC Code	L01XX50
Pharmacological Class (ASHP)	10:00 – Antineoplastic Agents
Drug Information	
Dosage Form	Capsule
Route of Administration	Oral
Dose (Adult) [DDD]*	4 mg once weekly on days 1, 8, and 15 of a 28-day treatment cycle
Dose (Pediatrics)	N/ A
Adjustment	Renal Impairment (Adult):

	- CrCl ≥30 mL/minute: The IMWG suggest that ixazomib may be safely administered to patients with a CrCl ≥30 mL/minute. - CrCl <30 mL/minute: Reduce initial dose to 3 mg once weekly on days 1, 8, and 15 of a 28-day treatment cycle - ESRD requiring dialysis: Reduce initial dose to 3 mg once weekly on days 1, 8, and 15 of a 28-day treatment cycle; ixazomib is not dialyzable. Hepatic Impairment (Adult): - Mild impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin >1 to 1.5 times ULN and any AST): No dosage adjustment is necessary. - Moderate (total bilirubin >1.5 to 3 times ULN) or severe (total bilirubin >3 times ULN) impairment: Reduce initial dose to 3 mg once weekly on days 1, 8, and 15 of a 28-day treatment cycle
Prescribing edits*	AGE, MD, ST, PE
AGE (Age Edit)	Not used in children
CU (Concurrent Use)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	Second-line treatment of AL amyloidosis
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Ixazomib/ dexamethasone Ixazomib/ lenalidomide/ dexamethasone
Maximum Daily Dose Adults*	N/A
Maximum Daily Dose Pediatrics*	N/A
Safety	High alert medication

Main Adverse Drug Reactions (most common and most serious)	- Most common: Peripheral edema, skin rash, constipation, diarrhea, nausea, vomiting, neutropenia, thrombocytopenia, peripheral neuropathy, peripheral sensory neuropathy, back pain, eye disease, bronchitis - Most serious: Peripheral neuropathy, Stevens-Johnson syndrome, TTP, Hepatotoxicity
Drug Interactions*	- Risk X: BCG Products, Cladribine, CYP3A4 inducers (Strong), Dipyrone, Fexinidazole, St John's Wort - Risk D: Deferipone, Hormonal contraceptives, Ropeginterferon Alfa-2b
Special Population	N/A
Pregnancy	Pregnancy Category D: Not used in pregnancy Causes harm to fetus, advice women on this treatment on the potential risks
Lactation	It is not known if ixazomib is present in breast milk. Breastfeeding should be discontinued during therapy and for 90 days after the last ixazomib dose.
Contraindications	N/A
Monitoring Requirements	Platelet counts at least monthly during treatment, CBC (with differential), renal function tests, and LFTs. Pregnancy status Monitor for signs/symptoms of GI toxicity, dermatologic toxicity, peripheral neuropathy, peripheral edema, and thrombotic microangiopathy. Monitor adherence.
Precautions	- Bone marrow suppression - Dermatologic toxicity

	- GI effects - Hepatotoxicity - Peripheral edema - Peripheral neuropathy - Thrombotic microangiopathy
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

A search for clinical economic recommendations from the HTA instances: National Institute for Health and Care Excellence (NICE), Haute Autorité de Santé (HAS), Canadian Agency for Drugs and Technologies in Health (CADTH), Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC) didn't yield any recent result for ixazomib in amyloidosis. This is probably due to the fact that ixazomib's use in amyloidosis is limited to later-lines treatment. HTA recommendations are being developed for ixazomib in multiple myeloma which is a growing indication for the drug.

Conclusion Statement – Ixazomib

In amyloidosis, ixazomib in combination with lenalidomide/dexamethasone is recommended as second-line treatment option for systemic light chain amyloidosis in patients exposed to a previous PI (i.e. bortezomib) and navive to IMiD therapy. It is also approved in the second-line setting in combination with dexamethasone only. There is no data issued by HTA bodies regarding its use.

2.6 Transthyretin Stabilizer

2.6.1 Tafamidis

Table 22. Tafamidis Drug Information

Scientific Name Tafamidis[40]	
Trade Name(s) on Saudi Market	Vyndamax
SFDA Classification	Prescription
SFDA approved Indication	Yes, 2021
FDA approved / off label	Yes, 2019
EMEA approved / off label	Yes, 2011
MHRA approved / off label	Yes, not mentioned
PMDA approved / off label	Yes, 2019
Indication (ICD-10)	E85. 4
Drug Class	Transthyretin Stabilizer
Drug Sub-class	N/A

SFDA Registration Number (New)	1602210522 (61mg)
ATC Code	N07XX08
Pharmacological Class (ASHP)	N/A
Drug Information	
Dosage Form	Capsule
Route of Administration	Oral
Dose (Adult) [DDD]*	Tafamidis (Vyndamax): 61 mg once daily. **Note:** Tafamidis (Vyndamax) and tafamidis meglumine (Vyndaqel-not SFDA registered) are not substitutable on a per mg basis.
Dose (Pediatrics)	N/A
Adjustment	N/A
Prescribing edits*	AGE, MD, ST
AGE (Age Edit)	Not used in children
CU (Concurrent Use)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	To be prescribed by an oncologist
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	First-line treatment of ATTR amyloidosis
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
Maximum Daily Dose Adults*	N/A
Maximum Daily Dose Pediatrics*	N/A
Safety	N/A
Main Adverse Drug Reactions (most common and most serious)	- Most common: Post-marketing: Diarrhea - Most serious: N/A
Drug Interactions*	- Risk X: Pazopanib, Topotecan: Increased of their serum level by tafamidis - Risk D: Alpelisib, Berotralstat, Cladribine, Rosuvastatin, Ubrogepant (increased serum concentrations by tafamidis)
Special Population	N/A
Pregnancy	Pregnancy Category D

Lactation	It is not known if tafamidis is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer.
Contraindications	N/A
Monitoring Requirements	N/A
Precautions	- Equivalency: Tafamidis (Vyndamax) and tafamidis meglumine (Vyndaqel) are not substitutable on a per mg basis.
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

The table below lists the Haute Autorité de Santé (**HAS)**, Canadian Agency for Drugs and Technologies in Health (**CADTH**), Institute for Quality and Efficiency in Health Care (**IQWIG**), and the Pharmaceutical Benefits Advisory Committee (**PBAC**) HTA review and recommendations of tafamidis in amyloidosis treatment options.

Table 23. Tafamidis HTA Analysis

Medication	Agency	Date – HTA Recommendation
Tafamidis	HAS[41,42]	09/20: **Favorable opinion for reimbursement in adult patients with wild-type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM).** - **Substantial clinical benefit** in the in the MA indication. - **Therapeutic improvement** in the management of wild-type or hereditary transthyretin amyloid cardiomyopathy. - Tafamidis provides an **important clinical added value (CAV II)** in the management of adult patients with wild-type or hereditary transthyretin amyloid cardiomyopathy, given a: • Demonstration in a clinical study (phase III, randomized, double-blind study) of **the superiority of tafamidis (20 mg and 80 mg) compared to placebo**, in patients with

		transthyretin amyloid cardiomyopathy in terms of: o All-cause mortality after 30 months with HR = 0.70 95% CI [0.51; 0.96] p=0.0259 and frequency of cardiovascular-related hospitalizations over 30 months RR = 0.68 95% CI [0.56; 0.81] p<0.0001 (primary endpoint). o 6-minute walk test and quality of life assessed by the Kansas City cardiomyopathy questionnaire (ranked secondary endpoints). • **Satisfactory safety profile** of tafamidis. • **Major medical need** in this serious disease 10/19: **Opinion in favor of maintaining reimbursement in the Marketing Authorization indication**. - A therapeutic progress but of small magnitude in the therapeutic strategy which includes symptomatic management. - Tafamidis remains a treatment option for stage 1 polyneuropathy in hATTR, given: o New data available for tafamidis in the indication of amyloid polyneuropathy which, although low level of evidence, makes it possible to characterize its tolerance and use profile with several years of follow-up o The partial availability of the two alternatives patisiran and inotersen, recently evaluated by the Committee having proven their effectiveness on stage 1 polyneuropathy with a good level of evidence
Tafamidis	NICE[43]	05/21: **Tafamidis is NOT recommended**, within its marketing authorization, for treating wild-type or hereditary transthyretin amyloidosis with cardiomyopathy (ATTR-CM) in adults. - Evidence from clinical trials shows that tafamidis reduces deaths and hospitalization from conditions affecting the heart and blood vessels compared with placebo.

		- However, clinical benefit varies across different types and stages of ATTR-CM. Also, the measure used to assess how severe ATTR-CM is has limitations. - This makes it difficult to clearly identify who benefits from tafamidis and whether they should continue treatment. - The cost-effectiveness estimates are higher than what NICE normally considers an acceptable use of NHS resources. This is because there is not enough evidence that recommending tafamidis would reduce diagnosis delays and uncertainty about how long the treatment works after it is stopped. - The company's preferred analysis estimated that the ICER for tafamidis compared with best supportive care, in the full population, was less than £30,000 per QALY gained: Tafamidis is not a cost-effective use of NHS resources.
Tafamidis	CADTH[44]	08/22: CADTH recommends that **Tafamidis should be reimbursed by public drug plans for the treatment of transthyretin-mediated amyloidosis (ATTR) if certain conditions are met**: 1. Tafamidis should only be covered to treat adult patients who have a documented diagnosis of cardiomyopathy caused by ATTR. 2. The type of ATTR cardiomyopathy could be either hereditary (inherited) or wild type (patients without a family history of the disease). 3. Patients who are eligible for Tafamidis coverage must also have a NYHA classification of I to III and a history of heart failure. 4. Patients who have received a heart transplant or a cardiac mechanical assist device or who are taking other disease-modifying treatments for ATTR are not eligible for reimbursement of tafamidis.

		- In 1 double-blind, phase III, randomized controlled trial in patients with wild-type or hereditary ATTR-CM, treatment with tafamidis 80 mg was associated with reduced mortality and cardiovascular-related hospitalizations after 30 months compared with placebo. At month 30, more patients were alive in the tafamidis 80 mg group compared with the placebo group (69.3% versus 57.1%). There were also more cardiovascular-related hospitalizations in the placebo group compared with the tafamidis 80 mg group among those patients who were alive at month 30 (mean: 0.46 per year versus 0.34 per year). - There is an unmet clinical need due to the absence of effective alternative treatments for ATTR-CM. - Based on a CADTH reanalysis of the sponsor-submitted economic model, the incremental cost-utility ratio (ICUR) for tafamidis compared with best supportive care (BSC) is $443,694 per quality-adjusted life-year (QALY) gained. However, this estimate is associated with significant uncertainty due to limitations in the submitted model structure. Based on the CADTH reanalysis, a price reduction of more than 92% is required for tafamidis to achieve an ICUR of $50,000 per QALY.
Tafamidis	IQWIG[45]	05/21: Patients with NYHA class I + II cardiac failure: **hint of considerable added benefit**. Patients with NYHA class III cardiac failure: **added benefit not proven.**
Tafamidis	PBAC[35]	09/21: Transthyretin amyloid cardiomyopathy**: Not recommended** - The PBAC acknowledged the high unmet need for treatments for this condition, and recognized. However, it considered that a further price reduction would be needed to reach an ICER, and a Risk Sharing Arrangement was needed to manage the high risk of use above the submission's estimates

		- The PBAC noted that the base case ICER was $155,000 to <$255,000 per QALY after corrections made during evaluation.

Conclusion Statement – Tafamidis

In amyloidosis, tafamidis is approved for the management of adult patients with wild-type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM). Tafamidis had a favorable opinion for reimbursement from the majority of the HTA bodies, except PBAC and NICE that didn't approve the reimbursement of the drug within its marketing authorization. The cost-effectiveness estimates were higher than what NICE and PBAC normally considers an acceptable use of healthcare resources. However, since there is an unmet clinical need in the management of ATTR cardiomyopathy due to the absence of effective alternative treatments, and since tafamidis has a clinical added value as per the majority of the HTA bodies, we consider that Tafamidis should be covered for patients with wild-type or hereditary ATTR-CM with a NYHA classification of I to III and a history of heart failure.

Section 3.0 Key Recommendations Synthesis

Treatment of the different types of amyloidosis generally varies with the cause of fibril precursor production (e.g., treatment of the plasma cell dyscrasia in patients with immunoglobulin light chain [AL] amyloidosis, control of underlying inflammatory or infectious disease in AA amyloidosis) [8,9,10,11,12,13,14,15].

3.1. Management of AL amyloidosis

To best treat patients with AL amyloidosis, the initial evaluation must confirm the diagnosis, establish the extent and sites of disease, and evaluate for comorbidities that are likely to have an impact on prognosis and treatment options. Simple staging systems that incorporate NT-proBNP and cardiac troponin are easily applied at the point of care. **In AL amyloidosis, treatment is directed primarily at suppressing the underlying plasma cell dyscrasia** [8,12,13]**.**

The approach to the initial management of patients with AL amyloidosis varies depending on whether patients are eligible to pursue high dose melphalan followed by autologous hematopoietic cell transplantation (HCT). In general, patients with poor performance status, major comorbidities, involvement of three or more organs, and advanced cardiac amyloidosis are not considered transplant candidates [8,12,13].

3.1.1 HCT-eligible patients

- **Induction therapy followed by high dose melphalan and autologous HCT** rather than chemotherapy alone is the preferred treatment approach (Recommendation Level A, Evidence Level II), provided that HCT can be performed in referral centers with adequate expertise in the procedure for this group of patients [8,12,13].
  - As induction therapy, **two to four cycles of a bortezomib-based regimen** are recommended. The preferred regimen is **daratumumab plus cyclophosphamide, bortezomib, and dexamethasone (Dara-CyBorD)** (Recommendation Level A, Evidence Level I) [8,12,13].
  - If daratumumab is not available, induction with CyBorD alone is an acceptable alternative (Recommendation Level A, Evidenve Level II). Other alternatives include Bortezomib ± Dexamethasone (Recommendation Level A, Evidence Level II) [8,12,13].
  - Bortezomib and dexamethasone doses need to be adapted to cardiac stage, presence of autonomic/ peripheral neuropathy, fluid retention status and patient's functional status [8,12,13].
  - Full high dose melphalan at 200 mg/m^2 is the preferred conditioning regimen prior to SCT and AMYLOID3 modified dose melphalan at 140 mg/m^2 should be used for patients with reduced renal function [8,12,13].
  - Consolidation and maintenance therapy are not routinely recommended after SCT in AL amyloidosis [8,12,13].

3.1.2 Patients not eligible for HCT

- For patients not eligible for HCT, a **bortezomib-based regimen** is recommended rather
  than melphalan plus dexamethasone (Recommendation Level A, Evidence Level II) [8,12,13].
  - **Daratumumab plus CyBorD is the preferred regimen** (Recommendation Level A, Evidence Level I) [8,12,13].
  - If daratumumab is not available, acceptable alternatives are CyBorD alone or bortezomib, melphalan, and dexamethasone (VMDex) (Recommendation Level A, Evidence Level II) [8,12,13].
  - Bortezomib and dexamethasone doses need to be adapted to cardiac stage, presence of autonomic/ peripheral neuropathy, fluid retention status and patient's functional status [8,12,13].
  - Daratumumab is offered as a single agent or in combination with cyclophosphamide and dexamethasone to patients who are not candidates for bortezomib (i.e. patients with neuropathy) (Recommendation Level B, Evidence Level II) [8,12,13].
  - Lenalidomide/Dexamethasone or oral melphalan-dexamethasone or Carfilzomib/Dexamethasone or Venetoclax are all other alternatives in patients with neuropathy (Recommendation Level B, Evidence Level II) [8,12,13].

3.1.3 Monitoring response

- Patients are monitored to determine whether the disease is responding appropriately to therapy and whether a change in management is needed.
- In general, alternative systemic therapy is recommended if there is hematologic or organ progression at any time; if there is <50% reduction in the difference between the involved and uninvolved free light chain levels (dFLC) after two cycles of chemotherapy; or if dFLC is ≥40 mg/L after four to six cycles of chemotherapy or on day 100 after transplant [8,12,13].

3.1.4 Relapsed or refractory disease

- For patients with relapsed or refractory disease, acceptable approaches include treatment with proteasome inhibitor-based regimens, immunomodulatory derivative-based regimens, daratumumab, or enrollment on a clinical trial [8,12,13].
- There are no sufficient data to determine which of these regimens will be of most benefit; the choice will be dictated by prior therapy, patient and physician preferences, expected toxicity, drug availability, and insurance coverage.
- Patients Proteasome inhibitor (PI) Naïve or had a prolonged response to 1st line PI:

- CyBorD/VMDex (Recommendation Level A, Evidence Level II); Ixazomib-Dex (Recommendation Level B, Evidence Level II); Dara-CyBorD (Recommendation Level C; Evidence Level III) [8,12,13].

- Proteasome inhibitor exposed Daratumumab Naïve:
  - Single agent daratumumab (Recommendation Level A; Evidence Level II), DaraCyBorD (Recommendation Level C; Evidence Level III), Dara-RD (Recommendation Level B; Evidence Level II), Isatuximab (Recommendation Level C; Evidence Level IV) [8,12,13].
- Proteasome inhibitor exposed IMiD Naïve:
  - Lenalidomide-Dexamethasone (±cyclophosphamide) (Recommendation Level A; Evidence Level II), Ixazomib-Lenalidomide dexamethasone (Recommendation Level A; Evidence Level II) [8,12,13].
- Lenalidomide Refractory:
  - Pomalidomide-Dexamethasone (Recommendation Level A; Evidence Level II), Bendamustine (Recommendation Level B; Evidence Level II) [8,12,13].
- Recommendation for patients with t(11;14) translocation:
  - Venetoclax (Recommendation Level B; Evidence Level II); Venetoclax-Bortezomib/Dexamethasone (Recommendation Level C; Evidence Level III), Melphalan Dexamethasone (Recommendation Level C; Evidence Level IV) [8,12,13].
- As an example, daratumumab may be preferred for patients with severe cardiac involvement while a lenalidomide-based regimen may be preferred for patients with peripheral neuropathy. Bendamustine-based regimens for patients who have received multiple prior regimens, or for those with toxicities that limit the use of other agents [8,12,13].

3.1.5 Prognosis

- The prognosis of AL amyloidosis varies considerably depending on the nature, number, and extent of organ involvement. AL amyloidosis has a poor long-term prognosis when detected at an advanced stage. Earlier diagnosis is associated with lower early mortality and improved survival [8,12,13].

3.2. Management of Transthyretin amyloidosis

Several approaches have become available for the treatment of hereditary TTR amyloidosis (ATTR). These include the use of ribonucleic acid (RNA)-targeted therapies that interfere with hepatic TTR synthesis and other agents that reduce formation of TTR amyloid through stabilization of the tetramer configuration, preventing release of amyloidogenic monomers. Liver transplantation has also been used for the treatment of hereditary (variant or mutant) ATTR (ATTRv) as a form of "surgical gene therapy." Liver transplantation is not applicable to wild-type ATTR (ATTRwt), and in most cases, access to heart transplantation is limited by the advanced age of the patient.

Treatments for ATTR are discussed briefly below, particularly with a focus on amyloid heart disease [9,10,11,14,15].

3.2.1 RNA-targeted therapies

RNA-targeted therapies for ATTR amyloidosis-related cardiomyopathy and neuropathy have become available that interfere with hepatic TTR synthesis and the resultant availability of misfolded monomers to aggregate and form amyloid deposits; these include patisiran, inotersen, and vutrisiran.

a) Patisiran

- Patisiran is a TTR-specific small interfering RNA (siRNA) formulation in lipid nanoparticles, which has been shown to substantially reduce the production of both variant and wild-type forms of TTR in patients with hereditary ATTR and in healthy individuals [16,17,18].
- Benefit has been shown in clinical trials in patients with FAP due to ATTR [16,17,18] and for patients with amyloid cardiomyopathy due to ATTR.
- Patisiran is administered every three weeks by intravenous infusion [16,17,18].

b) Vutrisiran

- Vutrisiran is a transthyretin-directed siRNA for treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) in adults as an every-three-month subcutaneous injection.
- It is a chemically modified double-stranded siRNA that targets mutant and wild-type TTR messenger RNA (mRNA) and is covalently linked to a ligand containing three N-acetylgalactosamine (GalNAc) residues to enable delivery of the siRNA to hepatocytes, which causes degradation of mutant and wild-type TTR mRNA through RNA interference, resulting in a reduction of serum TTR protein and TTR protein deposits in tissues.
- Benefits have also been shown in patients with amyloid cardiomyopathy due to ATTR[19].

c) Inotersen

- Inotersen is an antisense oligonucleotide (ASO) construct that inhibits hepatic production of TTR, resulting in reduced levels of TTR in both healthy controls and in patients with hereditary ATTR with polyneuropathy [20,2122].
- Moderate to severe thrombocytopenia and bleeding complications have been reported with this agent. Benefits have also been shown for amyloid cardiomyopathy due to ATTR [20,2122].
- Inotersen is administered once weekly by subcutaneous injection [20,2122].

3.2.2 Stabilization of transthyretin tetramers

- **Tafamidis** and **diflunisal** each can reduce formation of TTR amyloid through stabilization of the TTR tetramer configuration, preventing release of amyloidogenic monomers [9,10,11,14,15].

3.2.3 Other agents

- Other agents under investigation for ATTR amyloidosis include AG10, a TTR stabilizer that mimics the effect of the protective TTR T119M variant[46]; tolcapone, a previously licensed drug for Parkinson disease, which was shown to be a potent stabilizer in preclinical studies[23]; palindromic bivalent cross-linkers that deplete TTR; covalent stabilizers such as beta-aminoxypropionic acids; cyclic oligosaccharides (cyclodextrins); and polyamidoamine (PAMAM) dendrimers that inhibit formation and disrupt fibrils.

3.3. Specific organ involvment

a) Management of Amyloid cardiomyopathy

- The treatment of symptomatic cardiac amyloidosis is twofold: **therapy for heart failure (HF) and treatment of the underlying disease** [9,10,11,14,15].
- Treatment of HF in patients with cardiac amyloidosis differs from the therapy generally recommended in patients with diastolic or systolic HF. While loop diuretics are a mainstay of treatment of cardiac amyloidosis, beta blockers and angiotensin-converting enzyme inhibitors are often not tolerated despite their efficacy in other types of systolic HF. Similarly, calcium channel blockers that may be useful in treatment of diastolic HF are contraindicated in amyloid cardiomyopathy.
- **Anticoagulation** is recommended in patients with amyloid cardiomyopathy with atrial fibrillation, intracardiac thrombi, or an embolic event [9,10,11,14,15].
- **Beta-blockers** should be used with caution and may worsen outcomes. **Angiotensin inhibitors** may be poorly tolerated due to orthostatic hypotension. Retrospective analysis of trials suggests a beneficial effect of spironolactone. There is no evidence to guide use of SGLT-2 inhibitors in amyloidosis [9,10,11,14,15].
- The efficacy of implantable cardioverter-defibrillator therapy in patients with severe cardiac amyloidosis is unclear [9,10,11,14,15].
- The main treatment option in patients with light-chain **(AL) amyloidosis is chemotherapy** (cf. section A). A variety of regimens are used, including high-dose melphalan with autologous hematopoietic stem cell transplantation. Bortezomib-based regimens are first-line therapy for most patients who are not candidates for hematopoietic stem cell transplantation, even in patients with advanced cardiac disease (New York Heart Association [NYHA] functional class III or IV).

- For **transthyretin amyloidosis (ATTR) cardiomyopathy**, options include:
  - **For patients with ATTR cardiomyopathy with NYHA functional class I to III, treatment with tafamidis is recommended** (Recommendation level A, Evidence level II). In this population, a randomized trial found that tafamidis therapy reduced mortality as well as cardiovascular-related hospitalizations, and reduced declines in functional capacity and quality of life [9,10,11,14,15].
  - **Tafamidis is a TTR stabilizer and is the only Food and Drug Administration approved medication available for all ATTR-CM**. It delays disease progression but does not result in regression, and in trials, reduced all-cause mortality and cardiovascular hospitalizations. It has minimal side effects but has a high cost, needing copay assistance programs for patients [9,10,11,14,15].
    - The FDA-approved dosages are tafamidis 61 mg or tafamidis meglumine 80 mg.
    - In the **ATTR-ACT** study, **tafamidis compared with placebo demonstrated reductions in all-cause mortality and cardiovascular-related hospitalizations**. Benefits were consistent across pre-specified subgroups, including stratification by ATTRwt vs ATTRv status and NYHA functional class I or II vs III, **with the exception of higher cardiovascular hospitalization rates in NYHA functional class III participants who received tafamidis**.
    - The increased hospitalization rate was proposed to be driven by longer survival and expo-sure time in an advanced disease state, underscoring the importance of early diagnosis and treatment initiation.
    - A subsequent prespecified analysis from ATTR-ACT supported benefit from tafamidis, regardless of variant or wild-type status, with reductions in mortality and functional decline.
    - Additionally, **tafamidis slows the decline in patient-reported quality-of-life metrics**, and **the mortality benefit was evident up to 58 months** in the long-term extension of patients on continuous tafamidis compared with those initially on placebo who transitioned to tafamidis.
    - **The predominant barrier is risk for cost due to the high original list price of $225,000 annually. A cost-effectiveness analysis estimated a cost of $880,000 per quality-adjusted life-year gained** and that a 92.6% price reduction would be needed to make tafamidis meet established thresholds for cost-effectiveness [9,10,11,14,15].
    - Another barrier to prescribing tafamidis may be the **lack of data regarding the appropriate patient population who will benefit** [9,10,11,14,15].
      - Although not included in the approved labeling, uncertainty exists regarding the efficacy of tafamidis early along the

disease continuum, including **asymptomatic genetic carriers** without clinically –evident cardiac amyloidosis or those with **localized, non-cardiac disease**.

- Furthermore, some patients with **advanced disease** may not benefit from tafamidis, such as those excluded from the ATTR-ACT trial, including patients with NYHA functional class IV status and advanced HF, or those of advanced age (90 years or older), although use in such patients should be based on an individualized shared decision-making discussion.

- Although there are alternatives to tafamidis, they lack a similar evidence base and are not as well tolerated.

- **Alternatives to tafamidis include diflunisal**, also a TTR stabilizer, which is less effective but significantly cheaper. It is a nonsteroidal anti-inflammatory drug and should be avoided in chronic kidney disease, decompensated heart failure, and gastrointestinal (GI) bleeding [9,10,11,14,15].
  - Although tafamidis should remain the first-line agent in the treatment of ATTR-CM as the only available approved drug, the cost of diflunisal is approximately $25 to $50 per month, rendering it an alternative option for those who are "too well" or those patients who cannot afford tafamidis.
- In addition, patients diagnosed with familial ATTR (ATTRm) cardiomyopathy should undergo evaluation for liver transplantation, as this can be curative in selected patients with ATTRm but not in those with wild-type ATTR (ATTRwt) amyloidosis. However, cardiac disease has progressed after liver transplantation in some patients with ATTRm. Patients with advanced heart disease with ATTRm may be treated with combined heart and liver transplantation [9,10,11,14,15].

b) Management of Amyloid neuropathy:

- **TTR silencers such as patisiran, vutisiran, and inotersen are approved for hereditary (ATTRv) polyneuropathy**. These are currently only approved for amyloid polyneuropathy and not yet for cardiac amyloidosis [9,10,11,14,15].

  - Diflunisal and tafamidis are TTR stabilizers which also slow the progression of ATTRv polyneuropathy. However, **although approved for ATTR-CM, tafamidis does not have approval from the FDA for treatment of ATTRv polyneuropathy** [9,10,11,14,15].
  - Diflunisal was demonstrated effective in ATTRv polyneuropathy to slow disease progression but is not FDA approved for this indication [9].

- Symptomatic management includes treating sensory neuropathy with medications like pregabalin, gabapentin, duloxetine, or tricyclic antidepressants, alongside the management of autonomic dysfunction with compression stockings, increased salt and fluids intake, etc [9].

c) Treatment of gastric amyloidosis

- Dietary modifications include dietary modifications (small evening meals, longer intervals between evening meals and laying down, calorie-dense supplements for malnutrition, FODMAP diet) [9].
- For nausea and early satiety: Antiemetics: ondasetron, promethazine; Prokinetics: metoclopramide.
- For diarrhea: Opioid receptor agonists: loperamide, diphenoxylate/atropine; Antibiotics; Bile acid sequestrants; Octreotide.
- For constipation: Laxatives: polyethylene glycol, magnesium-containing products, senna [9].

3.4. Key HTA recommendations

From a pharmaco-economic point of vue, daratumumab and tafamidis were the drugs that had HTA recommendations for their use in amyloidosis.

Daratumumab had a favorable opinion for reimbursement in combination with CyBorD protocol in newly diagnosed systemic light chain (AL) amyloidosis from the HTA bodies (HAS, CADTH, IQWIG, PBAC) due to a substantial clinical benefit with an acceptable financial analysis.

- The efficacy assessment was based on the landmark ANDROMEDA trial that demonstrated the superiority of the addition of daratumumab to the CyBorD protocol in terms of complete hematological response, compared to CyBorD protocol alone with 53% versus 18% respectively, (i.e. an OR=5.13, 95% CI [3.22; 8.18], p<0.0001).
- The ICER of the combination was estimated from $75,000 to < $95,000 per QALY and the financial analysis was deemed acceptable by the several HTA bodies.
- The use of Dara-CyBorD was considered an acceptable choice of healthcare resources.

Tafamidis had a favorable opinion for reimbursement in adult patients with wild-type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM) from the majority of the HTA bodies (HAS, CADTH, IQWIG), except PBAC and NICE that didn't approve the reimbursement of the drug within its marketing authorization. The cost-effectiveness estimates were higher than what NICE and PBAC normally considers an acceptable use of healthcare resources.

- HAS, CADTH, IQWIG considered that tafamidis provided a substantial clinical benefit and a therapeutic improvement in the management of wild-type or hereditary transthyretin amyloid cardiomyopathy.
- The clinical efficacy was demonstrated in a phase III clinical study compared to placebo, in patients with ATTR-CM: All-cause mortality was reduced after 30 months with HR = 0.70 95% CI [0.51; 0.96] p=0.0259 as well as the frequency of

cardiovascular-related hospitalizations over 30 months RR = 0.68 95% CI [0.56; 0.81] p<0.0001.

- However, clinical benefit varies across different types and stages of ATTR-CM.
- The ICUR for tafamidis compared with best supportive care is $443,694 per QALY gained (CADTH). CADTH considered that there was an unmet clinical need due to the absence of effective alternative treatments for ATTR-CM and therefore recommended conditional reimbursement.
- The PBAC noted that the base case ICER was $155,000 to <$255,000 per QALY after corrections made during evaluation.
- NICE noted that the ICER for tafamidis compared with best supportive care, in the full population, was less than £30,000 per QALY gained.
- Therefore NICE and PBAC didn't recommend the reimbursement of tafamidis.

Since there is an unmet clinical need in the management of ATTR cardiomyopathy due to the absence of effective alternative treatments, and since tafamidis has a clinical added value as per the majority of the HTA bodies, we consider that Tafamidis should be covered for patients with wild-type or hereditary ATTR-CM with a NYHA classification of I to III and a history of heart failure.

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of amyloidosis.

These recommendations should be used to support and not supplant decisions in individual patient management.

Section 5.0 References

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

1. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)
Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age Edit):	Coverage may depend on patient age
CU (Concurrent Use Edit):	Coverage may depend upon concurrent use of another drug
G (Gender Edit):	Coverage may depend on patient gender
MD (Physician Specialty Edit):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limit):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another Drug
EU (Emergency use only):	This drug status on Formulary is only for Emergency use.
PE (Protocol edit)	Use of drug is dependent on protocol combination, doses and sequence of therapy

Examples:
Age edit: Desmopressin in Nocturnal Enuresis should not be prescribed for children < 5 years.
Concurrent Use Edit: Flavoxate in Nocturnal Enuresis should be used as add on to desmopressin after desmopressin failure and cannot be used alone.
Gender Edit: Exemestane in Endometriosis should be used only by Females.
Physician Specialty Edit: Fentanyl in Endometriosis should be prescribed by a gynecologist or pain management specialist.

Prior Authorization: Desmopressin in Nocturnal Enuresis: The prescriber must check the following before prescribing:

- Failure of combination of behavioral and alarm therapy.

Quantity Limit: Idarubicin in Acute Leukemia: Cumulative dose should not exceed 150 mg/m2. Please note that this Quantity Limit is different than the one based on maximum daily dose as this is not necessary based on Maximum Daily Dose

Step Therapy: Aripiprazole in Social Anxiety: should be used as third line after:

First-line: Escitalopram, fluvoxamine, fluvoxamine CR, paroxetine, paroxetine CR, pregabalin, sertraline, venlafaxine XR

Second-line: Alprazolam, bromazepam, citalopram, clonazepam, gabapentin

Emergency use only: Furosemide IV form in Hypertension is used only in emergency setting.

Protocol edit: Bendamustine Hydrochloride, Cyclophosphamide, Ifosfamide, Dacarbazine should be used in Lymphoma as per the following protocol

2. Adult and Pediatric Quantity Limit?

This is either the adult or pediatric maximum amount of a drug that can be administered per day based on a maximum daily dose.

If there is no clinical evidence supporting the quantity limit for that relevant indication, this column will be left as Blank.

3. What information are available in the notes?

“Notes” section provides details of the prescribing edits, extra important drug information and special warning and precautions.

4. Drug interactions

1. A: No known interaction
2. B: No action needed
3. C: Monitor therapy
4. D: Consider therapy modification
5. X: Avoid combination

6. Defined Daily Dose

The Defined Daily Dose (DDD) is to be set based on the WHO recommendations https://www.whocc.no/ddd/definition_and_general_considera/

7. REMS

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

Appendix B. Level of Evidence Description

1. **Level of Evidence Adopted:**

Grade of research[1]	
A	Strongly recommend; Good evidence
B	Recommend; At least fair evidence
C	No recommendation for or against; Balance of benefits and harms too close to justify a recommendation
D	Recommend against; Fair evidence is ineffective, or harm outweighs the benefit
E	Evidence is insufficient to recommend for or against routinely; Evidence is lacking or of poor quality; Benefits and harms cannot be determined.
Level of evidence	
Level I	Meta-analysis of multiple studies
Level II	Experimental studies
Level III	Well-designed, quasi-experimental studies
Level IV	Well-designed, non-experimental studies
Level V	Case reports and clinical examples

Appendix C. PubMed Search Methodology Terms

The following is the result of the PubMed search conducted for Myelodysplastic Syndromes guideline search:

Query	**Sort By**	**Filters**	**Search Details**	**Results**
(((((Amyloidosis[MeSH Major Topic]) OR (Amyloidosis[Title/Abstract]))		Guideline, in the last 5 years	("Amyloidosis"[MeSH Major Topic] OR "Amyloidosis"[Title/Abstract]	16

OR (Amyloidosis, Familial[MeSH Major Topic])) OR (Amyloidosis, Familial[Title/Abstract])) OR (Immunoglobulin Light-chain Amyloidosis[MeSH Major Topic])) OR (Immunoglobulin Light-chain Amyloidosis[Title/Abstract])		OR "amyloidosis, familial"[MeSH Major Topic] OR "amyloidosis familial"[Title/Abstract] OR "immunoglobulin light chain amyloidosis"[MeSH Major Topic] OR "immunoglobulin light chain amyloidosis"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	

Appendix D. Treatment Algorithms

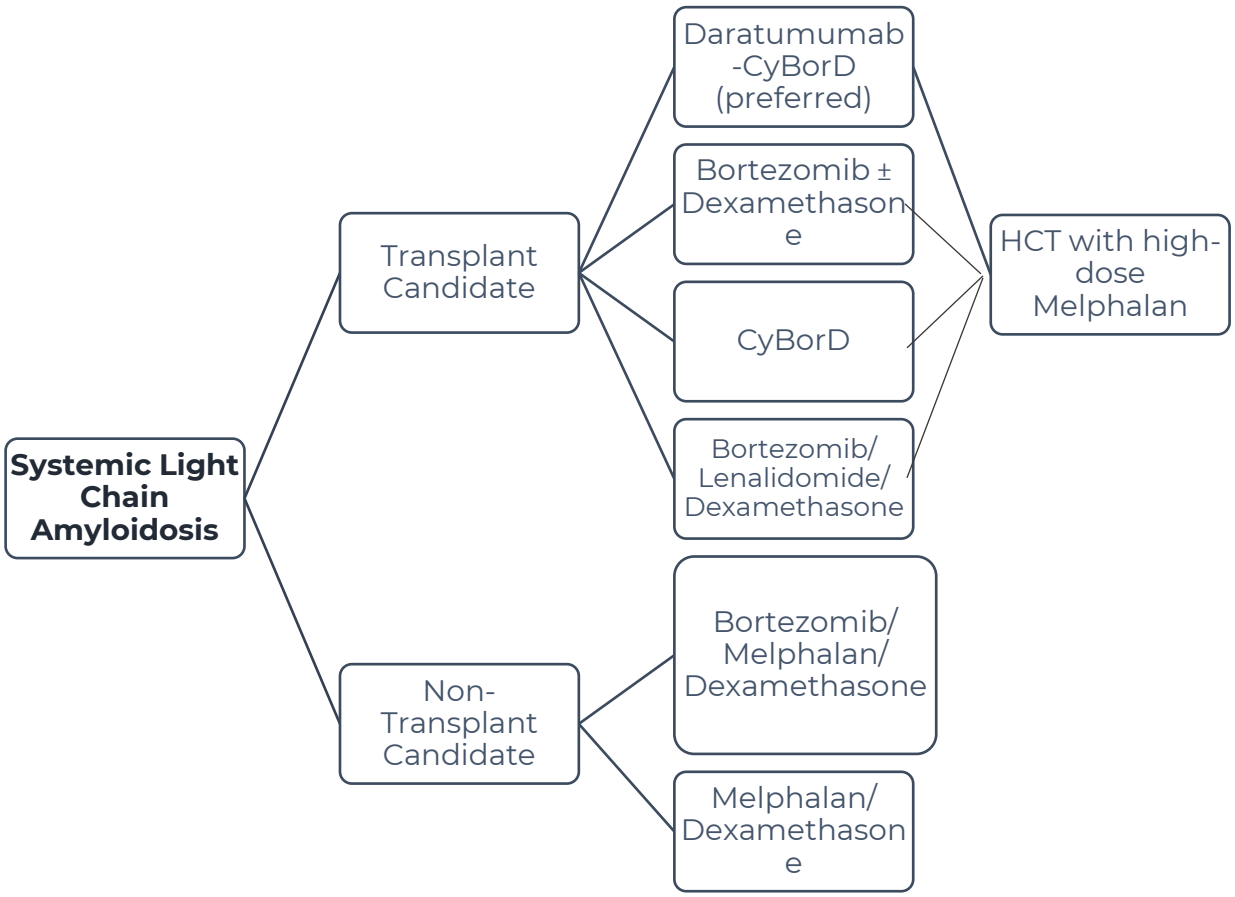


Figure 7. *Initial Management of Systemic Light Chain Amyloidosis*

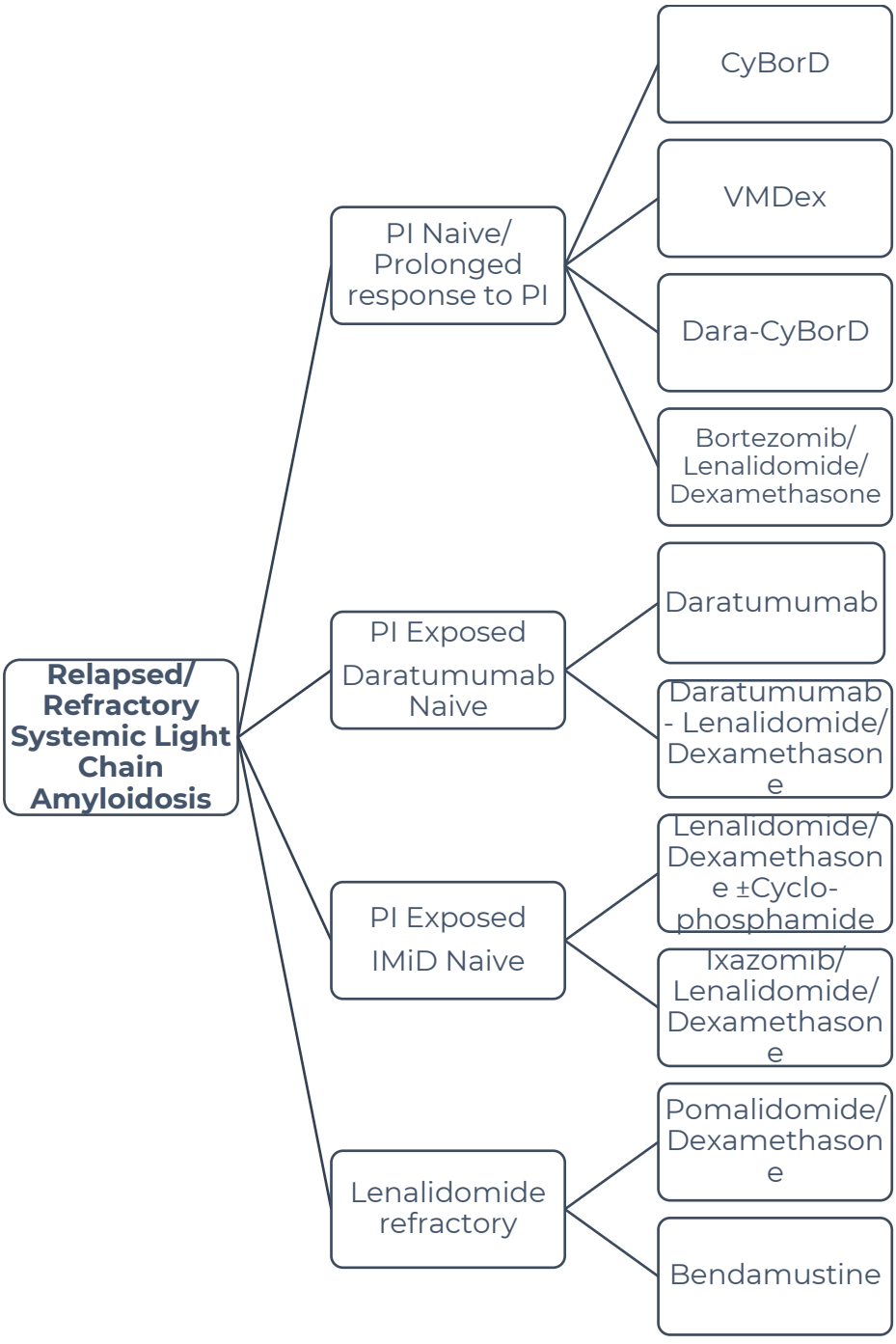


Figure 8. *Relapsed/Refractory Systemic Light Chain Amyloidosis*

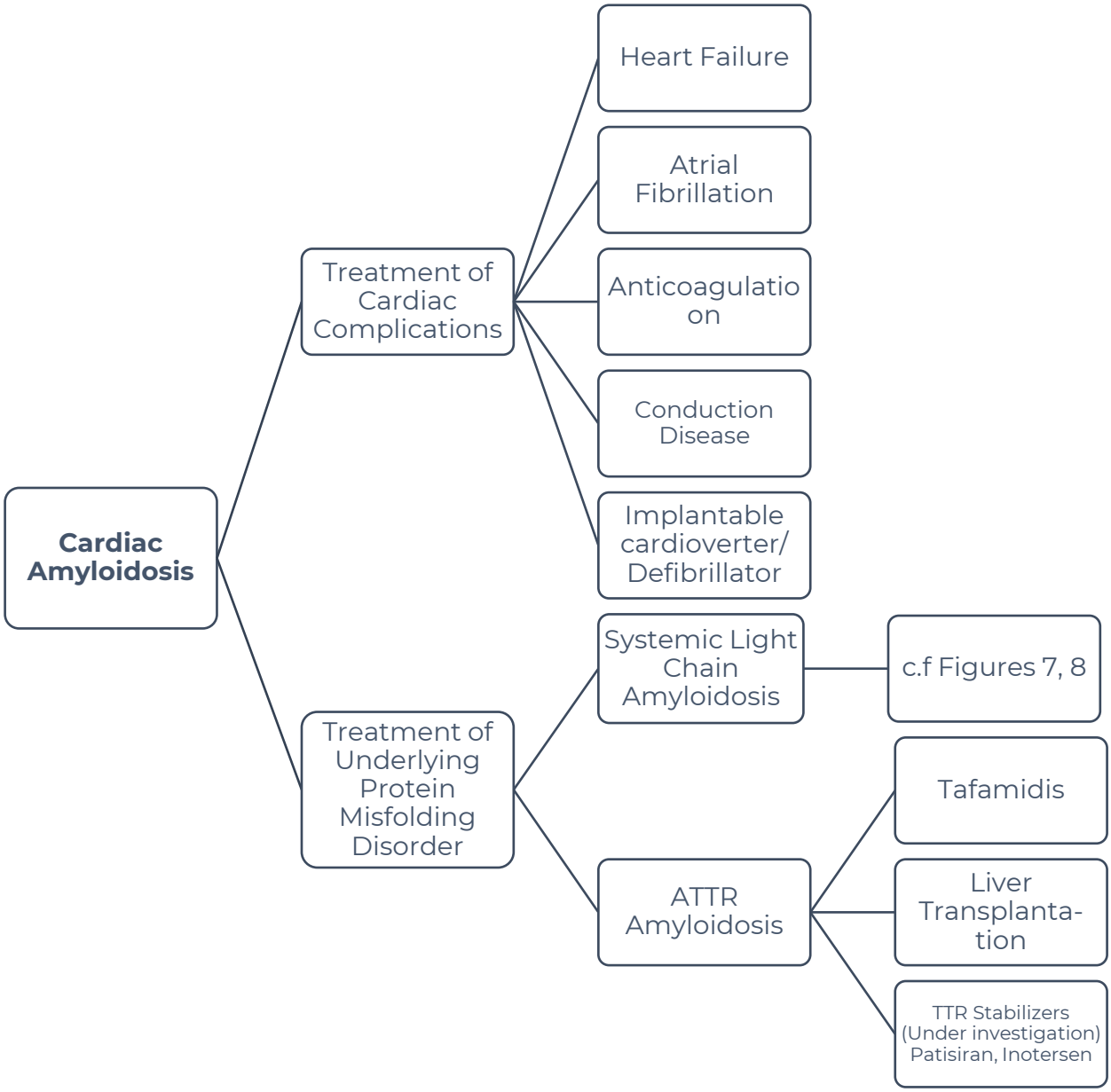
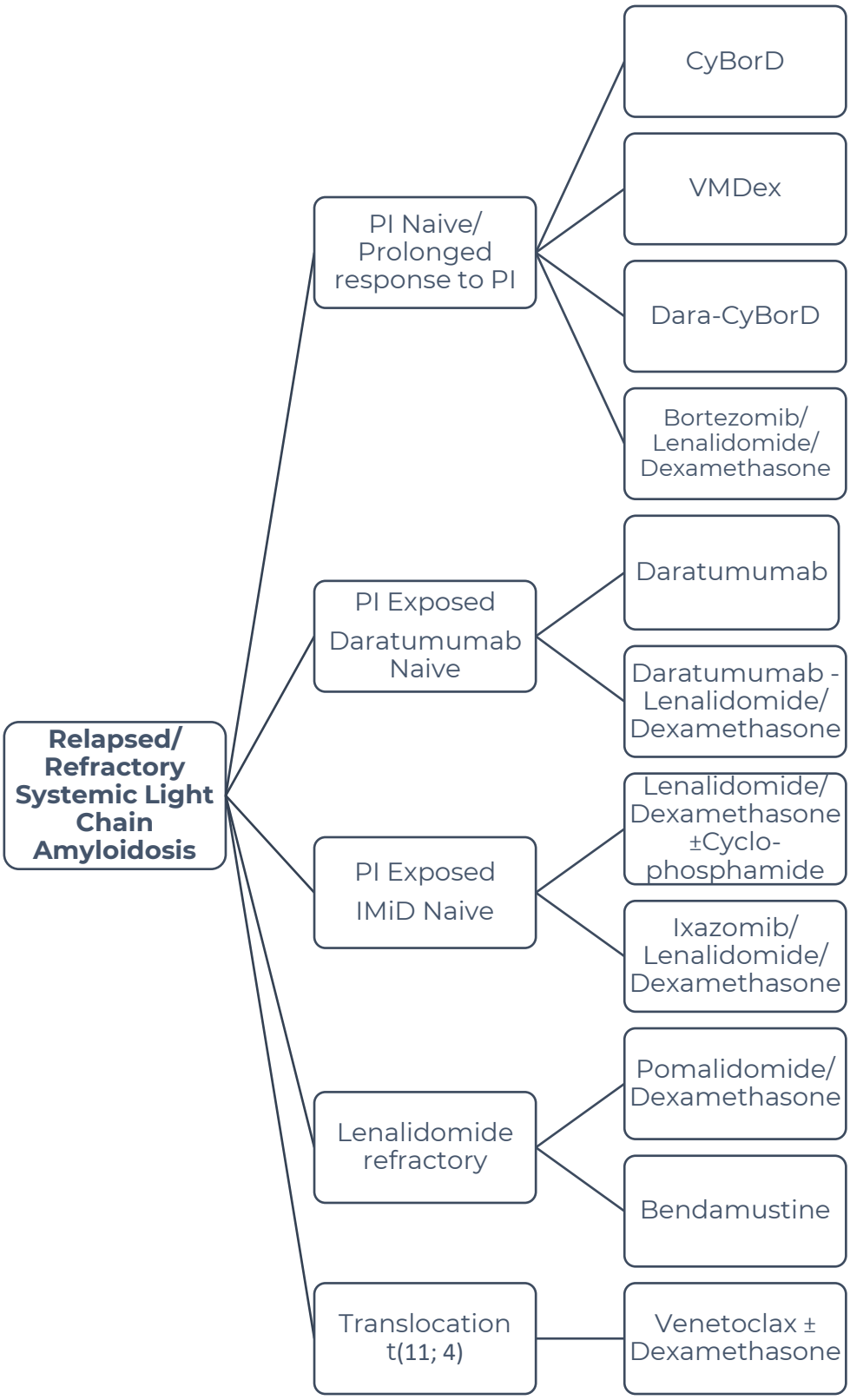


Figure 9. *Treatment of Cardiac Amyloidosis*


Relapsed/ Refractory Systemic Light Chain Amyloidosis
PI Naive/ Prolonged response to PI
CyBorD
VMDex
Dara-CyBorD
Bortezomib/ Lenalidomide/ Dexamethasone
PI Exposed Daratumumab Naive
Daratumumab
Daratumumab - Lenalidomide/ Dexamethasone
PI Exposed IMiD Naive
Lenalidomide/ Dexamethasone ±Cyclo-phosphamide
Ixazomib/ Lenalidomide/ Dexamethasone
Lenalidomide refractory
Pomalidomide/ Dexamethasone
Bendamustine
Translocation t(11; 4)
Venetoclax ± Dexamethasone