EM-65568
June 2021

HTAI PCIG project:

Summary of Information for Patients (SIP):

International SIP template

Introduction for patient organisations:

Background:

Understanding the experiences of patients, their families and carers, is becoming widely recognised as an important component in any Health Technology Assessment (HTA). Patients and patient organisations can help to provide this information through their engagement with the HTA process, and it is now becoming standard practice for HTA bodies to request input during the assessment process. It is therefore important that relevant patient representative have an informed and appropriate understanding of the medicine under review to optimise their input.

Why should I use a SIP?

This *Summary of Information for Patients (SIP) Version 1* is a supporting document that has been developed to provide you with relevant background information about the medicine under review. We hope it will help you / your organisation to structure a response to the HTA body, and comment on where you see the medicine adding most value to the patient community. Production of the SIP has been in response to patient organisations requesting this information. However, using the SIP template is optional.

The information within this template has been provided by the pharmaceutical company that is developing the medicine and sent to you by your HTA agency assessing the medicine. This has been reviewed by the HTA body to ensure that the content is not commercial in any way. **(NOTE TO HTA: Please delete last sentence if HTA body is not reviewing the industry content for accuracy and balance).**

It is important that the information included within this template is used as background reading to inform and support your input into the ongoing HTA assessment. Patient groups are requested to kindly not copy statements directly into their responses when providing input into the HTA review.

To help you navigate the SIP it has been divided into four sections:

- **SECTION 1: Submission summary.** This includes a summary about the medicine, the pharmaceutical company that makes it and the HTA body undertaking the assessment of the medicine.

- **SECTION 2: Current landscape.** This section has details about the condition, how it is diagnosed and currently treated. Patient-based evidence about the condition may be included here to help set the scene as to where the medicine will potentially fit in and provide benefit to patients.

- **SECTION 3: The medicine.** This is where all of the details about the medicine can be found, such as how it works, how it is given or taken, and its key attributes.

- **SECTION 4: Further information, glossary and references.**

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SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the guidance included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers.

Content development for this SIP has been informed following guidelines proposed by the National Adult Literacy Agency (NALA) available here: https://www.nala.ie/publications/plain-english-guidelines-at-a-glance/

1a) Executive summary: In only a few sentences please provide a top-level summary to describe the medicine. Please outline the main patient population it is proposed to treat:

Description of medicine

Daratumumab is a new treatment for a rare, debilitating condition called AL (Amyloid Light-chain) amyloidosis. AL amyloidosis is caused by an abnormality in certain cells found in the bone marrow, called plasma cells. When a person develops AL amyloidosis, an abnormal protein called 'amyloid' builds up and leads to organ damage in the heart, kidneys, nervous system, skin and digestive system.[1,2]

AL amyloidosis can lead to anxiety, frustration, and depression as patients can struggle due to how serious and rare their condition is.[3,4] The main cause of death from AL amyloidosis is heart failure.[5] Approximately 40% of patients die within the first two years of their diagnosis.[6] Therefore, there is an urgent need for treatments that improve survival and quality of life for these patients.

Daratumumab is a type of treatment known as a 'monoclonal antibody'. This means it targets and attacks cells in the body that have a protein called CD38 on their surface leading to the destruction of harmful cells. This protein indicates that a cell may not be working correctly, for example is producing too much amyloid. (More about this in Section 3a).

Regulatory authorities have considered daratumumab combined with three other drugs to be an effective treatment for AL Amyloidosis.[7] These other three treatment are (see glossary section):

- cyclophosphamide (a chemotherapy),
- bortezomib (a proteasome inhibitor), and
- dexamethasone (a steroid).

Who it proposes to treat

Daratumumab in combination with these three treatments is the first licensed treatment for adults with AL amyloidosis who have not yet received any treatment for their condition.[7]

1b) Name of the medicine (generic and brand name):

Active ingredient: Daratumumab
Brand name: DARZALEX®

1c) Authorisation: Please provide marketing authorisation information and link to the regulatory agency approval:

Authorisation (licence)

On 22 June 2021, the European Medicines Agency granted marketing authorisation for daratumumab administered subcutaneously (injected into the tissue between the skin and muscle) in combination with **cyclophosphamide, bortezomib and dexamethasone** for adults with **newly diagnosed systemic light chain (AL) amyloidosis.**[7]

1d) Name, address and contact details of SIP author at the pharmaceutical company making the submission. Please provide this for patients/patient groups should they require additional information. In some countries, this section may be removed depending on local compliance regulations:

Company name and address:
Janssen-Cilag Limited
50-100 Holmers Farm Way
High Wycombe
Buckinghamshire
HP12 4EG
Representative name and title: Rachel Howell – Patient Engagement & Advocacy Manager
Representative contact details (email/phone): rhowell5@its.jnj.com Tel:+44 7920 535476.

1e) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

The table below shows you our involvement with three patient advocacy charities in the United Kingdom (UK) in terms of how we engage and support them and or patients who use these charities. Our financial support varies from annual support of core services to support of individual patients and or staff to attend at meetings or events.

Patient group:	Janssen engagement/activity with each group:	Financial support we provided
WMUK	• Core activities in 2020 • Emergency Core Funding Support 2020 to continue to deliver key support services for patients during the COVID-19 pandemic • Haematology patient filming for internal company use	£10,000 £5,000 Payment made to the patient in line with our fair market value of £60 per hour for their time. No financial transaction with patient group.

	• Core activities in 2021	£7,500
Myeloma UK	• Myeloma UK supported the facilitation of patient involvement in our events: Darzalex Patient Experience Session for Haematology Team; Janssen with Me Co-Lab Patient Workshop; Myeloma Patient Insights Board; Janssen with Me Patient interview in digital experience; MyPOS workshop. • Workshop with a focus on the future commissioning pathway for CAR-T patients • Core activities in 2020 • Core funding to continue to deliver key support services for patients during the COVID 19 pandemic • Travel and accommodation costs for two members of Myeloma UK to attend a MyPOS workshop	- £540 £10,000 £30,000 £806.46 - no direct financial payment
Specialised HealthCare Alliance (SHCA members relevant to this disclosure – British Liver Trust)	• In 2020 Funding was paid directly to the Agency who provided secretariat support for their policy work	£14,500

Section 1f to be completed by the HTA organisation.

1f) Health Technology Assessment (HTA) organisation:

- HTA organisation name and address: **National Institute for Health and Care Excellence**
- Representative name and title: TAteam2@nice.org.uk – project team for submissions
- Representative contact details (email/phone): Heidi.livingstone@nice.org.uk for patient involvement support.
- Submission date: **23 June 2021**
- If known, please also include an indication of the overall timelines for this health technology assessment:

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation may wish to add country-level information where needed to provide local country-level context.

Please focus this submission on the **target indication** rather than sub-groups, as this could distract from the focus of the SIP and the HTA review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition

Please provide a few sentences to describe the main condition that the medicine is planned to treat.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available.

Main condition that the medicine plans to treat – AL (Amyloid Light-chain) amyloidosis is a rare and debilitating condition caused by an abnormality in certain cells found in the bone marrow, called plasma cells.

Plasma cells in healthy people produce normal proteins (called antibodies that are formed by light and heavy chains) to help protect the body from infection.

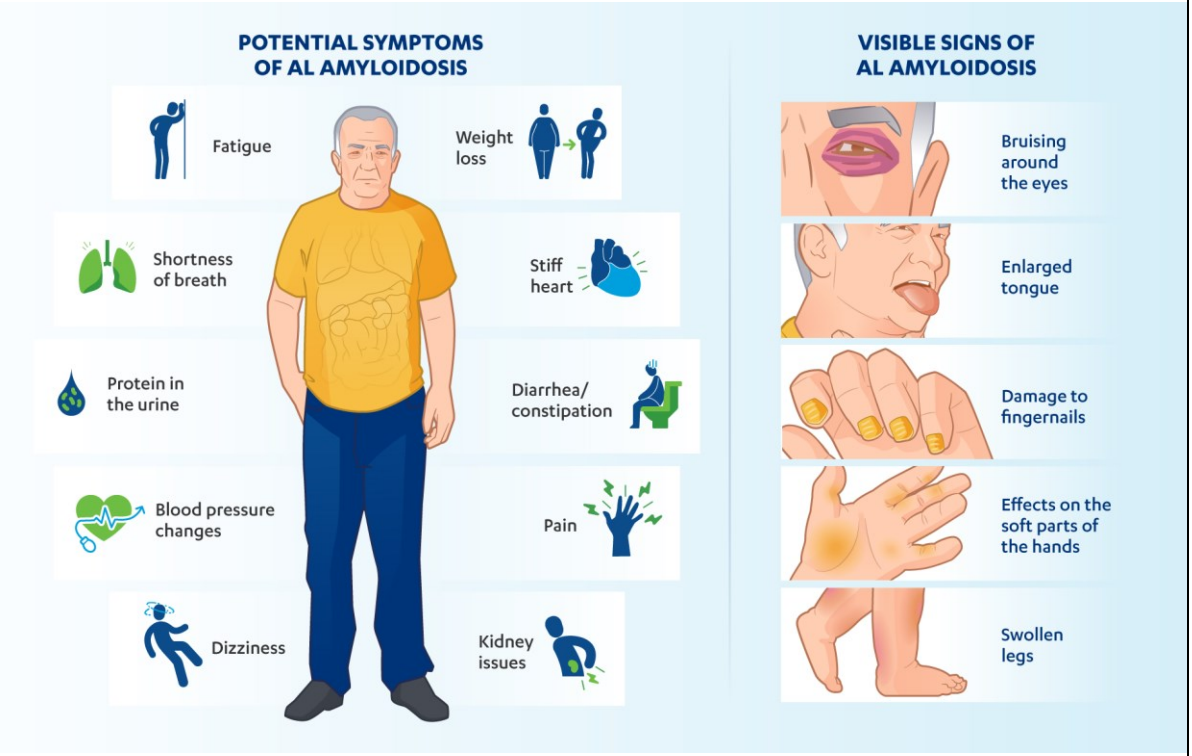
Plasma cells from patients with AL amyloidosis produce abnormal forms of normal proteins which clump together into thread-like strings (amyloid fibrils) that the body cannot clear away easily, and over time, build up as AL amyloid deposits (which are misfolded light chains) in tissues and organs. These deposits build-up gradually and stop the body's organs functioning properly and cause symptoms which make patients feel very unwell.

Main symptoms of disease - AL amyloidosis can affect the heart, kidneys, nervous system, skin, and digestive system.[1] The main symptoms of AL amyloidosis include: (Figure 1)

• Tiredness	• Weight loss
• Shortness of breath	• Stiff heart
• Protein in the urine	• Diarrhoea (or constipation)
• Blood pressure changes	• Pain
• Dizziness	• Kidney issues

Most common visible signs: The most common visible signs are bruising around the eyes, an enlarged tongue, damage to fingernails, effects on the soft parts of the hands and swollen legs (Figure 1).

Figure 1: AL Amyloidosis signs and symptoms[1]



How many people have the condition - Out of every million people, only about 10 to 50 people will develop AL amyloidosis.[8,9] Around 500 to 600 patients will develop AL amyloidosis every year in the UK.[2] People are more likely to develop the disease over the age of 40 and it is more common in men.[10,11]

Burden of disease - Patients with AL amyloidosis require a lot of medical care (such as needing to spend time in hospital, on dialysis, and having imaging tests) that can be very costly to the health system. Depending on how far patients live from their nearest hospital, they may also have to spend a lot of time traveling to and from medical appointments, often accompanied by a carer.

- Patients with AL amyloidosis which has affected their **heart** (50–70% of AL amyloidosis patients) are much more likely to be hospitalised due to heart-failure and may require a (heart) transplant.[12,13]
- 70% of AL amyloidosis patients have **kidneys** that are affected by the condition[14] and may need dialysis and/or kidney transplants, which are costly procedures requiring a lot of healthcare resources.[15]

A study of newly diagnosed patients in the United States found that more than half of patients with AL amyloidosis were admitted to hospital during the first year following diagnosis. On average, a patient stayed more than 2 weeks in hospital. Furthermore, patients visited their doctor to have tests performed and/or receive medical attention almost 4 times per month[16] which all add to the impact this disease has on the daily lives of patients and their carers.

Emotional effects - Since AL amyloidosis is such a rare disease, patients must also deal with the added uncertainty because their doctors may lack knowledge and experience of diagnosing and treating the condition.[17] Many patients experience delays in receiving a diagnosis and suffer from a lack of support and information about the condition, further worsening the overall impact on

their quality of life.[18] Being diagnosed with a rare disease can also make patients feel isolated.[19] AL amyloidosis can have a negative impact on patients' quality of life. Tiredness and shortness of breath can make it difficult for patients to perform everyday physical tasks[3] or play with children/grandchildren and so on.

Impact on carers - The burden of AL amyloidosis can also take its toll on carers. A study of a similar form of amyloidosis found that caring for a family member or friend with this condition was a full-time job, taking an average of 46 hours a week. The time and energy devoted by carers impacts their own lives in many ways, including be able to spend time with friends and family and this can also increase their risk of anxiety and depression.[20]

Life expectancy - About 40% of patients die within the first two years of diagnosis.[6] Just over half of patients are likely to survive for four years after being diagnosed with AL amyloidosis.[5,6] The main cause of death in patients with AL amyloidosis is heart failure.[5]

Patient outcomes depend on the number and type of organs affected by the disease. Life expectancy is particularly poor for patients in whom multiple organs have been affected, especially when it involves the kidneys and heart.

A patient with several organs affected by the disease will have more hospitalisations, imaging exams such as X-rays (high dense radiation), CT-scan (3D X-ray images) or MRI (radio waves) and heart exams.[21]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

If relevant to the medicine submission, please briefly explain how the condition is diagnosed and how this impacts patients:

How AL amyloidosis is diagnosed: Diagnosing AL amyloidosis can be tricky as the disease shares symptoms with other conditions.

However, in general, a diagnosis of AL amyloidosis presents as follows:

1) A person becomes aware of symptoms (mentioned above).
2) They go to their family doctor for advice.
3) Their doctor will likely arrange for some specialist tests to be done.
4) If AL amyloidosis is suspected, a doctor will take a very small sample of tissue from a patient's organ that is suspected of being affected. (This sample is called a biopsy). The organ could be the heart, kidney, or liver or a sample may be taken from other areas of the body (such as stomach fat or bone marrow).
5) This tissue sample is sent to a laboratory to see whether there is any build-up of amyloid.[22,23]
6) The diagnosis is then confirmed.

Why speed of diagnosis matters: A speedy diagnosis of AL amyloidosis is important for patients because damage to the organs worsens over time. This means that treatment can also be less effective because damage to the organs is already done. As a result, people who are diagnosed late may experience worse symptoms and poorer outcomes from treatment, than people who are diagnosed earlier. Only 37% of patients are diagnosed in the first year after symptoms initially appear,[24] and patients saw an average of 4 doctors before finally getting a confirmed diagnosis.[25] Unfortunately, a correct diagnosis can take months or even years because many of the disease symptoms are seen in other illnesses and so it can take some time to determine AL amyloidosis as being the cause of patients' symptoms.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is considered the standard of care for this condition? Please give emphasis to the specific setting and condition being considered by the HTA body in this review
- Please also consider:
  - Are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are
  - What are the short- and long-term implications of using current medicines?
- Please reference current treatment guidelines where needed
- Please conclude by stating how you feel the medicine will potentially address the unmet needs of patients

Challenge:
There is currently no cure for AL amyloidosis and the amyloid deposits cannot be directly removed.

What treatment are currently used – how they work and their side effects
Current treatments can prevent more of the abnormal proteins being produced. This alleviates patients' symptoms. Treatments can give the body time to gradually clear the deposits before they build up again, which can help to prevent organ damage.[1]

At this time, doctors use treatments approved for other diseases to treat AL amyloidosis. These treatments are referred to as **"**off-label**"** use because there is nothing else that has been licensed to treat AL amyloidosis.[23,26] While these treatments have been tested in clinical studies, the manufacturers of these treatments haven't sought regulatory approval for licensed use in patients with AL amyloidosis. Doctors are concerned that current treatments do not work as well as they would like for AL amyloidosis and have significant side effects.[27]

There are two main current treatments

- Autologous stem cell transplant.
- A combination of treatments

Autologous stem cell transplant: A small proportion of patients (~6%) will be eligible to receive a stem cell transplant[28] which will enable them to live longer.[29] Autologous stem cell transplant (ASCT) is a medical procedure where some of the patient's stem cells (a cell in the body that is still "immature") are collected from their own bone marrow or blood and saved for later use. The patient then receives a treatment that destroys the cells in the body that are overproducing amyloid. The patient's own healthy stem cells are then put back (transplanted) into their body where they can begin to grow into healthy cells that do not produce amyloid.[30]

While stem cell transplants have been proven (in more than 70% of patients) to reduce amyloid in the blood, they are aggressive treatments meaning not many patients are able to undergo the procedure. Unfortunately, there is also a risk of dying during or after a stem cell transplant procedure. In one study, 16% of patients died within 3 months after receiving the transplant.[31]

To see if a patient may be suitable for an autologous stem cell transplant, doctors will consider:[26]

- Patients' ECOG Performance score, which needs to be between 0-2;
  - ECOG performance score is a scale used to assess how the disease affects the daily living abilities of the patient. The scale goes from 0 to 5, 0 being the best score and 5 the worst score.

- The number and extent of organ involvement
- Which other health conditions a patient has (referred to as comorbidities) and/or
- How physically able a patient is to withstand this treatment.

A combination of treatments (Off-label treatments): Since most patients with AL amyloidosis cannot be treated with a stem cell transplant, a combination of different treatments have to be used. These treatments generally combine two or three medications from the list below:

- Steroids (which can help other treatments work better);
- Traditional chemotherapy treatments (which are often used to treat cancer); and
- Newer targeted therapies (treatments that have been designed to address specific unhealthy areas in the body, such as cells that produce amyloid, while limiting damage to healthy parts of the body) such as proteasome inhibitors and immunomodulators. (See section 3b).[32]

Current clinical guidelines recommend the off-label use of: cyclophosphamide (chemotherapy), bortezomib (proteasome inhibitor), and dexamethasone (steroid) (also abbreviated to BCd) for patients with newly diagnosed AL amyloidosis.[23] About 90–95% of newly diagnosed patients are treated with BCd as their first-line of therapy in the UK.[33]

AL amyloidosis is described in medical terms using stages of disease based on a scale originally used for heart failure, because cardiac involvement is a useful gauge for disease severity. The Mayo Clinic Cardiac Staging system is the most widely used method for doing this. There are four stages of disease (I, II, IIIA and IIIB), with stage IIIB reflecting the frailest patients.[34,35]

A recent European Registry publication reported that BCd or bortezomib-based treatments have substantially improved patients' survival rates, especially for patients with stage IIIA disease.[36] Despite the survival improvements achieved by BCd, current treatments in AL Amyloidosis have failed in a high number of patients to achieve the primary goal of treatment i.e., achieving a complete haematologic response. This measure of response is important as it is a predictor of overall survival and the reduction of deposits at organ level, which can prevent organ damage (see section 3d). [27,37] The European Myeloma Network (which is a group of expert doctors who perform clinical studies in patients with multiple myeloma and AL amyloidosis) therefore recognises a need for new treatments that reduce the abnormal proteins in blood with fewer side effects and better survival outcomes.

Daratumumab

Daratumumab is a novel, effective and well-tolerated treatment that can achieve higher rates of complete haematologic response, delay organ failure, improve patients' quality of life, and their survival.

Daratumumab, in combination with bortezomib, cyclophosphamide and dexamethasone is the first and only licensed treatment by the European Medicines Agency for AL amyloidosis in member states of the European Union.[7]

The key benefits of daratumumab for patients with AL amyloidosis, their carers and society include:

- **A treatment that most AL amyloidosis patients can use,** as compared to autologous stem cell transplant where only 6% of patients can be considered eligible to receive it
- **A treatment that can quickly reduce amyloid levels in the patient's blood,** which helps to **protect their organs** from damage for a long period of time

- **The opportunity to better control the disease which leads to improvements in patients' symptoms (such as fatigue) and allows patients to live longer with a better quality of life.**
- A treatment that is **less costly to the health system** (by avoiding organ transplant and dialysis)

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might include outputs from patient preference studies, when conducted in order to show what matters most to patients and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE evidence that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Any such evidence included in the SIP should be formally referenced wherever possible.

AL amyloidosis from the patient perspective

AL amyloidosis and its treatments can place a heavy physical and emotional burden on patients and their carers. Disease symptoms have a significant impact on patients' quality of life.

Feedback from patients' workshop

One participant from a Patient Focus Group described his ability to walk as 'greatly impaired' and his breathing as 'appalling'. He described himself as "unable to bend down and feeling exhausted".[18] Beyond their physical health, patients with AL amyloidosis experience significant mental health challenges.[24,27,38]

In the same Focus Group, patients expressed feelings of low self-worth, frustration at their declining physical ability and distress at their loss of independence.[18]

Furthermore, patients with AL amyloidosis must also deal with the uncertainty and difficulties associated with having a rare disease, including delayed diagnoses and, fewer support networks and the lack of information about the disease.[24,39]

Several UK-based patients described their journey to diagnosis as challenging.[18]

It took some patients up to two years to be diagnosed with AL amyloidosis.[18] This was due to the generic nature of their symptoms. One patient said they had to see several doctors, including a nephrologist (a doctor who has special training in diagnosing and treating kidney disease). The nephrologist misdiagnosed his condition as multiple myeloma (a type of cancer that begins in plasma cells, white blood cells that produce antibodies), before a haematologist provided the correct diagnosis of AL amyloidosis.[18]

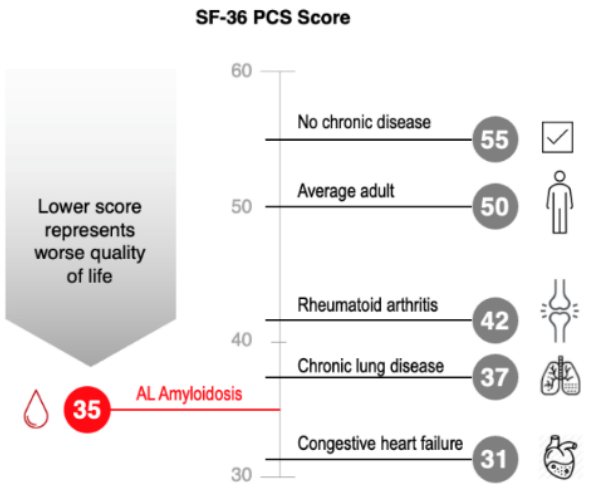
Worse quality of life if the heart is affected

People with AL amyloidosis have a poor quality of life, especially when the disease has affected their heart and when they have not responded to treatment.[40] Patients report severe psychological distress, anxiety and may also experience unintentional weight loss.[27] As well as being limited in their physical activity, patients also suffer feelings of unhappiness, loss of interest in seeing people, losing touch with friends and difficulties sleeping. AL amyloidosis can also cause some people to feel scared, hopeless, and depressed.[24,38] Almost half of patients with AL amyloidosis said they finished fewer daily activities because of anxiety and/or depression.[38]

Patients have a worse quality of life with AL amyloidosis than patients with chronic diseases

One of the most commonly used questionnaires to evaluate the quality of life of people with AL amyloidosis is the Short Form–36 (SF-36) questionnaire.
Figure 1 illustrates the mean (average) quality of life values for AL amyloidosis patients, using a scale that ranges from 0 to 100. Higher SF-36 scores indicate better quality of life for each scale.[41] AL amyloidosis is thought to impact patients' **quality of life** more than if they had a chronic disease such as rheumatoid arthritis or lung disease for example (**Figure 2**).[41]

Figure 2. A comparison of the quality of life of people with AL Amyloidosis with other diseases using the SF-36 questionnaire.[41]



SECTION 3: The medicine

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used if they will help to convey information more clearly.

3a) How does the medicine work?

What are the important features of this medicine?

Please outline as clearly as possible important details relating to the mechanism of action and how the medicine interacts with the body that you consider relevant to patient groups.

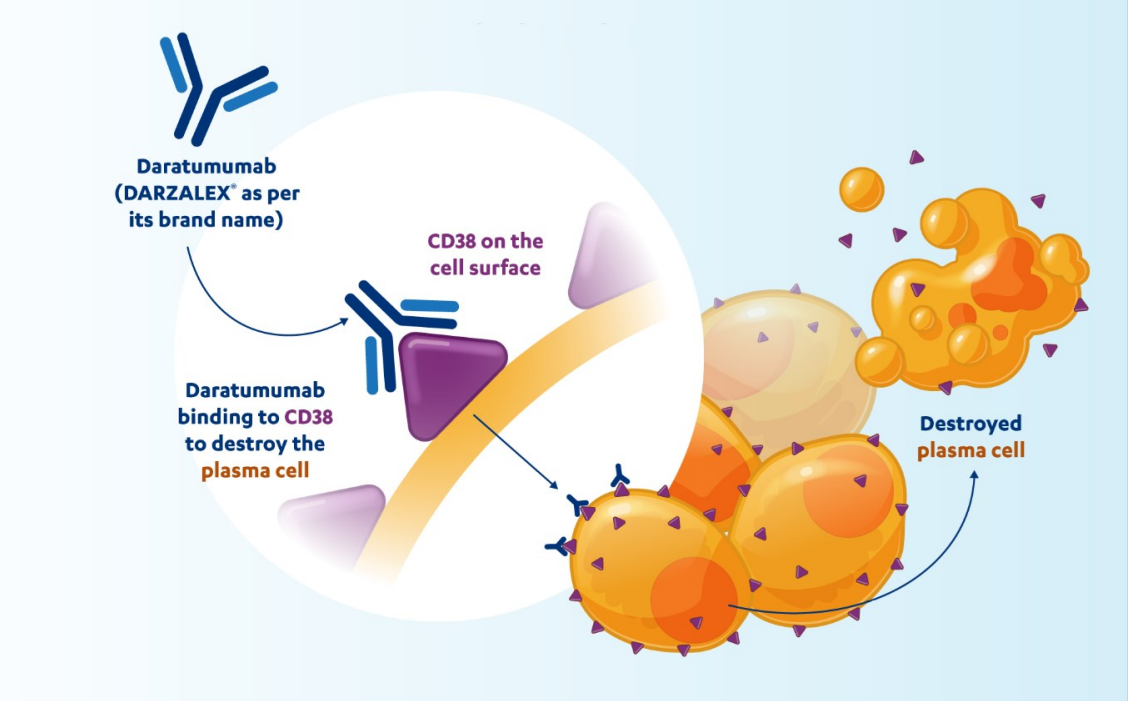
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

About daratumumab - its key features and how it works

Daratumumab is a medicine that has already been approved by the European Medicines Agency (EMA) for treating multiple myeloma (a type of cancer that begins in plasma cells, white blood cells that produce antibodies).[7,42] More than 189,000 patients with multiple myeloma have been treated world-wide under this indication.[43] It has recently been approved by the EMA for newly diagnosed patients with AL amyloidosis.

Daratumumab is a type of treatment known as a **monoclonal antibody (Figure 3)**. It targets and attacks cells in the body that have a protein called CD38 on their surface. This protein indicates that a cell may not be working correctly, for example, is producing too much amyloid. Daratumumab attaches itself to CD38 on cells that are producing amyloid. This leads to the destruction of harmful cells and reduces levels of amyloid which prevents further damage to the affected organs.[42]

Figure 3. How daratumumab works.



Innovation in patient care

Daratumumab works in a selective way by destroying harmful cells that have a protein called CD38 on their surface. Having cells with a higher number of CD38 proteins on the surface leads to poor outcomes in AL amyloidosis.[44] Daratumumab identifies and kill these cells.

DBCd is the first licensed therapy in the UK for the treatment of patients with AL amyloidosis. Patients with AL amyloidosis are currently treated with a range of treatment options;[45] many of which have limited efficacy.[46]

Patients with AL amyloidosis currently live with grief, distress, anger, and fear finding out there is a lack of standard treatment for their condition. The benefits to patients of receiving an innovative treatment, such as the addition of daratumumab to bortezomib-based treatments provides significant clinical benefits that are tailored to treat their condition more effectively.[47]

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes? / No?

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination medicine, please ensure the sections on efficacy (3d), QoL (3e) and safety/side effects (3f) focus on data that relate to the combination, rather than the individual medicine.

Daratumumab is used in combination with cyclophosphamide, bortezomib and dexamethasone

Cyclophosphamide is a chemotherapy: Chemotherapy has been used for more than 40 years to treat AL amyloidosis. Fine-tuning chemotherapy combinations has led to increasing success in destroying amyloid-producing cells, through DNA damage or stopping cell reproduction.[48,49] However, chemotherapy can cause unpleasant side effects for many patients, including tiredness and feelings of sickness. The tiredness felt by patients is often due to anaemia. Anaemia means a patient has too few red blood cells, which are needed to transport oxygen throughout the body. Fortunately, the side effects of chemotherapy can usually be managed by the doctors giving patients medicines to help them feel better. The side effects of chemotherapy also tend to go away after treatment stops.[30]

Bortezomib is a targeted therapy, a proteasome inhibitor: Amyloid-producing cells are particularly sensitive to destruction by proteasome inhibitors.[50] These treatments break down parts of cells called proteasomes, which help destroy the bad proteins inside the cells. By blocking the work of proteasomes, the bad proteins build up to the point where the cells producing them die. Most common side effects include a decrease in the number of blood cells (red blood cells, white blood cells and platelets), nerve pain, nausea and vomiting, diarrhoea, constipation, fatigue, asthenia (lack of energy) and fever.

Dexamethasone is a steroid: Steroids help to stop abnormal cells producing amyloid proteins and can also help reduce side effects from chemotherapy. The most common side effects of steroids include fatigue, asthenia, oedema of the face and arms/legs (swelling caused by excess fluid in body tissues), muscular weakness, muscle cramps, high glucose blood level and insomnia (difficulty sleeping).

Cyclophosphamide, bortezomib and dexamethasone destroy the abnormal cells causing AL Amyloidosis through working in different ways. Combining them with daratumumab increases this destructive effect. This helps to further reduce the number of abnormal cells in the body and does not increase the frequency of serious adverse events, compared to the combination of cyclophosphamide, bortezomib and dexamethasone.

3c) Administration and dosing

How and where is the medicine given or taken? Please include the amount and how often the medicine should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Daratumumab combined with cyclophosphamide, bortezomib and dexamethasone is given to patients for a maximum of 2 years. The medicines can be given to patients on the same day, so as not to inconvenience patients by having to make frequent visits to the hospital.

Patients received daratumumab in a hospital. A doctor or a nurse injects the patient with 1,800 mg of daratumumab. The doctor or nurse uses a short needle to inject the treatment into the tissue between the skin and the muscle. It can take between 3 to 5 minutes for the injection to be given.

For **daratumumab**, the patient will receive a maximum of 36 injections into the tissue between the skin and the muscle:[42]

- 1 injection is given to patients every week for the first 8 weeks (8 injections)
- 1 injection is given to patients at the start of the week every 2 weeks for the next 16 weeks (8 injections)

- 1 injection every 4 weeks until there are clinical signs the disease is getting worse or for a maximum of 2 years (20 injections).

For **cyclophosphamide**, the patient will need to receive a maximum of 24 doses:[42]

- 300 mg per each square meter of body surface area (up to a maximum of 500 mg per week) by mouth (orally) or intravenously (injected into veins) every week for up to 24 weeks (24 doses). Body surface area is calculated based on patient's height and weight.

For **bortezomib**, the patient will need to receive a maximum of 24 doses:[42]

- 1.3 mg per each square meter of body surface area subcutaneously (injected into the tissue between skin and muscle) every week for up to 24 weeks (24 doses)

For **dexamethasone**, the patient will need to receive:[42]

- 40 mg by mouth (orally) every week for up to 24 weeks (24 doses). This can be taken at home.

Patients will also need to travel to the hospital for follow-up visits with their doctor and have additional tests performed (blood tests, urine tests, liver panel tests, and tests such as X-rays (high density radiation), CT scan (3D X-ray images) or MRI (radio waves).

The addition of daratumumab to the standard treatment of cyclophosphamide, bortezomib and dexamethasone does not involve the need for additional visits to the hospital. This is beneficial for both patients and carers. The addition of daratumumab increases the time on treatment from 6 months for BCd to a maximum 2 years. However, patients' quality of life improves with the addition of daratumumab after the administration of BCd is stopped at 6 months.

3d) Efficacy

Efficacy is the measure of how well a medicine works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the medicine is at treating the main condition outlined in section 2a. If there are data available, please also describe how it is different to other medicines available outlined in section 2c?

388 patients' feedback about daratumumab combined with bortezomib, cyclophosphamide and dexamethasone (DBCd, also called DVCd)

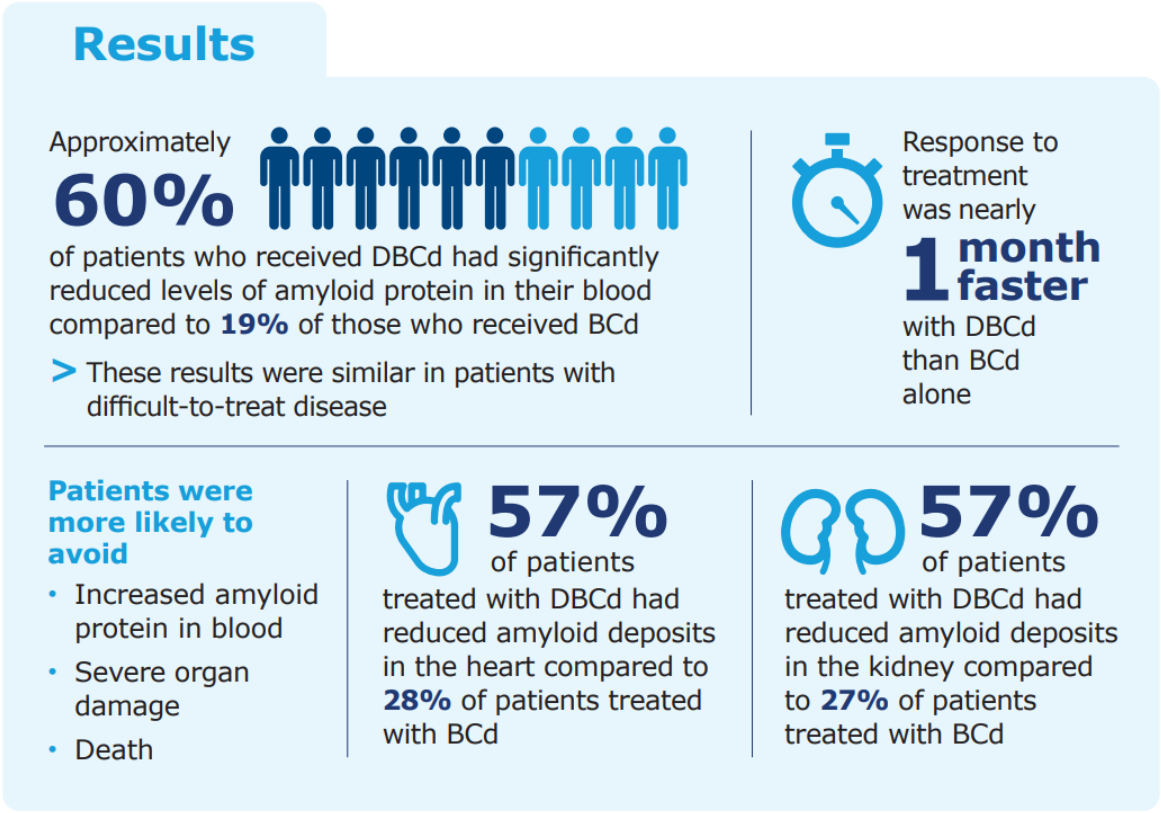
The European Medicines Agency has recently approved DBCd use in all newly diagnosed patients with AL amyloidosis.[7] It is doing this based on the results from a phase III clinical trial. A phase III clinical trial (also called clinical study) tests the safety and how well a new treatment works when compared to usual treatment.

Janssen did a phase III clinical trial (called the **ANDROMEDA study**) of 388 newly diagnosed (previously untreated) patients with AL amyloidosis. In this study, the efficacy and safety of daratumumab in combination with BCd (so-called DBCd) compared to BCd alone was compared.[51]

Patients with a more severe cardiac disease (stage IIIb) were not included in this study.

The results of the ANDROMEDA study are illustrated below (in Figure 4).

Figure 3: ANDROMEDA Phase III Trial Results[51,52,53]



In the ANDROMEDA study, the efficacy of DBCd was measured according to how well it improved 3 things:

- Patients' hematological response rate: this measures the level of amyloid protein in the blood
- Patients' organ response rate: this measures the improvement in the functioning of those organs affected by AL amyloidosis
- Patients' cardiac or renal (kidney) major organ damage progression-free survival: This measure determines the length of time during which patients are alive, have their amyloid protein blood levels under control, and where they are not experiencing either cardiac or renal (kidney) failure.

We explain each of these in turn below.

Hematological response rate

In patients who received DBCd for at least 20.3 months:

- We found that 59% of patients experienced a significant reduction of the amyloid protein in blood compared to 19% in patients receiving BCd.[53]
- We found that patients with difficult-to-treat stage IIIA disease achieved much higher hematological response rates with DBCd treatment than those patients receiving BCd treatment (62.5% compared to 10%).[53]
- We found that patients who received DBCd responded nearly one month faster to their treatment than those receiving BCd (2 months compared to 2.8 months).[53]

Organ response rate

Organ response is assessed through a combination of measures such as presence of symptoms and the results of blood and imaging tests.[54] Imaging tests include X-rays (high density radiation), CT scan (3D X-rays) or MRI (radio waves)

- We found that in patients whose **heart** was affected by the disease, about 57% of patients treated with DBCd experienced a reduction in amyloid deposits in their heart, compared to 28% of patients who received BCd after one year of treatment.[53] This reduction allowed those patients receiving DBCd to feel better, as their hearts were able to pump blood with greater strength.[55]
- We found that 57% of patients with disease affecting their **kidneys** had reduced amyloid levels after treatment with DBCd compared to 27% of patients receiving BCd after one year of treatment.[53]

Major organ deterioration progression-free survival measure

This measure determines the length of time during which patients are alive, have their amyloid protein blood levels under control, and where they are not experiencing either cardiac or renal (kidney) failure. Heart and kidney failure can lead to transplant or other interventions such as dialysis.[56,57]

- We found that after 11.4 months of treatment, 42% of patients treated with DBCd had a substantially reduced risk of suffering either heart of kidney failure, an increase in their amyloid protein blood levels or death compared to BCd.[52]

3e) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand the trade-offs and willingness to accept benefit/risk by patients. Please include all references as required.

Patients' health-related quality of life for the first 24 weeks of treatment was similar between those patients receiving DBCd and those receiving BCd. After 24 weeks when treatment finished with BCd, and patients were only receiving daratumumab they reported feeling less tired and had a better quality of life, compared to those patients that only received BCd.

The ANDROMEDA study found that patients who received DBCd had less amyloid protein in their bodies, compared to those patients receiving BCd. Reducing the amount of amyloid protein slows down the growth of the disease and the degree to which organs are affected, and therefore improves the symptoms of disease.

Patients who received DBCd experienced clinical improvements without any reduction in health-related quality of life during the first 24 weeks of treatment. Patients' quality of life continued to improve when they received daratumumab, after the 24 weeks where BCd was administered ended.[51] These improvements included feeling less tired and experiencing an improved quality-of-life (as measured using the Global Health Status scale of the EORTC QLQ C-30 questionnaire) compared to patients receiving BCd.[58] The EORTC QLQ-C30 questionnaire is a cancer-specific quality of life questionnaire.

Previously we also saw that patients had their heart affected have a worse quality of life.[59] DBCd also reduced amyloid protein deposits in the heart in 57% of patients after one year of treatment,

compared to 28% with BCd.[51] We know that reducing amyloid levels in the blood protects organs from a new build-up of amyloid. This is especially important for the heart, where pumping strength is closely linked to quality of life.[55]

3f) Safety of the medicine and side effects

When a regulatory or HTA body makes a decision about a medicine, it will pay close attention to the benefits of the medicine in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this medicine, and include benefit/risk assessment details where possible. This will support patient group reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen and how they could potentially be managed. Where appropriate and relevant to patients, please also highlight risk reduction comparisons with other treatments.

Where it will add value or context for patient readers please included references to the Summary of Product Characteristics from regulatory agencies etc.

Each medicine has its own side effects, and the same medicine can produce different reactions in different people. Both DBCd and BCd were generally well tolerated treatment options. However, about 4% of patients stopped taking either treatment because of side effects).[51]

In both treatment groups, the most common side effects in the ANDROMEDA study (in more than 25% of patients) included:

Side effect	**Symptoms**	**% of patients who have had this side effect (number out of 100)**
Diarrhoea	Passing of loose or watery stools more than three times a day[60]	35.8%
Peripheral oedema	Swelling of the legs or arms caused by excess fluid in body tissues	36.3%
Constipation	Having difficulty emptying their bowels	35.8%
Peripheral sensory neuropathy	Weakness, numbness, or pain in the hands or feet	33.7%
Fatigue	Feeling extreme tiredness, lethargy or exhaustion, which persists most or all of the time[61]	27.5%
Nausea	Feeling queasy, unease and discomfort in the upper stomach, with an urge to throw up or be sick[60]	28%
Infections at nose, sinuses, pharynx, or larynx.	Symptoms could be nasal obstruction, sore throat or fever. An infection occurs when disease causing organisms, or 'germs', such as bacteria, fungi or viruses enter the body and begin to multiply[62]	25.9%

The appearance of more serious (also called "Grade 3 or 4") adverse events was similar between the DBCd and BCd groups.[51] The most common serious side events were infections (10.1% compared to 19.2% in DBCd), decrease blood cells (17.6% compared to 18.1% in DBCd), metabolism disorders (mainly decrease in potassium blood levels) (15.4% compared to 13% in DBCd).[51]

Managing side effects

The side effects of DBCd can be managed by treatments such as: blood transfusions, antibiotics, and medicines to control the movements of the gut.

Patients who have side effects due to the reduction of blood cells are effectively managed by:

- blood transfusions (the transfer of blood from a donor to the patient), and
- growth factors (a type of supportive medicine that stimulates the bone marrow to make blood cells).[63]

Other measures include delaying dosing schedules and changing the doses of treatment. From the ANDROMEDA study, we know that, compared to BCd alone, adding daratumumab to BCd did not increase the level of side effects that would make patients stop treatment early.[53]

3g) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the medicine. Please provide a top-level summary for each, such as title, location, patient group size, completion dates etc.

The following table shows you eight clinical trials to date about daratumumab in AL amyloidosis. Six are ongoing and two have been completed. This information was taken from Clinicaltrials.gov website (www.clinicaltrials.gov) on 11 June 2021.

Study name	**Phase**	**Location**	**Patient group AL Amyloidosis patients**	**N**	**Treatments studied**	**Expected completion date**
NCT02841033[64]	I- II	United States	Newly diagnosed and previously treated patients	22	Daratumumab	completed
NCT04895917[65]	II	Italy	Previously treated patients with other therapies not including daratumumab	40	Daratumumab and pomalidomide	2024
NCT04474938[66]	II	China	Newly diagnosed and previously treated patients	40	Daratumumab Bortezomib and Dexamethasone	2024
NCT02816476[67]	II	France Italy	Newly diagnosed and previously treated patients	40	Daratumumab	completed
NCT04131309[68]	II	France Greece Italy Netherlands	Newly diagnosed patients	40	Daratumumab, Bortezomib and Dexamethasone	2023
NCT03283917[69]	I	United States	Newly diagnosed and previously treated patients	20	Daratumumab Ixazomib and dexamethasone	2022
NCT04270175[70]	II	United States	Previously treated Patients	21	Daratumumab, pomalidomide, and dexamethasone	2025
NCT04303144[71]	II	United States	Newly diagnosed and previously treated patients	25	Part A: CAEL-101 + CyBorD Part B: CAEL-101 +DBCd	2023

3h) Summary of key benefits to patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the medicine for patients, caregivers and their communities when compared with current medicines
- Please outline any data from the clinical trials listed above that support this
- This should inform any relevant cost or value considerations in the following section (3j)

The key benefits of daratumumab to AL amyloidosis patients, carers and society include:

- **Rapid reduction of patient´s amyloid in blood,** which can lead to a longer and better quality of life [72,73]
- **Prevention of cardiac and renal (kidney) damage** for a prolonged period of time, which leads to improvements in patients' quality of life
- **Improvements** to patients' **symptoms of disease for example fatigue**[73]
- Prevents relapses through a **sustained control of the disease**[52]

The subcutaneous daratumumab formulation can be administered quickly to patients.

3i) Value and economic considerations (this section may be considered as not relevant in some countries or HTA assessments and can be deleted by the HTA body in those cases)

Introduction for patient groups:

Health services want to get the most value from their budget and therefore needs to decide whether a new medicine provides good value compared with other medicines. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the medicines already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the HTA appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g. whether you feel these are the relevant endpoints, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or adverse events of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g. travel costs, time-off work)?

Instructions to manufacturer: This is intended as a single-page summary for patient groups and needs to be completed in non-technical language. Focus should be on a summary of the key costs/drivers used in any models, the value afforded by the medicine, and any financial implications that may be of relevance to patients/patient groups, rather than a detailed health economic justification (cost/QALY, for example).

- What were the important improvements in health from the medicine compared with the medicines already in use that support its value offering (e.g. longer survival times or reduction in severity or frequency of symptoms)? Were there important side effect differences between the medicines that support the value of the medicine?
- Would the medicine lead to any cost implications (positive or negative) for the health service (e.g. number of days in hospital)?
- Are there any important differences in the way the medicine is given compared with those already in use that will affect the experience of the patient or costs to the health service or patients (e.g. where it is given or the monitoring that is needed)?

Daratumumab meets an urgent, unmet need for effective treatment options for patients with AL Amyloidosis

- There is a high unmet need for a new treatment for AL Amyloidosis patients, especially for those patients with difficult-to-treat disease such as with cardiac or renal involvement.[74,75] The value of DBCd for patients with AL Amyloidosis is compelling for patients, carers and the NHS.

Main advantage to patients, carers and the health service

Based on available data from the ANDROMEDA study, we have found DBCd to be able to:

- Reduce patients' amyloid in their blood. This amyloid reduction leads to improvements to patients' symptoms of disease (for example, fatigue)
- Reduce patients' amyloid at heart and kidney, improving organ function.
- Work quickly in protecting organs from damage which could lead to dialysis or organ transplantation in the future.
- Improve patient´s quality of life, especially after 24 weeks when BCd treatment is finished, and patients are only treated with daratumumab monotherapy.
- Have a similar frequency on serious side events as BCd, mainly infections, decrease in white blood cells, diarrhoea and swelling in arms and legs.
- Improve organ response that has the potential to reduce disease burden and the use of health care services.[16]

Economic analysis

All of these considerations impact the decision on whether or not DBCd represent good value for money and a good use of NHS resources. Based on the evidence available and the company's economic analysis, daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone would be considered as offering a good use of NHS resources, as a new treatment for patients with newly diagnosed AL Amyloidosis.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patient groups would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the HTA assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.

Further information on health technology assessment (HTA) and the role of patient groups:

- EUPATI guidance on patient involvement in HTA
- EFPIA – Working together with patient groups
- National Health Council Value Initiative
- International Network of Agencies for Health Technology Assessment
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe

Patient groups and charities:

- Myeloma UK
- Myeloma Patients Europe
- AmyloidosisAlliance

Further information about AL Amyloidosis

- Video_MyelomaUK_Prof.Wechalekar_An Overview of AL Amyloidosis
- Video_ALAmyloidosisResearchConsortium_Understanding_AL Amyloidosis
- Video_MyelomaUK_ALAmylodosis_OrganInvolvement

- VideoWebinar_MyelomaUK_Impact of myeloma and AL amyloidosis in carers
- Myeloma Patients Europe_Factsheet_ALAmyloidosis
- Myeloma UK_Understanding AL Amyloidosis

Further information on Daratumumab

- Daratumumab_Mechanism of action (Multiple Myeloma)

4b) Glossary of terms

A

Adverse event/Side effect: An unexpected medical problem that arises during treatment with a drug or other therapy. Adverse events may be mild, moderate, or severe[76]

Amyloid. Proteins have a chain shape that needs to be folded in a certain way to be able to function. We call an amyloid protein the one that has not been folded correctly. A build-up of amyloid can make a patient feel sick.

Amyloidosis. The build-up of amyloid in the body.[50]

Antibody: A protein that plays an important role in the body's immune system. Each antibody is unique and recognizes a specific part of a germ or other invader. Antibodies can be custom designed for use as drugs[77]

Antibiotics: A drug used to treat infections caused by bacteria and other microorganisms.[76]

Autologous. A stem cell transplant may be autologous (using a patient's own stem cells that were collected and saved before treatment

B

Biopsy. A process in which a very small part of tissue in the body is removed to look for signs of disease.[78]

Body surface area. A formula to estimate the approximate surface area if height and weight be known.[79]

C

Clinical trial/clinical study: A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical study. When it is called "phase III clinical trial" it tests the safety and how well a new treatment works compared with a standard treatment. For example which group of patients has better survival rates or fewer side effects. In most cases, treatments move into phase III clinical trials only after they meet the goals of phase I and phase II clinical trials. Phase 3 clinical trials may include hundreds of people. Also called phase 3 clinical trial.[76]

Comorbidity: The term used to describe having two or more diseases at the same time.

CT scan / computerized axial tomography scan

A procedure that uses a computer linked to an x-ray machine to make a series of detailed pictures of areas inside the body. The pictures are taken from different angles and are used to create 3-dimensional (3-D) views of tissues and organs. A dye may be injected into a vein or swallowed to help the tissues and organs show up more clearly. A computerized axial tomography scan may be used to help diagnose disease, plan treatment, or find out how well treatment is working. Also called CAT scan, computed tomography scan, computerized tomography, and CT scan.[76]

D

Digestive system: The organs that take in food and liquids and break them down into substances that the body can use for energy, growth, and tissue repair. It also includes the salivary glands, liver, gallbladder, and pancreas, which make digestive juices and enzymes that help the body digest food and liquids.[80]

E

EMA: European Medicines Agency: The regulatory body that evaluates, approves, and supervises medicines throughout the European Union[81]

F

G

H

HTA: Health Technology Assessment (bodies): Bodies that make recommendations groups regarding the financing and reimbursing of new medicines and medical products based on the added value (efficacy, safety, medical resources saving) of a therapy compared to existing ones.

I

Imaging: A process that makes pictures of areas inside the body. Imaging uses methods such as x-rays (high-energy radiation), ultrasound (high-energy sound waves), and radio waves.[76]

Immune modulators: A substance that stimulates or suppresses the immune system and may help the body fight cancer, infection, or other diseases [76]
Immune system: A complex network of cells, tissues, organs, and the substances they make that helps the body fight infections and other diseases[82]
J
K
M
Monoclonal antibody: An antibody produced by a single antibody–producing cell or its descendants, usually referring to such an antibody developed as a medicine[76]
MRI A procedure in which radio waves and a powerful magnet linked to a computer are used to create detailed pictures of areas inside the body. These pictures can show the difference between normal and diseased tissue. MRI makes better images of organs and soft tissue than other scanning techniques, such as computed tomography (CT) or x-ray. MRI is especially useful for imaging the brain, the spine, the soft tissue of joints, and the inside of bones. Also called magnetic resonance imaging, NMRI, and nuclear magnetic resonance imaging
N
Nervous system: The organized network of nerve tissue in the body. It includes the central nervous system (the brain and spinal cord), the peripheral nervous system (nerves that extend from the spinal cord to the rest of the body), and other nerve tissue.[76]
O
P
Proteosome inhibitor: Amyloid-producing cells are particularly sensitive to destruction by proteasome inhibitors.[50] These treatments break down parts of cells called proteasomes, which help destroy the bad proteins inside the cells. By blocking the work of proteasomes, the bad proteins build up to the point where the cells producing them die.
Q
Quality of life. The overall enjoyment of life. Many clinical trials assess the effects of cancer and its treatment on the quality of life. These studies measure aspects of an individual's sense of well-being and ability to carry out activities of daily living[76]
R
S
SF-36 (36-Item Short Form Health Survey). A 36-question survey designed to measure the effects of a disease on a patient's quality of life.[83]
Stage. A description of how severe a disease is.[76]
Stem cell. A cell from which other types of cells develop. For example, blood cells develop from blood-forming stem cells.[76]
Stem cell transplant. The process of providing a patient with healthy stem cells that can replace diseased cells intentionally destroyed by therapy.[76]
Steroid: Steroids help to stop abnormal cells producing amyloid proteins and can also help reduce side effects from chemotherapy
T
Targeted therapy. Treatment that has been designed to fix at specific unhealthy areas in the body, such as cells that produce amyloid, while limiting damage to healthy parts of the body.[84]
Transfusion. Introduction of whole blood or parts of blood into a patient's bloodstream through a vein.[76]
U
V
W
X
X-ray imaging: A procedure that uses a type of high-energy radiation called x-rays to take pictures of areas inside the body. X-rays pass through the body onto film or a computer, where the pictures are made. The tissues and organs usually appear in various shades of black and white because different tissues allow different amounts of the x-ray beams to pass through them. X-ray imaging is used to help diagnose disease and plan treatment. Also called radiography.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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