MSAC application 1806

Marstacimab for routine prophylaxis to prevent bleeding in patients with haemophilia

Application for MBS eligible service or health technology

HPP Application number:

HPP200223

Application title:

Marstacimab for routine prophylaxis to prevent bleeding in patients with haemophilia

Submitting organisation:

PFIZER AUSTRALIA PTY LTD

Submitting organisation ABN:

50008422348

Application description

Succinct description of the medical condition/s:

Haemophilia is an X-linked congenital bleeding disorder caused by deficiency of clotting factor VIII (FVIII) or clotting factor IX (FIX). The characteristic phenotype in haemophilia is the tendency to bleed due to reduced levels of factor concentrate.

Succinct description of the service or health technology:

Marstacimab is a human monoclonal antibody (immunoglobulin G isotype, subclass 1 [IgG1]) for children and adults aged 12 years and over with severe haemophilia A or severe haemophilia B, without inhibitors to FVIII or FIX. It is administered prophylactically as a once-weekly subcutaneous injection, eliminating the need for regular infusions of factor concentrate.

Application contact details

Are you applying on behalf of an organisation, or as an individual?

Organisation

Is the applicant organisation the organisation you are representing in the HPP today?

Yes

Applicant organisation name:

PFIZER AUSTRALIA PTY LTD

Application details

Please select the program through which the health technology would be funded:

National Blood Agreement

Please provide justification for selecting the above program:

Marstacimab is a humanised monoclonal antibody (immunoglobulin G isotype, subclass 1 [IgG1]) administered prophylactically as a once-weekly subcutaneous injection to prevent bleeding in children and adults aged 12 years and over with severe haemophilia A (HMA) or severe haemophilia B (HMB), without inhibitors. The current standard of care for these patients is factor replacement therapy. Patients with HMA also have the option to be treated prophylactically with emicizumab. Factor products and emicizumab are both funded via the National Blood Agreement.

The primary policy objectives of the National Blood Agreement are:
• to provide an adequate, safe, secure and affordable supply of blood products, blood-related products and blood-related services in Australia, and
• to promote the safe, high-quality management and use of blood products, blood-related products and blood-related services in Australia.

As marstacimab will reduce demand for blood products and blood-related services in Australia, its funding will help to meet the primary policy objectives of the National Blood Agreement.

Pfizer did explore the possibility of funding via the PBS in July 2023 (via request of a pre-PBAC meeting) but was advised:

"The Secretariat has reviewed your application and our proposed position is to decline your request at this time, as we do not believe the PBS is the appropriate funding mechanism for marstacimab. We noted your suggested comparators are provided through the National Blood Authority and got in touch with our colleagues at the NBA, who concurred that given the nature of the request and proposed

comparators, that listing through the NBA was likely to be more appropriate."**What is the type of service or health technology?**

Therapeutic

PICO sets

PICO set 1: Severe haemophilia A (FVIII < 1%)

Population

Describe the population in which the proposed health technology is intended to be used:

Marstacimab is intended to treat children and adults aged 12 years and over with severe Haemophilia A (HMA) or severe Haemophilia B (HMB), without inhibitors. Haemophilia is an X-linked congenital bleeding disorder caused by deficiency of coagulation factor VIII (FVIII; HMA) or coagulation factor IX (FIX; HMB). The deficiency is the result of mutations of the respective clotting factor genes, F8 and F9.

Haemophilia is a rare disease. The best estimates of the prevalence of haemophilia, based on the most reliable national patient registry data and recent World Federation of Hemophilia (WFH) annual global surveys, indicate that there are an expected 1,125,000 males with haemophilia worldwide, of whom the majority are undiagnosed. There are an estimated 418,000 males with severe haemophilia (Sirvastava, Santagostino, & Dougall, 2020). In Australia, there are more than 3,000 people diagnosed with haemophilia. Approximately 1 in 6,000 males has HMA and 1 in 25,000 to 30,000 males has HMB (Haemophilia Foundation Australia, 2023).

Haemophilia generally affects males on the maternal side; however, women who carry a genetic mutation in a clotting factor gene may also have reduced factor levels and be classified as having haemophilia. Both F8 and F9 genes are prone to new mutations, and as many as one-third of all cases are the result of spontaneous mutation where there is no prior family history (Sirvastava, Santagostino, & Dougall, 2020).

The characteristic phenotype in haemophilia is the tendency to bleed due to reduced levels of factor concentrate. The normal clotting process is compared to the clotting process in haemophilia in Figure 1 in the attached PICO Set Document. In the normal clotting process, when a capillary is injured, it tightens to slow the bleeding. Platelets

then make a plug to patch the hole, and clotting factors in the plasma knit together to form a clot over the plug. This works to stop the bleeding. In haemophilia, there is not enough factor for the clot to stay together, so bleeding continues for longer than usual (Haemophilia Foundation Australia, 2023).

The severity of bleeding is generally correlated with clotting factor level, as shown in Table 1 in the attached PICO Set Document. A person with haemophilia will have the same level of severity over their lifetime. Within a family, males with haemophilia will also have the same level of severity, i.e., if a grandfather has severe haemophilia and his grandson has inherited haemophilia, the grandson will also have severe haemophilia. However, females with haemophilia may not have the same severity as other females within the same family (Haemophilia Foundation Australia, 2023).

Internal bleeding episodes or "bleeds" are the main problem for most people with haemophilia. Bleeds are most commonly into the joints (70–80% of all bleeds) or muscles (10–20%) (Sirvastava, Santagostino, & Dougall, 2020). They can occur without an obvious cause ("spontaneous") or as a result of injury. If internal bleeding is not treated quickly it will result in pain and swelling which, if repeated over time, can cause permanent damage such as arthritis, chronic pain and loss of mobility (Haemophilia Foundation Australia, 2023). Up to 70% of people with haemophilia report limitations on their ability to do daily activities (Buckner, et al., 2018).

Some bleeds can be life-threatening, for example those which occur intracranially, in the neck or throat, or in the gastrointestinal tract (Sirvastava, Santagostino, & Dougall, 2020). The mortality rate for people with severe haemophilia is 2.4 times that of the general population (Table 2, attached PICO Set Document).

There is a substantial clinical and humanistic burden of disease associated with haemophilia. The key driver of disease burden is chronic arthropathy and pain resulting from repeated bleeding into joints which can limit activities of daily living and independence (O'Hara, et al., 2018). If haemophilia is inadequately treated, this can become apparent in the first one to two decades of life (Sirvastava, Santagostino, & Dougall, 2020). It is thus unsurprising that a high frequency of disease-related anxiety and depression is reported for haemophilia in the literature. The impact of haemophilia on health-related quality of life (HRQoL) is reported to be similar to other chronic diseases such as rheumatoid arthritis and diabetes (D'Angiolella, 2018), with those with more severe disease generally the most impacted (Carroll, et al.,

2019).

In addition to the humanistic burden, haemophilia is associated with an increased risk for numerous other acute and chronic conditions including arthritis, osteoporosis, obesity, anaemia, kidney disease and haemorrhagic stroke (National Hemophilia Foundation, 2019).

Select the most applicable Medical condition terminology (SNOMED CT):

Severe hereditary factor VIII deficiency disease without inhibitor

Intervention

Name of the proposed health technology:

Marstacimab is a human monoclonal antibody (immunoglobulin G isotype, subclass 1 [IgG1]) for children and adults aged 12 years and over with severe HMA or severe HMB, without inhibitors. It is administered prophylactically as a once-weekly subcutaneous injection, eliminating the need for regular infusions of factor concentrate.

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:

For patients with severe HMA, the nominated comparators are emicizumab (Hemlibra) and factor replacement therapy in the form of FVIII prophylaxis.

Like marstacimab, emicizumab is a humanised antibody delivered prophylactically as a subcutaneous injection, eliminating the need for factor prophylaxis. It was the treatment used by 52% of children and adults aged 12 years and older with severe HMA in 2021-22 (National Blood Authority, 2023b). The same ABDR analyses reported that 63% of this population were receiving FVIII prophylaxis in 2021-22, and 10% were receiving FVIII on-demand (in response to bleeding). Totals do not sum to 100% as some patients were treated under multiple regimens (i.e., a proportion of patients with severe HMA receiving factor product were also receiving emicizumab). Based on utilisation reported for emicizumab, the maximum size of the severe HMA population aged 12 years and older receiving factor product only (without

emicizumab) was 48%.

The ABDR report for 2022-23 (Table 6) found that average yearly FVIII consumption for patients with severe HMA (n=758) was 1,753 IU/kg (National Blood Authority, Dec 2023). Similar to HMB, both SHL and EHL factor products are available for HMA. In 2021-22, the majority (n=225 [39.9%]) of adults with HMA on a prophylaxis regimen were using Eloctate, a recombinant EHL product (National Blood Authority, 2023). Other recombinant FVIII products used for prophylaxis included Xyntha (SHL; n=113 [20.0%]), Adynovate (EHL; n=111 [19.7%]) and Advate (SHL; n=104 [18.4%]). Overall, 59.5% of adults were using an EHL product and 38.5% were using an SHL product. A small proportion of HMA patients (n=11 [2.0%]) were using Biostate, a plasma-derived FVIII product, for prophylaxis.

Outcomes

Outcome description:

The Phase 3 "BASIS" clinical trial (B7841005) is the pivotal trial which will inform the clinical claims for marstacimab (described in the attached PICO Set Document). Endpoints of BASIS related to efficacy, health-related quality of life (HRQoL) and resource use (factor products and bypassing agents) will inform health benefits, while safety endpoints will inform any health harms.

The primary efficacy endpoint of BASIS, and key health outcome which will inform the clinical efficacy claims, is annualised bleeding rate (ABR) of treated bleeding events. This was derived for each subject using the following formula: ABR = number of bleeds requiring treatments / (days on treatment period/365.25). The trial was powered in the non-inhibitor cohort to detect both superiority of marstacimab prophylaxis over on-demand treatment with FVIII or FIX replacement, and non-inferiority and superiority of marstacimab prophylaxis over FVIII or FIX prophylaxis, using within-subject comparison.

Secondary efficacy endpoints of BASIS included incidence of joint bleeds, target joint bleeds, spontaneous bleeds, and total bleeds; change in joint health, and HRQoL measures. Data for these endpoints will support the clinical efficacy claims.

Safety endpoints of BASIS included adverse events (AEs) and serious adverse events (SAEs), thrombotic events, injection site reactions, and development of anti-drug antibodies. Data for safety endpoints will inform the clinical safety claims for

marstacimab. A summary of outcomes and claims is presented in Table 4 of the attached PICO Set Document.

The BASIS trial made its assessment of efficacy and safety for marstacimab versus factor therapy (each patient acted as his or her own control). As such, evidence will be directly applicable to the clinical claims versus factor prophylaxis in HMA. An indirect treatment comparison (ITC) will be required to establish clinical claims for marstacimab versus emicizumab. The primary efficacy endpoint of BASIS (ABR of treated bleeds) was also the primary efficacy endpoint of the HAVEN clinical trials of emicizumab. This endpoint will be used in the main ITC, with secondary efficacy and safety endpoints indirectly compared between the trials when clinically and statistically appropriate.

Change in Patient Management

Preparation for using marstacimab: None.

Use of marstacimab: No other healthcare resources are required to be used in conjunction with marstacimab. As marstacimab is self-administered via a pen device, fewer healthcare resources will be used versus factor replacement therapy, particularly when considering patients who receive their infusions at an Haemophilia Treatment Centre (HTC) (e.g., syringes, swabs, HCP time, overheads). No significant change in healthcare resource utilisation is expected between patients who use marstacimab and those with HMA currently using emicizumab.

After marstacimab: Healthcare resource utilisation after treatment with marstacimab is expected to be lower than for patients currently receiving factor prophylaxis, given patients will no longer be required to undergo routine inhibitor testing. Healthcare resource utilisation after marstacimab and emicizumab is expected to be similar.

Specified restrictions for funding

Proposed item:

AAAAA

Is the proposed item restricted?

Yes - restricted

Provide a short description of the restriction:

Children and adults aged 12 years and older with severe HMA (FVIII < 1%), without inhibitors.

Please draft a proposed restriction to define the population and health technology usage characteristics that would define eligibility for funding:

Pfizer seeks listing for marstacimab on the National Products List (NPL), funded by the National Blood Authority (NBA), similar to emicizumab (Hemlibra). Thus, no MBS item number is proposed.

Reimbursement is sought for children and adults aged 12 years and older with severe HMA (FVIII < 1%), without inhibitors. This population aligns with the population included in the pivotal clinical trial (BASIS; described in Section of 8 of the attached PICO Set Document).

Proposed price of supply:

$0.00

Indicate the overall cost per patient of providing the proposed health technology:

$0.00

Provide details and explain:

Price for marstacimab is not yet available. This will be included in the ADAR submission.

How is the technology / service funded at present? (For example: research funding; State-based funding; self-funded by patients; no funding or payments):

Marstacimab is not currently funded.

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

Superior

Please state what the overall claim is, and provide a rationale:

Among children and adults aged 12 years and older with severe HMA (FVIII < 1%) without inhibitors:

- Marstacimab has superior efficacy to FVIII prophylaxis and non-inferior efficacy to emicizumab in terms of annualised bleeding rate of treated bleeds; and
- Marstacimab has a non-inferior safety profile to FVIII prophylaxis and emicizumab in terms of adverse events.

This is in line with evidence from the pivotal BASIS trial of marstacimab, and the HAVEN 3 clinical trial of emicizumab.

Estimated utilisation

Estimate the prevalence and/or incidence of the proposed population:

Haemophilia is a rare disease. The best estimates of the prevalence of haemophilia, based on the most reliable national patient registry data and recent World Federation of Hemophilia (WFH) annual global surveys, indicate that there are an expected 1,125,000 males with haemophilia worldwide, of whom the majority are undiagnosed. There are an estimated 418,000 males with severe haemophilia (Sirvastava, Santagostino, & Dougall, 2020). In Australia, there are more than 3,000 people diagnosed with haemophilia. Approximately 1 in 6,000 males has HMA and 1 in 25,000 to 30,000 males has HMB (Haemophilia Foundation Australia, 2023).

Haemophilia generally affects males on the maternal side; however, women who carry a genetic mutation in a clotting factor gene may also have reduced factor levels and be classified as having haemophilia. Both F8 and F9 genes are prone to new mutations, and as many as one-third of all cases are the result of spontaneous mutation where there is no prior family history (Sirvastava, Santagostino, & Dougall, 2020).

Current Australian Estimates

Patients proposed to be eligible for reimbursed treatment with marstacimab are children and adults aged 12 years and over with severe HMA (FVIII < 1%) or severe HMB (FIX < 1%), without inhibitors. Data from analyses requested from the Australian Bleeding Disorders Registry (ABDR) in June 2023 (National Blood Authority, 2023b) reported the size of the HMA population as follows (based on 2021-22 data; note that the numbers below reflect the size of the population aged ≥ 12 years):

- Severe HMA: 561
- Severe HMA without inhibitors*: 488

* Estimated as 87% of HMA population: hereditary HMA with inhibitors (n=146) / hereditary HMA who received factor product (n=1149) = 13% (ABDR 2022-23)

Provide the percentage uptake of the proposed health technology by the proposed population:

Year 1 estimated uptake (%):

See below

Year 2 estimated uptake (%):

See below

Year 3 estimated uptake (%):

See below

Year 4 estimated uptake (%):

See below

Estimate the number of patients who will utilise the proposed technology for the first full year:

33

Optionally, provide details:

In HMA, marstacimab is expected to replace use of FVIII prophylaxis in some patients, and a small number of patients treated with either emicizumab or FVIII on-demand.

Utilisation will be estimated by calculating the expected uptake among newly eligible patients with severe HMA without inhibitors (i.e., those turning 12 years of age) and those who would already be eligible for marstacimab at the time of listing. The uptake rate is expected to be higher among younger, newly eligible patients than older, established patients, based on the utilisation experience in emicizumab (National Blood Authority, 2023b). Uptake is also expected to be higher in HMB relative to HMA due to the availability of emicizumab in HMA.

Initial estimates of marstacimab utilisation are based on the annual ABDR reports,

physician input and local patient interviews. In HMA, 33 patients are estimated to use marstacimab in the first year of listing, increasing to 187 patients in the fourth year of listing, based on the following uptake rates:
- Newly eligible patients with severe HMA:
Year 1: 20%; Year 2: 25%; Year 3: 30%; Year 4: 35%
- Established patients with severe HMA:
Year 1: 5%; Year 2: 10%, Year 3: 10%, Year 4: 5%

The utilisation estimates will be refined ahead of the full MSAC submission.

Will the technology be needed more than once per patient?

Yes, multiple times

Over what duration will the health technology or service be provided for a patient? (preferably a number of years):

Ongoing weekly administration at 150 mg.

What frequency will the health technology or service be required by the patient over the duration? (range, preferably on an annual basis):

Weekly.

PICO set 2: Severe haemophilia B (FIX < 1%)

Population

Describe the population in which the proposed health technology is intended to be used:

Marstacimab is intended to treat children and adults aged 12 years and over with severe Haemophilia A (HMA) or severe Haemophilia B (HMB), without inhibitors. Haemophilia is an X-linked congenital bleeding disorder caused by deficiency of coagulation factor VIII (FVIII; HMA) or coagulation factor IX (FIX; HMB). The deficiency is the result of mutations of the respective clotting factor genes, F8 and F9.

Haemophilia is a rare disease. The best estimates of the prevalence of haemophilia, based on the most reliable national patient registry data and recent World Federation of Hemophilia (WFH) annual global surveys, indicate that there are an expected 1,125,000 males with haemophilia worldwide, of whom the majority are undiagnosed. There are an estimated 418,000 males with severe haemophilia (Sirvastava, Santagostino, & Dougall, 2020). In Australia, there are more than 3,000 people diagnosed with haemophilia. Approximately 1 in 6,000 males has HMA and 1 in 25,000 to 30,000 males has HMB (Haemophilia Foundation Australia, 2023).

Haemophilia generally affects males on the maternal side; however, women who carry a genetic mutation in a clotting factor gene may also have reduced factor levels and be classified as having haemophilia. Both F8 and F9 genes are prone to new mutations, and as many as one-third of all cases are the result of spontaneous mutation where there is no prior family history (Sirvastava, Santagostino, & Dougall, 2020).

The characteristic phenotype in haemophilia is the tendency to bleed due to reduced levels of factor concentrate. The normal clotting process is compared to the clotting process in haemophilia in Figure 1 in the attached PICO Set Document. In the normal clotting process, when a capillary is injured, it tightens to slow the bleeding. Platelets then make a plug to patch the hole, and clotting factors in the plasma knit together to form a clot over the plug. This works to stop the bleeding. In haemophilia, there is not enough factor for the clot to stay together, so bleeding continues for longer than usual (Haemophilia Foundation Australia, 2023).

The severity of bleeding is generally correlated with clotting factor level, as shown in

Table 1 in the attached PICO Set Document. A person with haemophilia will have the same level of severity over their lifetime. Within a family, males with haemophilia will also have the same level of severity, i.e., if a grandfather has severe haemophilia and his grandson has inherited haemophilia, the grandson will also have severe haemophilia. However, females with haemophilia may not have the same severity as other females within the same family (Haemophilia Foundation Australia, 2023).

Internal bleeding episodes or "bleeds" are the main problem for most people with haemophilia. Bleeds are most commonly into the joints (70–80% of all bleeds) or muscles (10–20%) (Sirvastava, Santagostino, & Dougall, 2020). They can occur without an obvious cause ("spontaneous") or as a result of injury. If internal bleeding is not treated quickly it will result in pain and swelling which, if repeated over time, can cause permanent damage such as arthritis, chronic pain and loss of mobility (Haemophilia Foundation Australia, 2023). Up to 70% of people with haemophilia report limitations on their ability to do daily activities (Buckner, et al., 2018).

Some bleeds can be life-threatening, for example those which occur intracranially, in the neck or throat, or in the gastrointestinal tract (Sirvastava, Santagostino, & Dougall, 2020). The mortality rate for people with severe haemophilia is 2.4 times that of the general population (Table 2, attached PICO Set Document).

There is a substantial clinical and humanistic burden of disease associated with haemophilia. The key driver of disease burden is chronic arthropathy and pain resulting from repeated bleeding into joints which can limit activities of daily living and independence (O'Hara, et al., 2018). If haemophilia is inadequately treated, this can become apparent in the first one to two decades of life (Sirvastava, Santagostino, & Dougall, 2020). It is thus unsurprising that a high frequency of disease-related anxiety and depression is reported for haemophilia in the literature. The impact of haemophilia on health-related quality of life (HRQoL) is reported to be similar to other chronic diseases such as rheumatoid arthritis and diabetes (D'Angiolella, 2018), with those with more severe disease generally the most impacted (Carroll, et al., 2019).

In addition to the humanistic burden, haemophilia is associated with an increased risk for numerous other acute and chronic conditions including arthritis, osteoporosis, obesity, anaemia, kidney disease and haemorrhagic stroke (National Hemophilia Foundation, 2019).

Select the most applicable Medical condition terminology (SNOMED CT):

Hereditary factor IX deficiency disease without inhibitor

Intervention

Name of the proposed health technology:

Marstacimab is a human monoclonal antibody (immunoglobulin G isotype, subclass 1 [IgG1]) for children and adults aged 12 years and over with severe HMA or severe HMB, without inhibitors. It is administered prophylactically as a once-weekly subcutaneous injection, eliminating the need for regular infusions of factor concentrate.

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:

For patients with severe HMB, the nominated comparator is factor replacement therapy in the form of FIX prophylaxis.

In haemophilia, prophylaxis involves the regular IV infusion of the missing clotting factor (FVIII in HMA and FIX in HMB), given to increase factor levels and reduce bleeding frequency. The focus of prophylaxis is primarily to prevent joint bleeds and maintain musculoskeletal health (Sirvastava, Santagostino, & Dougall, 2020).

FIX prophylaxis is the standard of care for the majority of patients with severe HMB (FIX < 1%) in Australia. Data from the Australian Bleeding Disorders Registry (ABDR) for 2021-22 found that 92% of patients aged 12 years and older with severe HMB were receiving factor product, with 86% on a prophylaxis regimen (National Blood Authority, 2023b). The remaining 14% received factor product "on-demand," i.e., in response to bleeding rather than as a preventative measure. On-demand factor therapy could be considered as a secondary comparator for marstacimab.

Recombinant factor is the most widely used type of concentrate in Australia as it contains little to no material from human blood or animals. In HMB it is the product used by 99% of patients, while the remaining 1% use plasma-derived factor product (Mason, Parikh, Rowell, & McRae, 2018). Both recombinant and plasma products are

listed on the National Products List (NPL), managed by the National Blood Authority (NBA).

There are two types of recombinant factor product available in Australia: standard half-life (SHL) and extended half-life (EHL). Table 3 in the attached PICO Set Document shows conventional dosing regimens for factor prophylaxis with SHL products. It is not yet determined what constitutes high-, intermediate-, and low-dose prophylaxis with EHL products, but overall, EHLs allow people with haemophilia to reduce the number of infusions needed to achieve levels of protection similar to SHLs, or to increase levels of bleed protection with a similar number of infusions, or a combination of both. Dosing regimens with either product type should be adjusted based on patient response (Sirvastava, Santagostino, & Dougall, 2020).

The ABDR report for 2022-23 (Table 7) found that average yearly FIX consumption for patients with severe HMB (n=114) was 2,952 IU/kg (National Blood Authority, Dec 2023). The amount of product consumed varies between patients due to age, physical activity level, type of factor product used (SHL vs EHL) and healthcare professional (HCP) practices.

The FIX product used by the majority of HMB patients for prophylaxis in 2021-22 was Alprolix, an EHL product (n=103 [80.5%]), followed by BeneFIX, an SHL product (n=25 [19.5%]). No other FIX products were used by Australian HMB patients for prophylaxis in 2021-22 (National Blood Authority, 2023) or 2022-23 (National Blood Authority, Dec 2023).

Outcomes

Outcome description:

The Phase 3 "BASIS" clinical trial (B7841005) is the pivotal trial which will inform the clinical claims for marstacimab (described in the attached PICO Set Document). Endpoints of BASIS related to efficacy, health-related quality of life (HRQoL) and resource use (factor products and bypassing agents) will inform health benefits, while safety endpoints will inform any health harms.

The primary efficacy endpoint of BASIS, and key health outcome which will inform the clinical efficacy claims, is annualised bleeding rate (ABR) of treated bleeding events. This was derived for each subject using the following formula: ABR = number of bleeds requiring treatments / (days on treatment period/365.25). The trial was

powered in the non-inhibitor cohort to detect both superiority of marstacimab prophylaxis over on-demand treatment with FVIII or FIX replacement, and non-inferiority and superiority of marstacimab prophylaxis over FVIII or FIX prophylaxis, using within-subject comparison.

Secondary efficacy endpoints of BASIS included incidence of joint bleeds, target joint bleeds, spontaneous bleeds, and total bleeds; change in joint health, and HRQoL measures. Data for these endpoints will support the clinical efficacy claims.

Safety endpoints of BASIS included adverse events (AEs) and serious adverse events (SAEs), thrombotic events, injection site reactions, and development of anti-drug antibodies. Data for safety endpoints will inform the clinical safety claims for marstacimab. A summary of outcomes and claims is presented in Table 4 of the attached PICO Set Document.

The BASIS trial made its assessment of efficacy and safety for marstacimab versus factor therapy (each patient acted as his or her own control). As such, evidence will be directly applicable to the clinical claims in HMB where factor prophylaxis is the comparator.

Change in Patient Management

Preparation for using marstacimab: None.

Use of marstacimab: No other healthcare resources are required to be used in conjunction with marstacimab. As marstacimab is self-administered via a pen device, fewer healthcare resources will be used versus factor replacement therapy, particularly when considering patients who receive their infusions at an Haemophilia Treatment Centre (HTC) (e.g., syringes, swabs, HCP time, overheads).

After marstacimab: Healthcare resource utilisation after treatment with marstacimab is expected to be lower than for patients currently receiving factor prophylaxis, given patients will no longer be required to undergo routine inhibitor testing.

Specified restrictions for funding

Proposed item:

AAAAA

Is the proposed item restricted?

Yes - restricted

Provide a short description of the restriction:

Children and adults aged 12 years and older with severe HMB (FIX < 1%), without inhibitors.

Please draft a proposed restriction to define the population and health technology usage characteristics that would define eligibility for funding:

Pfizer seeks listing for marstacimab on the National Products List (NPL), funded by the National Blood Authority (NBA). Thus, no MBS item number is proposed.

Reimbursement is sought for children and adults aged 12 years and older with severe HMB (FIX < 1%), without inhibitors. This population aligns with evidence in the pivotal clinical trial (BASIS; described in Section of 8 of the attached PICO Set Document).

Proposed price of supply:

$0.00

Indicate the overall cost per patient of providing the proposed health technology:

$0.00

Provide details and explain:

Price for marstacimab is not yet available. This will be included in the ADAR submission.

How is the technology / service funded at present? (For example: research funding; State-based funding; self-funded by patients; no funding or payments):

Marstacimab is not currently funded.

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

Superior

Please state what the overall claim is, and provide a rationale:

Among children and adults aged 12 years and older with severe HMB (FIX < 1%) without inhibitors:

- Marstacimab has superior efficacy to FIX prophylaxis in terms of annualised bleeding rate of treated bleeds; and
- Marstacimab has a non-inferior safety profile to FIX prophylaxis in terms of adverse events.

This is in line with evidence from the pivotal BASIS trial of marstacimab.

Estimated utilisation

Estimate the prevalence and/or incidence of the proposed population:

Haemophilia is a rare disease. The best estimates of the prevalence of haemophilia, based on the most reliable national patient registry data and recent World Federation of Hemophilia (WFH) annual global surveys, indicate that there are an expected 1,125,000 males with haemophilia worldwide, of whom the majority are undiagnosed. There are an estimated 418,000 males with severe haemophilia (Sirvastava, Santagostino, & Dougall, 2020). In Australia, there are more than 3,000 people diagnosed with haemophilia. Approximately 1 in 6,000 males has HMA and 1 in 25,000 to 30,000 males has HMB (Haemophilia Foundation Australia, 2023).

Haemophilia generally affects males on the maternal side; however, women who carry a genetic mutation in a clotting factor gene may also have reduced factor levels and be classified as having haemophilia. Both F8 and F9 genes are prone to new mutations, and as many as one-third of all cases are the result of spontaneous mutation where there is no prior family history (Sirvastava, Santagostino, & Dougall, 2020).

Current Australian Estimates

Patients proposed to be eligible for reimbursed treatment with marstacimab are

children and adults aged 12 years and over with severe HMA (FVIII < 1%) or severe HMB (FIX < 1%), without inhibitors. Data from analyses requested from the Australian Bleeding Disorders Registry (ABDR) in June 2023 (National Blood Authority, 2023b) reported the size of the HMB population as follows (based on 2021-22 data; note that the numbers below reflect the size of the population aged ≥ 12 years):

- Severe HMB: 90
- Severe HMB without inhibitors*: 88

* Estimated as 98% of the HMB population (Sirvastava, Santagostino, & Dougall, 2020)

Provide the percentage uptake of the proposed health technology by the proposed population:

Year 1 estimated uptake (%):

See below

Year 2 estimated uptake (%):

See below

Year 3 estimated uptake (%):

See below

Year 4 estimated uptake (%):

See below

Estimate the number of patients who will utilise the proposed technology for the first full year:

21

Optionally, provide details:

In HMB, marstacimab is expected to replace use of FIX prophylaxis in some patients, and a small number of patients treated with FIX on-demand.

Utilisation will be estimated by calculating the expected uptake among newly eligible patients with severe HMB without inhibitors (i.e., those turning 12 years of age) and those who would already be eligible for marstacimab at the time of listing. The uptake rate is expected to be higher among younger, newly eligible patients than

older, established patients, based on the utilisation experience in emicizumab (National Blood Authority, 2023b). Uptake is also expected to be higher in HMB relative to HMA due to the availability of emicizumab in HMA.

Initial estimates of marstacimab utilisation are based on the annual ABDR reports, physician input and local patient interviews. In HMB, 21 patients are estimated to use marstacimab in the first year of listing, increasing to 64 patients in the fourth year of listing, based on the following uptake rates:
- Newly eligible patients with severe HMB:
Year 1: 40%; Year 2: 55%; Year 3: 70%; Year 4: 75%
- Established patients with severe HMB:
Year 1: 20%; Year 2: 25%, Year 3: 20%, Year 4: 10%

The utilisation estimates will be refined ahead of the full MSAC submission.

Will the technology be needed more than once per patient?

Yes, multiple times

Over what duration will the health technology or service be provided for a patient? (preferably a number of years):

Ongoing weekly administration at 150 mg.

What frequency will the health technology or service be required by the patient over the duration? (range, preferably on an annual basis):

Weekly.

Consultation

List all entities that are relevant to the proposed service / health technology. The list can include professional bodies / organisations who provide, request, may be impacted by the service/health technology; sponsor(s) and / or manufacturer(s) who produce similar products; patient and consumer advocacy organisations or individuals relevant to the proposed service/health technology.

Entity who provides the health technology/service

- Australian Haemophilia Centre Directors' Organisation (AHCDO)

Entity who may be impacted by the health technology/service

- Roche

Entity relevant to the proposed service/health technology

- Haemophilia Foundation Australia (HFA)

Entity who produces similar products

- Australian Haemophilia Centre Directors' Organisation (AHCDO)

Regulatory information

Would the proposed health technology involve the use of a medical device, in-vitro diagnostic test, radioactive tracer or any other type of therapeutic good?

Yes

Has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)? *(if 'Yes' above)*

Yes

Is the therapeutic good classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

No

Please enter all relevant ARTG IDs:

ARTG ID	ARTG name
438990	HYMPAVZI marstacimab 150mg/mL solution for injection, prefilled pen

Is the intended purpose in this application the same as the intended purpose of the ARTG listing(s)?

Yes