Haematology Subcommittee of PTAC
Meeting held 4 October 2017

(minutes for web publishing)

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Note that this document is not necessarily a complete record of the Haematology Subcommittee meeting; only the relevant portions of the minutes relating to Haematology Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

The Haematology Subcommittee may:

a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical
Schedule and the priority it gives to such a listing;
b) defer a final recommendation, and give reasons for the deferral (such as the supply of
further information) and what is required before further review; or
c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

These Subcommittee minutes will be reviewed at the May 2018 meeting of PTAC.

1. Correspondence and Matters Arising

NOACs

1.1. The Subcommittee noted the paper on novel oral anticoagulants (NOACs, also called direct oral anticoagulants or DOACs) from PHARMAC staff outlining the commercial situation and future options in this market.

1.2. The Subcommittee noted correspondence from Dr Dean Boddington, Cardiologist/Electrophysiologist at BOPDHB, Dr Sue O'Malley, Cardiologist and Clinical Leader of Nuclear Medicine at CDHB and Dr Clive Low, Cardiologist supporting the funding of an alternative NOAC, being either rivaroxaban or apixaban.

1.3. The Subcommittee noted the relative clinical benefits and risks of the NOACs had been widely discussed by PHARMACs clinical advisory committees previously. The Subcommittee considered there was little new trial evidence of value, except the growing real-world data supporting a clinical preference for the NOACs over and above convenience, due to lower rates of major bleeding, particularly intracerebral haemorrhage.

1.4. The Subcommittee considered that there is an unmet clinical need in the patient group who are not able to take dabigatran because of intolerance or contraindications, particularly gastrointestinal intolerance and moderate-severe renal impairment. The Subcommittee estimated this would be around 15% of dabigatran-treated patients, although a higher percentage of patients may currently be continuing to take dabigatran at a reduced dose or experience tolerable adverse events, which may lead to poor compliance or early discontinuation.

1.5. The Subcommittee considered that it would be desirable to have one additional NOAC listed on the Pharmaceutical Schedule.

1.6. The Subcommittee considered that clinicians are unlikely to prescribe NOACs based on the availability of reversal agents, and that given the lower renal clearance of apixaban and rivaroxaban, less bleeding events may be observed in the elderly.

1.7. The Subcommittee noted that there was significant international divergence with New Zealand's NOAC use and considered that it would be appropriate to fund at least two NOACs.

1.8. Members discussed possible restriction criteria for a second NOAC as a second-line alternative to the currently listed dabigatran, noting that gastrointestinal disturbance was difficult to define in a robust manner. Various options were raised, including previous MI, gastrointestinal bleeding whilst on dabigatran, requiring a trial of omeprazole or re-challenge in the event of dabigatran-associated dyspepsia, requiring a trial of warfarin (with inability to maintain 70% time in therapeutic range). Members had reservations with all these options, but considered a trial of warfarin might be reasonable, but not preferred, due to the management difficulties and higher bleeding risks.

1.9. The Subcommittee considered the following criteria would be most appropriate:

1. Patient has persistent moderate renal impairment (CrCl <50 ml/min) in the absence of a reversible cause; or

2. Documented evidence of severe and persistent gastrointestinal intolerance requiring discontinuation of dabigatran after an adequate trial period.

1.10. The Subcommittee **recommended** another NOAC was funded for those unable to take dabigatran, especially those with poor renal function, with a medium priority.

Boehringer Ingelheim correspondence regarding March 2016 minutes

1.11. The Subcommittee noted correspondence from Boehringer Ingelheim dated 13 May 2016 received during commercial negotiations for price reductions for dabigatran and the listing of idarucizumab.

1.12. The Subcommittee noted there were a large number of publications on NOACs, of which a number were reviewed by the Subcommittee at their March 2016 meeting. The Subcommittee considered that much of the additional published literature on NOACs provides little additional information of value over that provided by the key clinical trials and meta-analyses. Various publications include minor differences in the rates of outcome and adverse event occurrence, but are not based on new clinical trial evidence. The Subcommittee reiterated their view that dabigatran, apixaban, and rivaroxaban have the same or similar therapeutic efficacy, with similar risks and that switching between the NOACs would be possible.

1.13. The Subcommittee considered the minutes could be published and disagreed with the assertion made by Boehringer Ingelheim that they would cause patients to cease dabigatran anticoagulation as a result.

Posaconazole

1.14. The Subcommittee noted a suggestion from a Paediatric Infectious Diseases Specialist on PHARMACs NPPA Panel for the Subcommittee to consider widened access to posaconazole for the treatment and prophylaxis of invasive fungal infection in high risk haem-oncology patients intolerant to voriconazole and the treatment of microbiologically confirmed mucormycoses / zygomycetes infection.

1.15. The Subcommittee noted that voriconazole and liposomal amphotericin B were available, would generally be appropriate alternatives in the majority of patients and NPPA was available for patients with exceptional clinical circumstances. The Subcommittee considered that no changes were required to the Special Authority criteria for posaconazole at this time.

Enoxaparin DVT prophylaxis in immobilized patients

1.16. The Subcommittee noted correspondence from Dr Nicolas Ribet requesting PHARMAC review whether access to enoxaparin should be widened to patient with lower leg immobilisation. Dr Ribet provided a Cochrane review (Testroote M et al. Cochrane Database Syst Rev. 2014;4:CD006681), which the Subcommittee noted has recently been updated (Zee AA et al. Cochrane Database Syst Rev. 2017;8:CD006681). These reviews concluded that the use of low-molecular-weight heparin significantly reduces VTE when immobilisation of the lower leg is required.

1.17. The Subcommittee also noted the recent trial comparing a prophylactic dose of low-molecular-weight heparin as thromboprophylaxis after knee arthroscopy or lower-leg casting versus no anticoagulant therapy (van Adrichem et al. N Engl J Med. 2017;376:515-525). This study concluded that prophylaxis with low-molecular-weight heparin (for the 8 days after knee arthroscopy or during the full period of immobilisation) was not effective for the prevention of symptomatic venous thromboembolism.

1.18. Given the recent and potentially contradictory evidence of benefit in this setting and large numbers of patients who have a period of lower leg immobilisation, the

Subcommittee **recommended** that widened access to enoxaparin for patients with lower leg immobilisation be discussed as a full agenda item at the next meeting of the Subcommittee.

Aspen Correspondence

1.19. The Subcommittee noted correspondence from Aspen dated 7 June 2016 regarding anticoagulants within its portfolio.

1.20. The Subcommittee noted that Aspen had suggested that nadroparin is very similar to enoxaparin and dalteparin in efficacy, but had an additional benefit in terms of reduced injection site pain, which is explained by the differing salts (calcium rather than sodium). The Subcommittee noted the weight-based dosing of enoxaparin was very familiar to clinicians and there was a safety advantage to only having one low-molecular-weight heparin available. The Subcommittee considered that nadroparin provided no additional health benefit over enoxaparin, and therefore a listing was not required.

1.21. The Subcommittee noted that Aspen had also enquired as to whether there was a need for fondaparinux and danaparoid which were listed in the HML upon creation in 2013. The Subcommittee noted that fondaparinux had traditionally been used in cases of heparin-induced thrombocytopenia, but that dabigatran may now be used as an alternative anticoagulant. The Subcommittee noted that danaparoid has not been available for some time. The Subcommittee considered there was no ongoing need for fondaparinux or danaparoid to remain listed.

2. Ruxolitinib

Application

2.1. The Subcommittee considered a funding application from Novartis New Zealand Limited (Novartis) for a new listing of a Janus Associated Kinase (JAK) inhibitor, ruxolitinib, for the treatment of myelofibrosis in the Pharmaceutical Schedule.

Recommendation

2.2. The Committee **recommended** that ruxolitinib for the treatment of high risk and intermediate-2 risk myelofibrosis, be funded with a high priority.

2.3. The Committee **recommended** that ruxolitinib for the treatment of symptomatic intermediate-1 risk myelofibrosis, be funded with a medium priority.

Discussion

6.5 The Subcommittee noted the minutes of PTACs consideration of ruxolitinib for the treatment of myelofibrosis in November 2016 along with a Technology appraisal guidance by NICE (NICE. 2016;TA386). The Subcommittee considered these provided a good summary of the current evidence for ruxolitinib. The Subcommittee noted that NICE had recommended ruxolitinib for Intermediate-2 and high-risk myelofibrosis.

6.6 The Subcommittee noted risk factors used in the IPSS scoring system included age > 65 years, constitutional symptoms, Hb < 100 g/L, WBC > 25 x 109/L and blood blasts > 1%. The Subcommittee noted the intermediate-1 risk group by IPSS only required one risk factor (i.e. all of those above 65 years), intermendiate-2 required two and high-risk require 3 or more. The Subcommittee considered it was only appropriate to fund the intermediate-1 risk group if symptomatic, rather than just on age for which the median age at presentation is 67 years.

6.7 The Subcommittee considered that there was considerable unmet health need in patients with high risk and intermediate-2 risk myelofibrosis. The Committee noted that myelofibrosis was very difficult to treat and had very few treatment options, which amounted to supportive care only. The Subcommittee noted bone/muscle pain, fatigue/inactivity, pruritis, early satiety, night sweats and abdominal pain and a requirement for transfusional support were common. Current treatments include hydroxyurea, and very occasionally danazoll, but they have limited effectiveness.

6.8 The Subcommittee noted the COMFORT-I randomised double-blind placebo-controlled trial (Verstovsek et al. N Engl J Med. 2012;366:799-802). The Subcommittee noted deaths at the planned cut-off, after a median follow-up of 51 weeks, was 8.4% for ruxolitinib and 15.6% for placebo. The Subcommittee noted this study was limited due crossover design, in which patients were allowed to crossover from the control arms to receive ruxolitinib after only 6 months if splenomegaly worsened. The Committee noted a follow up of COMFORT-I after a median of three years (Verstovsek et al. Haematologica. 2015;100:479-88). The hazard ratio for overall survival when unadjusted for cross-over favoured patients originally randomized to ruxolitinib (hazard ratio 0.69 [95% CI 0.46-1.03; P=0.067) but did not reach statistical significance.

6.9 The Subcommittee noted the open-label COMFORT-II trial and extension phases comparing the efficacy of twice-daily oral ruxolitinib versus best available therapy (BAT) (Harrison et al. N Engl J Med. 2012;366:787-98; Cervantes et al. Blood. 2013;122:4047-53; Harrison et al. Leukemia. 2016;30:1701-7). The Subcommittee noted deaths, after a median follow-up of 151 weeks, were 19.9% for ruxolitinib and 30.1% for BAT. The hazard ratio for overall survival when unadjusted for cross-over favoured patients originally randomized to ruxolitinib (hazard ratio 0.48 [95% CI 0.28-0.85; P=0.009). The Subcommittee noted this study was less limited by crossover as patients were allowed to crossover to receive ruxolitinib after 12 months and BAT was a better control than placebo.

6.10 The Subcommittee noted a pooled analysis of overall survival in COMFORT-I and COMFORT-II (Vannuchi et al. Haematologica 2015;100:1139) and review articles (Martí-Carvajal et al. Cochrane Database Syst Rev. 2015;(4):CD010298; Barosi et al. Onco Targets Ther. 2015;8:1091-102), but considered these provided little additional relevant information.

6.11 The Subcommittee noted a cohort study and related extension study (Verstovsek et al. NEJM 2010;363:1117, Verstovsek et al. Blood 2012;120:1202). Overall survival favoured ruxolitinib compared to a historical control resulting in a hazard ratio of 0.58 (95% CI: 0.39 to 0.85; P=0.005). Survival probability was increased in those with a reduction in spleen length.

6.12 The Subcommittee noted a large cohort study (Al-Ali et al. Haematologica. 2016;101:1065-73) examining the safety and efficacy of ruxolitinib in 1,144 patients. The Committee noted this trial included a separate group with intermediate-1 risk disease and splenomegaly. Of the intermediate-1 risk patient group (n=48), 63.8% and 60.5% of patients achieved a ≥50% reduction from baseline in palpable spleen length at weeks 24 and 48 respectively. The Subcommittee noted the median time to spleen reduction was 4.7 weeks and that patients had 30-40% objective symptom improvement on quality of life scoring systems.

6.13 The Subcommittee noted a small cohort study by Mead et al. (Br J Haematol. 2015;170:29-39) in 48 patients with myelofibrosis, including 14 intermediate-1 risk patients who had a palpable spleen measuring ≥5 cm from the costal margin. The Subcommittee noted that 50% of patients had a reduced spleen size and 21.4% of

patients had a >50% improvement in specific MF symptom score (MF-SAF-TSS) at week 48.

6.14 The Subcommittee considered that ruxolitinib appeared well tolerated. The Subcommittee noted that withdrawal syndrome had been raised as a potential concern by PTAC, however the Subcommittee considered that while it was worthwhile noting, this effect is likely to be rare, manageable with gradual tapering of the dose and would be unlikely to add additional resources compared to the majority of other treatments managed by haematologists. The Subcommittee considered the main area of uncertainly in risk versus benefit related to use in the pre-transplant setting.

6.15 The Subcommittee considered the estimated incidence of primary myelofibrosis of 0.5-1.5 per 100,000 per year (Mesa et al. Am J Hematol. 1999;61:10; Woodliff & Dougan. Med J Aust. 1976;1:523-5) and age-adjusted rates of 0.1 to 0.4 per 100,000 for post-polycythemia vera myelofibrosis and 0.2 to 0.4 per 100,000 for post-essential thrombocythemia myelofibrosis (Mehta et al. Leuk Lymphoma. 2014;55:595-600) could be used to guide patient number estimates. The Subcommittee was not aware of any evidence to suggest this rare disease affects any population groups disproportionally.

6.16 The Subcommittee considered that the COMFORT trials were limited by not being powered to detect a survival benefit, were open-label and had substantial crossover. The Subcommittee however considered that the non-interventional studies support the outcomes observed in the COMFORT trials, and thus there is high likelihood of comparable quality of life and overall survival and gains if ruxolitinib was funded for the New Zealand population.

6.17 The Subcommittee noted that about 50% of patients would be expected to derive significant benefit without significant ADR's and would remain on treatment at 3 years and that at the current proposed price, the cost would be large.

6.18 The Subcommittee noted that a confirmatory bone marrow biopsy was standard practice for the diagnosis and was not required for targeting despite its inclusion in PBS restrictions.

6.19 A Member noted that patients in COMFORT I could move to 25 mg twice day if there was a lack of efficacy, but it was unclear on how many did this and if dose increase was beneficial. In COMFORT II the median dose was 30 mg per day (range, 10 to 49). Members considered a maximum dose of 20 mg twice day would be reasonable if required to limit expenditure.

6.20 The Subcommittee considered the following Special Authority restrictions would be appropriate:

Ruxolitinib – Special Authority for Subsidy – Retail pharmacy
Initial application - only from a haematologist. Approvals valid for 12 months for applications meeting the following criteria:

All of the following:

1. The patient has primary myelofibrosis or post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis; and
2. A maximum dose of two tablets (5 mg, 15 mg or 20 mg) per day; and
3. Either:
   - 3.1. A classification of intermediate-2 and high-risk myelofibrosis according to either the IPSS, DIPSS, or the Age-Adjusted DIPSS; or
   - 3.2. A classification of intermediate-1 risk myelofibrosis according to either the IPSS, DIPSS, or the Age-Adjusted DIPSS and severe disease-related symptoms that are resistant, refractory or intolerant to available therapy.

Renewal only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criterion:

1. The treatment remains appropriate and the patient is benefiting from treatment; and;
2. A maximum dose of two tablets (5 mg, 15 mg or 20 mg) per day.

3. Extended PEG-rFVIII half-life (EHL) haemophilia treatments including funding application for PEG-rFVIII (Adynovate)

Application

3.1. The Subcommittee considered a funding application from Shire New Zealand Limited (Shire) for its extended half-life pegylated recombinant Factor Eight (PEG-rFVIII), for the treatment of Haemophilia A in the Pharmaceutical Schedule.

3.2. The Subcommittee considered a paper from PHARMAC staff applicable to extended half-life haemophilia treatments which sought advice from the Subcommittee on the following aspects:

3.2.1. Consideration of PTAC's August 2017 review of rFVIIIFc and rFIXFc and correspondence from the New Zealand Haemophilia Treaters Group (HTG) on these products

3.2.2. The comparison of PEG-rFVIII to rFVIIIFc

3.2.3. Implementation considerations if extended half-life were to be introduced in advance of the next haemophilia Request for Proposals (RFP), and possible switching considerations within a reasonably short timeframe if this was the outcome of the next RFP.

Recommendation

3.3. The Subcommittee **recommended** that PEG-rFVIII be considered as clinically equivalent to rFVIIIFc for the purposes of funding of an extended half-life rFVIII.

3.4. The Subcommittee **recommended** an extended half-life rFVIII be funded for haemophilia A, with a low priority, but not implemented prior to the next RFP if further treatment changes may be required as part of that process.

3.5. The Subcommittee **recommended** an extended half-life rFIX be funded for haemophilia B, with a medium-high priority, and that a listing could be implemented prior to the next RFP.

Discussion

3.6. The Subcommittee noted minutes from PTAC's August 2017 review of rFVIIIFc and rFIXFc and previous minutes from the Haematology Subcommittee relevant to extended half-life (EHL) haemophilia treatments.

PEG-rFVIII

3.7. The Subcommittee noted PEG-rFVIII was still undergoing Medsafe registration in New Zealand, but given meeting timing and the specialised advice required, PHARMAC had agreed to accept a funding application before this occurs.

3.8. The Subcommittee noted the key trials applicable to PEG-rFVIII that it had not seen previously included Konkle et al. Blood. 2015;126:1078-85; Mullins et al. Haemophilia. 2017;23:238-46 and Brand et al. Haemophilia. 2016;22:251-8.

3.9. The Subcommittee noted that although a direct comparison had not been performed, it was possible to consider the pivotal trial outcomes in children and adult populations. The Subcommittee discussed key outcomes for small numbers of children in Mullins et al. Haemophilia. 2017;23:238-46 compared to Young et al. (J Thromb Haemost. 2015;13:967-77) and for adults in Konkle et al. Blood. 2015;126:1078-85 compared to Mahlangu el al. (Blood. 2014;123:317-25 along with Nolan et al. (Haemophilia. 2016;22:72-80).

3.10. The Subcommittee noted that PEG-rFVIII compared favourably when used prophylactically versus on demand causing a highly clinically significant reduction in the annualised bleeding rate (ABR) from 41.5 to 1.9 in adults. The Subcommittee considered that PEG-rFVIII was effective when used prophylactically twice-weekly, and this was as at least as effective as the established efficacy of short-acting factors used three times weekly.

3.11. The Subcommittee however noted the strength and quality of evidence is low and requires extrapolation from the benefits established for prophylaxis with short-acting factors. There are no long-term studies on joint outcomes, no local studies on infusion frequency impacts, unclear long-term impacts of PEG dosing at this frequency and no information on vial sizes was provided. Although there is no clear evidence, it is reasonable to suggest that there would be reduced breakthrough bleeds and fewer doses required to control established bleeds.

3.12. The Subcommittee noted that it was unclear what would be required for laboratory monitoring in New Zealand, as the submission and the Konkle et al. paper note one-stage clotting and chromogenic assays were used, despite providing similar results. The Subcommittee noted chromogenic assays are not widely available in New Zealand. The Subcommittee considered that population-based pharmacokinetic data should be provided specific to this product if funded to support its use.

3.13. The Subcommittee considered that based on the available evidence, both PEG-rFVIII and rFVIIIFc have the same or similar therapeutic efficacy in both adults and children, with the same or similar risks. The Subcommittee considered there were no notable benefits for PEG-rFVIII over rFVIIIFc. Similar to rFVIIIFc, there appeared to be no increased risk of inhibitory antibodies. There were no PEG-related adverse reactions, but the Subcommittee noted the duration of use in the trials was short.

3.14. The Subcommittee considered that the same population group using rFVIII prophylaxis may benefit from PEG-rFVIII as any reduction in injections would be welcome, although the group most likely to benefit from PEG-rFVIII, and other EHL treatments, would be paediatric patients (due to less injections and possibly not requiring Port-A-Cath insertion), those with difficult intravenous access, those unable to manage three times weekly injections and those with severe haemophilia using only on-demand treatment due to the treatment burden associated with prophylaxis.

General EHL discussion

3.15. The Subcommittee noted a paper on a preliminary real-world usage paper from Canada (Keepanasserlin et al. Haemophilia. 2017:1–2) and that this could potentially better inform a 'conversion factor' that may be used to determine cost-neutrality to short-acting factors at the population level. The Subcommittee noted that this study included small numbers of patients (n=139) compared with the total population (806 with severe and 270 with moderate haemophilia A and 169 with severe and 230 with moderate haemophilia B in 2016) and was centred around a limited number of treatment centres, a single centre treating 54% of the patients. The Subcommittee noted the majority of patients were switched with the aim of improving quality of life or compliance due to reduced infusion frequency rather than aiming for improved clinical outcomes with 69% of those changing being <18 years of age.

3.16. The Subcommittee noted New Zealand current data on usage is lacking. It was reasonable to suggest prophylactic dosing of rFVIII at 25-40 iu/kg/dose 2-3 times weekly and rFIX at 25-40 iu/kg/dose once weekly. The Subcommittee noted that 16 New Zealand patients on rFVIIIFc are on a supplier initiated extension programme and due to rapid on trial dose escalation their doses were likely higher than the New Zealand average.

3.17. The Subcommittee noted that patients are reluctant to switch products if their current treatment is working well, especially if the product they are changing to may be changed again in the near future. The Subcommittee noted there is considerable impact, on both people with haemophilia and Haemophilia Treatment Centres, associated with product changes and there is variability in enthusiasm amongst both patients and treaters for product changes unless there is a likelihood of significant benefits.

3.18. The Subcommittee noted that in the United Kingdom patients are carefully evaluated for suitability to switch and there is a significant monitoring requirement which may place a burden on patients and their families.

3.19. The Subcommittee noted a best-practice switch to an EHL treatment is likely to require initial education, a pharmacokinetic assessment, trough levels after 5-10 treatments, new inhibitor screening and additional follow-ups for the first three months (Collins et al. Haemophilia. 2016;22:487-98).

3.20. The Subcommittee considered access criteria for EHL treatments could include:

- Exclusion: Previously Untreated Patients (PUPs), <2 years of age and <50 exposure days

- Inclusion: Severe or moderate haemophilia A or B with severe bleed phenotype (already on prophylaxis or very frequent bleeding), if on prophylaxis: requiring ≥ 3 injections of short-acting rFVIII per week or ≥ 2 infusions of short-acting rFIX per week, experiencing breakthrough bleeding despite reasonable prophylactic dosing, very frequent bleeding but unwilling to start prophylaxis with short-acting treatments, short-acting treatments leading to a poor quality of life or adherence difficulties due to injection frequency.

3.21. The Subcommittee noted PHARMACs intention to include EHL treatments in the next RFP, which is likely to be run in 2018, and that the end date for the current preferred brand of FVIII is end-February 2019. The Subcommittee discussed the positives and negatives for an interim listing, given that brand changes could potentially be required

depending on the RFP outcome. The Subcommittee considered that given the more substantial potential benefits per patient switched offered by EHL rFIX it would be reasonable to list an EHL rFIX treatment pre-RFP, but on balance, the Subcommittee considered it would be preferable to await a more long-term supply arrangement to give certainty before introducing an EHL rFVIII.

4. Long-acting erythropoietin's for the next RFP

Application

4.1. The Subcommittee considered a clinical information package from Roche Products (New Zealand) Limited (Roche) for their product - methoxy polyethylene glycol epoetin beta (Mircera). This submission was prepared by Roche at the request of PHARMAC staff with the intended purpose of PHARMAC seeking clinical advice to determine whether longer-acting erythropoietin's should be included in the next RFP.

4.2. PHARMAC staff had also received an expression of interest from Amgen about seeking updated clinical advice on their product - darbepoetin alfa (Aranesp).

Recommendation

4.3. The Subcommittee **recommended** that from a haematology perspective, there were no reasons to exclude long-acting erythropoietin's from the next RFP, but given the lack of established health benefits they should only be funded if cost-neutral to short-acting products.

4.4. The Subcommittee **recommended** that PHARMAC seek advice from the Nephrology Subcommittee.

Discussion

4.5. The Subcommittee noted methoxy polyethylene glycol epoetin beta (Mircera) differs from erythropoietin through the integration of an amide bond between either the N-terminal amino group or the ε-amino group of lysine, predominantly Lys52 and Lys45 and methoxy polyethylene glycol butanoic acid. It shows different activity to recombinant erythropoietin at the receptor level. It is characterised by slower association to the receptor and slightly faster dissociation, resulting in a lower affinity for the receptor. This lower affinity may result in less receptor-mediated endocytosis and contribute together with reduced subsequent lysosomal degradation and/or increased recycling to the slower elimination. It thus has a longer half-life (134 or 142 hours after intravenous or sc injection in patients with CRF) than human erythropoietin, which enables it to be administered subcutaneously in a two-weekly or once monthly dosing regimen.

4.6. The Subcommittee noted darbepoetin alfa (Aranesp) is a hyperglycosylated derivative of epoetin; it has a half-life (21 to 70 hours after intravenous or subcutaneous injection respectively in patients with CRF) and can be administered less frequently than epoetin. Darbepoetin can be administered subcutaneously in a two-weekly or once monthly dosing regimen.

4.7. The Subcommittee noted that the longer-acting agents have not generally been used for myelodysplasia or chemotherapy induced anaemia, thus their primary use has been in adult patients with anaemia associated with chronic kidney disease. The Subcommittee considered the subcutaneous administration that the patient can usually self-administer means the health benefits as a result of less injections is likely to be very small.

4.8. The Subcommittee noted there was a lack of head-to-head evidence to inform a product comparison.

4.9. The Subcommittee noted a Cochrane network meta-analysis that included studies up to 2014 (Palmer et al. Cochrane Database Syst Rev;(12):CD010590). The Subcommittee considered the authors' conclusions were appropriate.

4.10. The Subcommittee considered robust product comparisons with respect to clinically relevant endpoints such as Hb, transfusional requirements or adverse-drug reactions are lacking, but based on the available evidence it would be reasonable to assume the same or similar benefits and risks and thus including the products in the RFP and funding if cost-neutral would be to provide greater choice for patients and be useful in some instances.