



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1579 – Emicizumab for routine prophylaxis to prevent or reduce frequency of bleeding episodes in patients with haemophilia A without factor VIII inhibitors

Applicant: Roche Products Pty Ltd

Date of MSAC consideration: MSAC 76th Meeting, 1-2 August 2019

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

An application requesting MSAC advice on including emicizumab on the National Product List managed by the National Blood Authority (NBA) for routine prophylaxis in patients with moderate to severe haemophilia A (HMA, also called congenital factor VIII deficiency) without factor VIII (FVIII) inhibitors, was received from Roche Products Pty Ltd by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported funding of emicizumab via the National Blood Authority on the basis of acceptable clinical effectiveness and safety compared with FVIII in patients with moderate or severe haemophilia A without FVIII inhibitors. MSAC advised on the appropriate prices for different subpopulations it considered should be applied in setting the overall subsidy price and in the calculation of the financial impact of funding. MSAC considered the sponsor's proposed risk sharing arrangement (RSA) was not adequate for addressing risk of use outside the proposed patient population.

Specifically, MSAC advised that this support was subject to pricing negotiations based on the following shadow prices in the re-calculation of weighted average price and the proposed RSA, to be implemented alongside the related shadow prices in the MSAC advice for Application No. 1510.1 (HMA with FVIII inhibitors), and noting that some of the shadow prices relate to possible use of emicizumab beyond that requested:

- patients with severe HMA, but without inhibitors, who previously received FVIII prophylaxis: \$**redacted**/mg [
- patients with severe HMA, but without inhibitors, who previously received FVIII on demand: \$**redacted**/mg
- patients with severe HMA, but without inhibitors, who did not receive any HMA blood product treatment in the preceding year: \$**redacted**/mg

- patients with moderate HMA, but without inhibitors, who previously received FVIII prophylaxis: \$redacted/mg
- patients with moderate HMA, but without inhibitors, who previously received FVIII on demand: \$redacted/mg
- patients with moderate HMA, but without inhibitors, who did not receive any HMA blood product treatment in the preceding year: \$redacted/mg
- patients with mild HMA, but without inhibitors, who previously received FVIII prophylaxis: \$redacted/mg
- patients with mild HMA, but without inhibitors, who previously received FVIII on demand: \$redacted/mg
- patients with mild HMA, but without inhibitors, who did not receive any HMA blood product treatment in the preceding year: \$redacted/mg.

Consumer summary

Roche Products Pty Ltd applied for public funding for routine administration of emicizumab to prevent or reduce the frequency of bleeding episodes in patients with haemophilia A without factor VIII inhibitors.

People with haemophilia A (HMA) cannot clot blood properly, which results in spontaneous bleeds or excessive bleeding from injury. People with severe or moderate HMA are often treated with the clotting factor VIII (FVIII) on a regular basis to reduce rates of bleeding (prophylaxis), or only receive FVIII when they have bleeding (treatment on demand). People with mild HMA may only require treatment with FVIII when they have a bleeding episode (treatment on demand).

This application is for emicizumab, a medicine that reduces rates of bleeding, and also reduces the need for FVIII to manage those bleeds which do occur.

MSAC's recommendation to the Commonwealth Health Minister

MSAC considered that emicizumab is easier to administer than FVIII, and is acceptably safe. MSAC supported public funding on the National Product List for people with severe or moderate HMA without FVIII inhibitors. However, MSAC advised that the application did not justify the expense of emicizumab for all patients, and this supportive advice was subject to pricing negotiations with the applicant.

3. Summary of consideration and rationale for MSAC's advice

MSAC recalled its consideration of Application 1510 (HMA with FVIII inhibitors) at its November 2018 meeting, where it accepted that emicizumab decreases bleed frequency. However, MSAC had queried the cost-effectiveness of emicizumab for that population, as it was compared with bypass agents (BPAs) which had a high cost per patient and had not been assessed for cost-effectiveness. MSAC noted the resulting high cost of emicizumab per patient, and considered that this cost would need to decrease before it could consider emicizumab to be acceptably cost-effective for the population with FVIII inhibitors.

For the requested moderate to severe HMA population without FVIII inhibitors requested in this Application 1579, MSAC noted the clinical need for emicizumab, and its acceptable safety profile and ease of administration, which is both less invasive than FVIII and less frequently injected when given as prophylaxis. It reduces the risk of bleeds in HMA,

eliminates the peaks and troughs of FVIII concentration currently seen when using FVIII prophylaxis, and reduces the risk of developing FVIII inhibitors.

MSAC advised that the most convincing clinical evidence comparing emicizumab with FVIII came from the randomised comparison against FVIII given on demand in adult patients with severe HMA in HAVEN 3, which showed reduced annualised bleed rates with emicizumab. Given the expected substitution patterns of emicizumab for FVIII, the more relevant but less convincing (non-randomised) comparisons of emicizumab versus FVIII prophylaxis were also in adult patients with severe HMA, and indirectly suggested varying reduced annualised bleed rates with emicizumab. MSAC further noted that no evidence comparing emicizumab and FVIII in terms of effectiveness was presented for the smaller subpopulations of paediatric patients and/or patients with moderate HMA. MSAC advised that the evidence in adults could be extrapolated to the paediatric population, and that the extrapolation of the evidence for reductions in annualised bleed rates across patients receiving prophylaxis in severe HMA to patients receiving prophylaxis in moderate or mild HMA should be on the basis of assuming a constant relative reduction applying to different annualised bleed rates with FVIII prophylaxis.

MSAC advised that the application's economic evaluation provided an acceptable basis for calculating a price for emicizumab of **\$redacted**/mg that results in a cost per patient just less than that for FVIII prophylaxis in severe HMA. MSAC accepted that the calculation of this cost-minimisation approach was acceptable because it also estimated cost offsets of FVIII management of bleeds (2% of total costs) from the inpatient before-and-after comparison, rather than from the indirect comparison.

However, MSAC did not accept that this approach justified the use of this price for emicizumab in the other requested subpopulations of patients with moderate HMA and/or patients currently receiving FVIII on demand. In addition, MSAC did not accept the inference that this approach justified the use of this price for emicizumab in the subpopulations of HMA beyond those requested, including patients with mild HMA and/or patients with HMA who did not receive any HMA blood product in the previous year.

The applicant initially estimated that a maximum of 100% of patients with severe and moderate HMA on FVIII prophylaxis treatment would switch to emicizumab after the first year of funding. In the related application 1510.1, the applicant then revised its uptake estimate for adults to 60% based on clinical input and international experience, but did not present evidence to support either estimate. MSAC considered that at least 80% of this subpopulation would likely switch to emicizumab if it were available.

The related re-application 1510.1 proposed a weighted average price arrangement across the requested HMA subpopulations with and without FVIII inhibitors and an associated risk sharing arrangement (RSA). MSAC noted the applicant's proposed shadow price of **\$redacted**/mg for all requested patients without inhibitors and **\$redacted**/mg for all requested patients with inhibitors in year 1 (estimating a weighted average price of **\$redacted**/mg). The shadow price for the population with inhibitors would then decrease each year to **\$redacted**/mg at year 5, with the shadow price for the population without inhibitors remaining the same, giving a weighted average price of **\$redacted**/mg in year 5. These proposed shadow prices were contingent on funding emicizumab for both populations before the end of 2019. The resulting weighted average price would reflect the applicant's estimated ratio of 9% with inhibitors to 91% without inhibitors in the target HMA population. MSAC noted that the population with inhibitors would likely decrease over time, but so slowly as unlikely to affect the 4-year timeframe of the proposed initial RSA. MSAC also

noted that Australian Bleeding Disorders Registry (ABDR) data shows that the proportion of patients with inhibitors is approximately 2% in the overall HMA population, not 9%. MSAC considered that this was a significant difference in estimates and the true proportion needs to be determined.

MSAC noted that the resubmission for application 1510.1 also proposed expenditure caps for emicizumab of **\$redacted** million in year 1 increasing each year to **\$redacted** million in year 5. If an expenditure cap is exceeded, then the lower price of **\$redacted**/mg would apply to all emicizumab usage beyond the cap. MSAC considered this RSA to be inadequate, as it would not disincentivise treating mild patients and thus does not address the concern of leakage beyond the requested subpopulations. MSAC noted that, currently, very few patients with mild HMA are treated prophylactically, but the RSA should still account for emicizumab prophylaxis as a future possibility for such patients. MSAC also noted that the RSA is based on the cost of FVIII. MSAC considered that the cost of FVIII would decrease in the future, and thus the cost of emicizumab could be linked to the falling cost of FVIII.

MSAC advised that using the proposed weighted average price was not adequately justified in economic terms, and would also still result in uncertainties for overall financial impact, as on-demand patients are not accounted for, and leakage into the mild and untreated HMA populations remains a concern. On-demand patients have a higher annualised bleeding rate as compared to those receiving prophylaxis, and treating these bleeds is costly and must be factored into the financial calculations. In addition, the applicant's RSA did not eliminate all financial risks of leakage.

In this context, MSAC also noted the strong consumer and industry support for emicizumab, and their expectations of an increase in patient quality of life and flow-on consequences for families and productivity associated with using it compared with FVIII.

MSAC therefore advised that alternative approaches were needed to generate shadow prices and a revised RSA for emicizumab across all the affected HMA subpopulations, whether requested or not. MSAC further advised that the most recent ABDR data be used in calculating these shadow prices and so the calculations and results of this approach in this MSAC-ratified document were finalised using ABDR data that became available soon after the MSAC meeting itself.

For patients starting emicizumab who previously received prophylaxis, MSAC advised that the shadow price for emicizumab be linked to its ability to reduce annualised bleed rates, noting the consequences of bleeds for patient outcomes and extra costs. MSAC noted the growing clinical trend towards achieving zero annualised bleeds, and accepted this as clinically valuable, and possibly more important clinically. However, MSAC considered that annualised bleed rates have been estimated with greater confidence, and are therefore a preferred basis by which to benchmark shadow prices for emicizumab for patients starting emicizumab who previously received prophylaxis.

At the requested price of **\$redacted**/mg justified by the applicant using a cost- consequences analysis for patients with severe and moderate HMA without inhibitors who previously received prophylaxis, MSAC calculated the cost per annualised bleed averted for severe HMA patients on a cost-minimisation basis from Table 5 is **\$redacted**/(4.8-1.5) = **\$redacted**/mg. The associated relative rate is 0.32 (95% CI: 0.195, 0.514), and the associated relative rate reduction is $1-0.32 = 0.68$.

Applying this cost per annualised bleed averted to the observed annualised bleed rates for non-inhibitor patients with moderate¹ or mild² HMA who previously received FVIII prophylaxis, and assuming a constant relative treatment effect of emicizumab across these varying annualised bleed rates, gives:

- for patients with moderate HMA without inhibitors who previously received FVIII prophylaxis (a requested subpopulation) = **\$redacted** = **\$redacted/mg**
- for patients with mild HMA without inhibitors who previously received FVIII prophylaxis (not a requested subpopulation) = **\$redacted** = **\$redacted/mg**.

Noting that patients starting emicizumab who previously received treatment on demand would have experienced a greater number of bleeds than patients who previously received prophylaxis (and treatment on demand as required for breakthrough bleeds), MSAC advised that the ratio of the existing overall blood product treatment costs for on demand versus prophylaxis use for each of the prophylaxis subpopulations be used to calculate the relative cost per mg for emicizumab on the basis that this grandfathers the relative increase in costs already being paid for prophylaxis over on demand. The basis for the estimates of the overall blood product treatment costs is attached to the PSD for 1510.1, and applying this approach gives:

- for patients with severe HMA without inhibitors who previously received FVIII on demand (a requested subpopulation): **\$redacted** x (**redacted**) = **\$redacted/mg**
- for patients with moderate HMA without inhibitors who previously received FVIII on demand (a requested subpopulation): **\$redacted** x (**\$redacted**) = **\$redacted/mg**
- for patients with mild HMA without inhibitors who previously received FVIII on demand (not a requested subpopulation): **\$redacted** x (**\$redacted**) = **\$redacted/mg**

For patients starting emicizumab who did not receive any HMA blood product treatment in the previous year, MSAC advised that no basis was available to justify any price for emicizumab, so a shadow price of **\$redacted** should be applied for this subpopulation, noting that, like patients with mild HMA, this is a contingency for any use of emicizumab beyond the requested subpopulations, but would reflect a “hard cap” in the RSA.

MSAC further advised that the Department of Health should negotiate with the applicant to finalise how these shadow prices should be aggregated to generate the weighted average price for inclusion in the financial analyses for all requested subpopulations (including patients with inhibitors), and also how they should be best incorporated into the proposed RSA to account for any usage of emicizumab in patients with HMA beyond the requested subpopulations. Noting the proposed 4-year timeframe of this proposed initial RSA, MSAC also advised that the fact of its existence should be public, and it should not inadvertently exclude the possibility of funding other emerging therapies for HMA.

Reflecting the residual uncertainty about expected rates of emicizumab uptake across the subpopulations, MSAC advised that this approach would also inform a review 12 to 24 months after emicizumab listing using data from the ABDR and haemophilia treatment centres to confirm the nature of the previous treatment and the HMA severity for each patient who starts emicizumab. Further, as this approach is most relevant to the prevalent pool of patients at the time that emicizumab is listed, consideration of how this approach might need to deal with incident patients could be considered at the time of this recommended review.

¹ Mean 3.5, range 1.0 to 9.0, from Berntorp. E et al. European retrospective study of real life haemophilia treatment. *Haemophilia* 2017; 23:105-114

² Peyvandi F, Tavakkoli F, Frame D, et al. Burden of mild haemophilia A: Systematic literature review. *Haemophilia*. 2019;00:1–9. <https://doi.org/10.1111/hae.13777>

For implementation purposes, MSAC advised that prescription of funded emicizumab should be limited to haematologists working in Haemophilia Treatment Centres, and that FVIII would still be needed to manage breakthrough bleeds.

4. Background

MSAC has not previously considered this application for emicizumab for patients with moderate to severe HMA without FVIII inhibitors.

MSAC previously considered a related submission for emicizumab for patients with HMA and FVIII inhibitors (Application 1510). A resubmission for this smaller population (Application 1510.1), which also proposed an approach for considering emicizumab for all requested patients with HMA, was considered by MSAC alongside this Application 1579.

5. Prerequisites to implementation of any funding advice

Emicizumab is listed on the Australian Register of Therapeutic Goods (ARTG) for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in adult and paediatric patients with HMA (congenital FVIII deficiency) with and without FVIII inhibitors (Table 1). This is a recent extension (November 2018) of the previous indication which was limited to patients with FVIII inhibitors.

Table 1 Emicizumab products included in the ARTG

Strength, dose form, presentation	ARTG number	ARTG start date
Hemlibra 30 mg/1 mL solution for injection vial	AUST R 293761	23/02/2018
Hemlibra 60 mg/0.4 mL solution for injection vial	AUST R 293760	23/02/2018
Hemlibra 105 mg/0.7 mL solution for injection vial	AUST R 293758	23/02/2018
Hemlibra 150 mg/0.7 mL solution for injection vial	AUST R 293759	23/02/2018

Source: Generated for the Critique from the Australian Register of Therapeutic Goods⁹

Abbreviation: ARTG = Australian Register of Therapeutic Goods

6. Proposal for public funding

The requested inclusion in the National Products List (NPL) is provided in Table 2.

Table 2 Proposed inclusion in the NPL

Product type	Name	Presentation	Supplier	Effective price
Emicizumab	HEMLIBRA®	30 mg/1 mL (30 mg/mL), 1 vial	Roche Products Pty Ltd	\$redacted
		60 mg/0.4 mL (150 mg/mL), 1 vial		\$redacted
		105 mg/0.7 mL (150 mg/mL), 1 vial		\$redacted
		150 mg/1 mL (150 mg/mL), 1 vial		\$redacted

Source: Table A.2, p14 of the SBA

The Critique stated a key issue with the submission was the differential pricing proposal for patients with inhibitors (Application 1510; refer to Public Summary Document) and without inhibitors.

7. Summary of public consultation feedback/consumer issues

Eleven responses were received during the consultation phase – two responses from professional organisations, five responses from patients, one response from a consumer/patient advocacy organisation, one response from a haematologist, one response from a haemophilia nurse and one from a social worker. The feedback was unanimously positive about the treatment, and supportive of public funding emicizumab on the NPL.

Feedback stated that patients with severe and moderate haemophilia A currently require regular (minimum twice weekly, but often every second day) factor VIII intravenous infusions to prevent musculo-skeletal bleeds (and associated significant morbidity). This is a major treatment burden for patients and their families/partners/carers. The novelty of emicizumab, which allows weekly (or less often, up to monthly) subcutaneous injections, with 50% of patients experiencing no bleeds over a six month period, facilitates freedom, normality and productivity (work and school).

Professionals who treat patients are mindful of the cost of novel therapies, have experience in following criteria and the appropriate/sustainable use of high cost drugs and blood products.

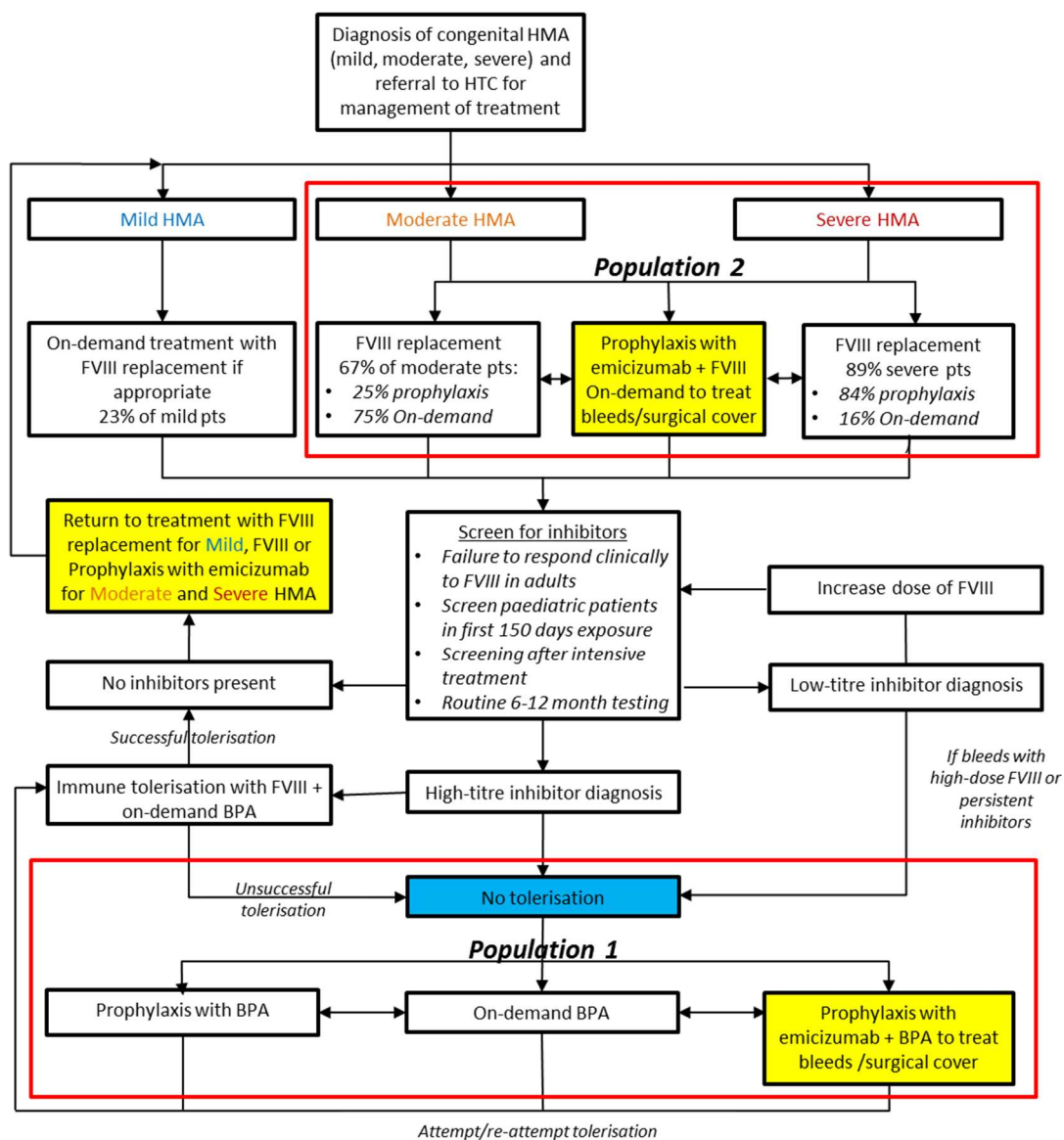
Feedback confirmed that emicizumab's registration in Australia has provided over two and a half years of patient experience, through clinical trials. Current (alternative) treatments are painful and stressful, because of the invasive nature of infusions. Needle phobia, thrombosis, infection risk, deteriorating vein access and disruption to daily living are some of the difficulties patients face. Poor psychosocial and economic outcomes are exacerbated by mental health issues, family breakdown, sub-optimal education outcomes and reduced work capacity. All family members are affected.

While the feedback acknowledged that some patients currently 'intravenously' self-inject the existing (funded) treatments, it clarified this is burdensome, because of vein issues and self-cannulisation difficulties. Reduced current treatment compliance leads to worsening outcomes, late night presentations to emergency departments (after falls/injuries during the day) and longer term joint disease from bleeds (with associated surgeries and poorer quality of life).

In the feedback, patients who participated in Australian emicizumab clinical trials talked about forgetting haemophilia for the first time, allowing them to get on with life, school and work.

8. Proposed intervention's place in clinical management

The proposed clinical management algorithm for patients with HMA is provided in Figure 1. This application addressed Population 2 only (without inhibitors). Emicizumab is shown as an additional treatment option for patients with moderate to severe HMA (without inhibitors). Specifically, emicizumab prophylaxis is shown as an alternative to FVIII, which can be given as either on-demand or prophylaxis.



- The reasons for "No tolerisation" include:**
- Patient's inhibitor titre needs to drop before commencing ITI
 - Patient is unable to tolerate ITI because of venous access issues
 - Patient has low titre inhibitors but requires BPA treatment due to bleeding on high-dose FVIII
 - Patient has failed ITI

Figure 1 Proposed clinical management algorithm for patients with congenital HMA

Source: PICO confirmation for MSAC application 1510 March 2018

9. Comparator

The proposed comparators are:

1. prophylaxis with FVIII plus on-demand FVIII to treat bleeds; and
2. no prophylaxis plus on-demand FVIII to treat bleeds or as surgical cover.

The Critique stated that the comparators are consistent with the PICO Confirmation. The main comparator is comparator one (prophylaxis with FVIII) as this is the predominant treatment strategy in Australia for patients with severe HMA, which is more prevalent than moderate HMA.

The Critique provided the currently-available products on the NPL and recommended prophylaxis regimens (Table 3).

Table 3 Factor VIII products available on the NPL and EHL factor VIII products registered with the TGA

Product	Supplier	Dose (frequency) required when prescribed as prophylaxis
SHL factor VIII products available on the NPL		
rch FVIII rAHF-PFM (Advate)	Baxalta	20 – 40 IU/kg every other day (3 or 4 x per week)
rFVIII (Xyntha)	Pfizer	10 – 50 IU/kg at least 2 x per week
pdFVIII/VWF (Biostate)	CSL Behring	12.5 – 20 IU/kg 1 – 3 x weekly
EHL factor VIII products registered with the TGA		
BAX-855 (Adynovate)	Baxalta / Shire	40-50 IU/kg/2 x weekly (starting dose 55 IU/kg/2 x weekly in patients <12 years of age, maximum 70 IU/kg)
BAY 81-8973 (Kovaltry)	Bayer Australia	Patients >12 years old: 20 – 40 IU/kg 2 or 3 times per week
CSL 627 (Afstyla)	CSL Behring	Patients ≥12 years old: 20 – 50 IU/kg/2 or 3 x per week Patients <12 years old: 30 – 50 IU/kg/2 or 3 x per week. More frequent or higher doses may be required
rFVIII-Fc (Eloctate)	Bioverativ Australia	50 IU/kg every 3-5 days or 65 IU/kg/week More frequent doses up to 80 IU/kg may be required in children <12 years of age

Abbreviations: IU=international units; rFVIII= recombinant coagulation factor VIII; pdFVIII=plasma-derived factor VIII; rFVIII-Fc = recombinant factor VIII Fc fusion protein; SHL – standard half-life; EHL = extended half-life.

Source: This table has been adapted from the PICO Confirmation documents for 1510 and 1511 (extended half-life FVIII).

10. Comparative safety

Emicizumab prophylaxis versus on-demand FVIII

One randomised controlled trial (HAVEN 3) was included comparing emicizumab prophylaxis administered weekly (Arm A; n=36) and every two weeks (Arm B; n=35) compared to on-demand use of FVIII (Arm C; n=18) in adult and adolescent patients with severe HMA. This trial report also included an intra-patient (before-and-after) comparison of emicizumab prophylaxis (subgroup of Arm D; n=48/63) compared to these patients' historical use of FVIII prophylaxis when they had previously participated as Cohort C in the non-interventional study NIS BH29768.

The Critique stated that emicizumab prophylaxis appears safe across the trial period (range of follow-up 7.3-50.6 weeks) compared with on-demand FVIII in patients with severe HMA patients without inhibitors. The most commonly reported adverse event related to emicizumab was local injection site reaction. Other common adverse events were nasopharyngitis, upper respiratory tract infection, influenza, arthralgia and headache. No serious adverse events or adverse events of grade 3 or above were attributed to emicizumab.

There were no thromboembolic or thrombotic microangiopathy events (which were identified in HMA patients with inhibitors treated concomitantly with bypassing agents, as discussed in the MSAC PSD for 1510).

However, the Critique highlighted that on-demand FVIII is representative of a minor subgroup of severe HMA patients in Australia (the majority [80%] of patients with severe HMA are treated with FVIII prophylaxis), and may represent a less well managed population.

On the basis of the benefits and harms reported in the evidence base, the submission proposes that, relative to on-demand FVIII, emicizumab prophylaxis provides a different, non-inferior safety profile for severe HMA patients without inhibitors.

Emicizumab prophylaxis versus FVIII prophylaxis

An indirect trial comparison was also undertaken using on-demand FVIII as the common reference and evidence from HAVEN 3 for emicizumab (Arm A versus Arm C), and from

five randomised trials for FVIII prophylaxis. One randomised trial of FVIII (SPINART) was used as the base case, with the other randomised trials providing a sensitivity analysis.

The Critique stated that neither emicizumab prophylaxis nor FVIII prophylaxis are associated with serious adverse events. However, the submission did not provide an overall conclusion regarding safety in the non-inhibitor subgroup. Furthermore, the Critique highlighted that comparative safety in this subgroup is subject to uncertainty and is not supported by any statistical evaluation of frequency and severity of adverse events.

Overall, the Critique stated that the safety profiles of each therapy vary depending on product (emicizumab or FVIII) and delivery (prophylaxis or on-demand), noting the therapy with fewest adverse events is on-demand FVIII. However, adverse events with emicizumab and FVIII are typically mild and all serious events are unrelated to the therapy.

11. Comparative effectiveness

Emicizumab prophylaxis versus on-demand FVIII (direct evidence)

For the primary endpoint of treated bleeds for the randomised population in HAVEN 3, a 96% reduction in treated annualised bleed rate (ABR) was observed for comparison of emicizumab prophylaxis 1.5 mg/kg weekly with on-demand FVIII (Arm A versus Arm C) and a 97% reduction for the comparison of 3.0 mg/kg two-weekly with on-demand FVIII (Arm B versus Arm C) (Table 4). On the basis of the benefits and harms reported in the evidence base, the submission proposed that, relative to on-demand FVIII, emicizumab prophylaxis has superior effectiveness in reducing the rate of treated bleeds for patients with severe HMA without FVIII inhibitors.

The Critique stated that the open-label nature of the trial and the subjective nature of the outcomes introduced the potential for bias. Disparate efficacy periods between the arms has the potential to over-represent the benefits of emicizumab. Follow-up is relatively short and is extrapolated to annualised data. However, for the direct evidence, the magnitude of the effect is large and unlikely to be impacted by issues in study design, analysis or reporting. The Critique also highlighted other uncertainties for assessing effectiveness of emicizumab including the lack of long term evidence (therapy for HMA is lifelong), there were no data for patients with moderate HMA and paediatric patients, use of FVIII in clinical practice, requirement for up-titration of emicizumab in clinical practice and impact of emicizumab on quality of life.

Table 4 Treated bleeding events

Parameter	HAVEN 3 Arm A 1.5 mg/kg emicizumab prophylaxis N = 36	HAVEN 3 Arm B 3.0 mg/kg emicizumab prophylaxis N = 35	HAVEN 3 Arm C No prophylaxis / On-demand FVIII N = 18
Median efficacy period (weeks)	29.57	31.29	24.00
ABR	1.5	1.3	38.2
ABR ratio: Arm A OR Arm B /Arm C (95% CI)	0.04 (0.020, 0.075)	0.03 (0.017, 0.066)	-
p-value	<0.0001	<0.0001	-
Zero treated bleeds n (%); no descriptive statistics	20 (55.6%)	21 (60.0%)	0

Source: Submission Table B.19 and Table B.20

Abbreviations: ABR = Annualised bleed ratio; CI = confidence interval; FVIII = factor VIII

Emicizumab prophylaxis versus FVIII prophylaxis

On the basis of the benefits and harms reported in the evidence base, the submission proposes that, relative to FVIII prophylaxis, emicizumab prophylaxis has superior effectiveness in reducing the rate of treated bleeds for severe HMA patients without inhibitors (see also Table 5 for the before-and-after comparison and Table 6 for the indirect comparison).

Table 5 Treated bleeding events, calculated with the NBR model – Arm D compared to NIS FVIII prophylaxis

Parameter	HAVEN 3 Arm D 1.5 mg/kg per week emicizumab prophylaxis N = 48	NIS BH29768 Cohort C FVIII prophylaxis N = 48
Median efficacy period (weeks)	33.71	30.07
ABR	1.5	4.8
ABR ratio (95% CI)	0.32 (0.195, 0.514)	-
p-value	<0.0001	-
Zero treated bleeds n (%); no descriptive statistics	26 (54.2%)	19 (39.6%)

Source: Table B.19 and Table B.20 of the Submission

Abbreviation: ABR = annualised bleeding events; CI = confidence interval; CSR = clinical summary report; FVIII = factor VIII

Table 6 Annualised bleed rate, HAVEN 3 and SPINART

	HAVEN 3 Arm A 1.5 mg/kg per week emicizumab prophylaxis N = 36	HAVEN 3 Arm C FVIII on-demand N = 18	SPINART FVIII prophylaxis N = 42	SPINART FVIII on-demand N=42
Exposure (years) ^a	18	9		
Exposure (years) ^b	22.14	8.17	127 (median)	126 (median)
Number of treated bleeds	37	369	264	4338
ABR calculated by the SBA	2.06	41.0	2.1	34.4
ABR reported by the trial	1.5	38.2	0.7	37.4
Log rate ratio (on-demand / prophylaxis) (calculated by the SBA)	-0.19			
Log rate ratio (on-demand / prophylaxis) ^b	-0.49 (using rate ratios reported by each trial)			
Indirect treatment effect (emicizumab prophylaxis versus FVIII prophylaxis) (calculated by the SBA)	0.83			
Indirect treatment effect (emicizumab prophylaxis versus FVIII prophylaxis) ^b	0.61			

Source: Submission and SPINART published data

Abbreviation: ABR = annualised bleeding rate; FVIII = factor VIII; SBA = submission-based assessment

Note: a = used by the Submission; b = calculated by the Critique

However, the Critique stated that the point estimate of the rate ratio of treated bleeds ABRs is uncertain due to the number of sensitivity analyses showing the effect size to be variable. In addition, the Critique highlighted that the indirect trial comparison is limited due to uncertainty in the exchangeability of the trial populations, variability in study design and quality, and the use of different outcome measures.

Clinical claim

The clinical claim is that “Prophylaxis with subcutaneous emicizumab is associated with superior health outcomes for HMA patients without FVIII inhibitors through improved efficacy (reduction in bleeds), improved convenience and acceptable safety in comparison to

treatment with the SHL FVIII agents (ADVATE, BIOSTATE, XYNTHA) administered as prophylaxis.” The Critique highlighted the issue that the clinical claim did not consider emicizumab relative to on-demand FVIII.

12. Economic evaluation

The submission stated that, given that the clinical assessment does not warrant a claim of survival benefit or a significant incremental gain of quality of life versus treatment with FVIII prophylaxis, a cost-consequences analysis (CCA) was provided comparing prophylaxis with emicizumab and prophylaxis with FVIII in patients with severe and moderate HMA without inhibitors (Table 7).

Table 7 Elements of the economic model included in the evaluation

Element of economic evaluation	MSAC’s preference for the base-case scenario
Perspective	Healthcare payer perspective including only direct treatment-related costs
Population	Severe and moderate HMA without inhibitors
Comparator	FVIII prophylaxis only considered in the economic model, <i>however, the budget impact model also allows for uptake among patients with severe and moderate HMA receiving FVIII on demand.</i>
Type of economic evaluation	Cost-consequences analysis. <i>Primarily a cost-minimisation analysis with the small cost consequence of break-through bleed costs included in the intervention arm. The economic approach essentially estimates the price of emicizumab that results in cost-equivalence against current FVIII prophylaxis in Australia.</i>
Sources of evidence	Key health outcome is ABR as reported in the clinical trials of emicizumab, specifically: HAVEN 3 Arm D and NIS BH29768 Cohort C Australian FVIII utilisation patterns based on Mason (2018) and ABDR annual report 2015/16 (NBA 2017)
Time horizon	One year at steady state treatment dosing
Outcomes	Annual total treatment costs per kilogram body weight
Method	Trial- and real world data based estimation of direct medical resource utilisation
Cycle length	One year
Software packages used	Excel

Source: Submission, with comments by the Critique in italics

Abbreviations: ABR = annualised bleeding rates; ABDR = Australian Bleeding Disorders Registry; FVIII = factor VIII; HMA = haemophilia

The submission’s CCA indicated using an effective price of emicizumab of **\$redacted** per mg, cost equivalence was evident for the intervention and current FVIII prophylaxis among patients with severe and moderate HMA without inhibitors (Table 8).

Table 8 Results of cost-consequences analysis

Annual treatment cost per kilogram body weight	Emicizumab arm	Factor VIII arm	Incremental cost
Emicizumab prophylaxis	\$redacted	-	\$redacted
Factor VIII prophylaxis	-	\$1,530.47	-\$redacted
Factor VIII for breakthrough bleeds	\$redacted	Included above	\$redacted
Total annual treatment cost	\$redacted	\$1,530.47	-\$redacted

The Critique highlighted two major areas of uncertainty. Firstly, annual costs of FVIII prophylaxis are derived from the reported data of FVIII use in Australia, reported by Mason et al (2018) and in Australian Bleeding Disorders Registry (ABDR) annual reports. These estimates include wastage and compliance, whereas the modelled estimates of emicizumab usage does not. However, as compliance with emicizumab is likely to be higher than with FVIII prophylaxis, this assumption favours the comparator. In contrast, the submission’s modelling assumption that there would be no emicizumab wastage favours the intervention (relative to wastage and compliance of FVIII prophylaxis included in the observed Australian data (Mason et al. 2018; and annual ABDR reports). Secondly, on-demand patients may

adopt emicizumab. The volume of FVIII used per year among on-demand patients is lower than that for prophylaxis. The Critique’s additional sensitivity analyses confirmed that compliance with emicizumab, and the proportion of on-demand and prophylaxis treatment patients in the comparator arm, were key driver assumptions for the cost estimates.

The exclusion of the on-demand subgroups results in a higher emicizumab price to achieve cost parity with current FVIII usage than if on-demand patients were included in the eligible patient population. This explains the net cost increase in the financial analyses (Table 9), which includes all requested subgroups in the overall non-inhibitor HMA sub-population.

13. Financial/budgetary impacts

An epidemiological approach was used to estimate the financial implications (Table 9).

Table 9 Final cost summary and the net cost to the NPL over the five-year prediction

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients treated					
Adult	redacted	redacted	redacted	redacted	redacted
severe HMA	redacted	redacted	redacted	redacted	redacted
moderate HMA	redacted	redacted	redacted	redacted	redacted
Paediatric	redacted	redacted	redacted	redacted	redacted
severe HMA	redacted	redacted	redacted	redacted	redacted
moderate HMA	redacted	redacted	redacted	redacted	redacted
Total patients treated	redacted	redacted	redacted	redacted	redacted
Cost of emicizumab to NPL					
Adult	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Paediatric	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total cost of emicizumab	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Cost of FVIII for breakthrough bleeds in patients treated with emicizumab					
Adult	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Paediatric	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Total cost of FVIII	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Cost of FVIII substituted by emicizumab					
Severe	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Moderate	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Substituted cost of FVIII	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Net cost to NPL					
Total net cost to NPL	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

Source: Submission, Section E, Table E.15, p. 18

Abbreviations: NPL= National Product List.

The Critique stated that the major uncertainty in the financial analysis relates to estimated uptake across patient subgroups. Given the size of the moderate patient subgroup, even 25% adoption among those availing on-demand FVIII would have significant budget impacts. Other uncertainties in the analysis (such as bleed rate and inhibitor background prevalence) had limited impact on estimated net financial costs.

Critique Addendum

The addendum to the Critique sought to facilitate the consideration of Application 1579 by identifying those budgetary impact analyses in the submission for 1579 and relevant to the non-inhibitor population of 1579, which appeared to have been superseded by information presented in the resubmission for Application 1510.1. The differences in the uptake data estimated in 1579 and 1510.1 have been extracted and presented in Table 10 (adult subgroup) and Table 11 (paediatric subgroup). At the end of each table, the estimated number of emicizumab users were also provided to illustrate the overall impact on the reduced uptake.

Table 10 Comparison of emicizumab uptake between 1579 and 1510.1, adult subgroup

Emicizumab uptake estimates and sources	Year 1	Year 2	Year 3	Year 4	Year 5	Impact to BIA
Prophylaxis uptake among adult patients with moderate haemophilia						
Estimates in 1579	50.0%	100.0%	100.0%	100.0%	100.0%	Claimed to be the worst case
Updated figure in 1510.1	16.3%	46.3%	60.0%	60.0%	60.0%	Overall cost reduction to NPL
On-demand uptake among adult patients with severe haemophilia						
Estimates in 1579	12.5%	25.0%	25.0%	25.0%	25.0%	Stabilised in the second year
Updated figure in 1510.1	6.8%	19.3%	25.0%	25.0%	25.0%	Gentler up-ramp, lower costs
Prophylaxis uptake among adult patients with severe haemophilia						
Estimates in 1579	50.0%	100.0%	100.0%	100.0%	100.0%	Claimed to be the worst case
Updated figure in 1510.1	21.7%	55.8%	60.0%	60.0%	60.0%	Overall cost reduction to NPL
Estimated patient numbers receiving emicizumab						
Estimates in 1579	redact	redact	redact	redact	redact	
Updated figure in 1510.1	redact	redact	redact	redact	redact	
Number of patients reduced	109	171	150	154	157	Over 30% reduction

Table 11 Comparison of emicizumab uptake between 1579 and 1510.1, paediatric subgroup

Emicizumab uptake estimates and sources	Year 1	Year 2	Year 3	Year 4	Year 5	Impact to BIA
Prophylaxis uptake among paediatric patients with moderate haemophilia						
Estimates in 1579	50.0%	100.0%	100.0%	100.0%	100.0%	Claimed to be the worst case
Updated figure in 1510.1	28.9%	74.4%	80.0%	80.0%	80.0%	Overall cost reduction to NPL
On-demand uptake among paediatric patients with severe haemophilia						
Estimates in 1579	12.5%	25.0%	25.0%	25.0%	25.0%	Stabilised in the second year
Updated figure in 1510.1	9.0%	23.2%	25.0%	25.0%	25.0%	Gentler up-ramp, lower costs
Prophylaxis uptake among paediatric patients with severe haemophilia						
Estimates in 1579	50%	100.0%	100.0%	100.0%	100.0%	Claimed to be the worst case
Updated figure in 1510.1	43.3%	80.0%	80.0%	80.0%	80.0%	Overall cost reduction to NPL
Estimated patient numbers receiving emicizumab						
Estimates in 1579	redact	redact	redact	redact	redact	
Updated figure in 1510.1	redact	redact	redact	redact	redact	
Number of patients reduced	14	36	36	37	37	Up to 20% reduction

The addendum to the Critique identified that the new uptake rates were not supported by clinical evidence. Specifically, the “reduced uptake” as rationalised in 1510.1 did not represent explicit estimates on the magnitude of the reduction, but qualitative indications on how emicizumab may be used if funded. The addendum to the Critique summarised by saying uptake data should be supported by evidence, and robust sensitivity analyses should assess their associated uncertainties. The Pre-ESC response to the Critique Addendum stated that as emicizumab is new innovative product with unique mode of action (compared with current blood products available to treat HMA) that uptake of this product in the community is inherently uncertain.

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Does the trial evidence from adults with severe haemophilia A (HMA) without factor VIII (FVIII) inhibitors reliably extrapolate to: <ul style="list-style-type: none"> adults with moderate HMA without FVIII inhibitors paediatric patients with severe HMA without FVIII inhibitors paediatric patients with moderate HMA without FVIII inhibitors? 	Given the nature of the condition and the low likelihood of additional randomised trial data being forthcoming, extrapolating is necessary; perhaps there should be a requirement for future data collection via the Australian Bleeding Disorders Registry?
Is the reliance on evidence with a minor comparator (on-demand FVIII rather than FVIII prophylaxis) offset by the cost-minimisation approach to the economic evaluation for the subgroup without inhibitors?	The claim of superior efficacy for emicizumab in reducing the frequency of bleeding episodes (which is also based on the before-and-after intra-patient and indirect comparisons) is not used to justify any price advantage for the non-inhibitor subgroup receiving FVIII prophylaxis – at face value this seems conservative, against emicizumab.
Does the applicant's confidential risk sharing agreement address the clinical, economic and financial uncertainties (including potential use in mild HMA without inhibitors)?	The inclusion of 'for routine prophylaxis' for emicizumab in the requested listing may discourage use in most mild HMA patients.
What advice can ESC give regarding the approach used by the applicant to derive a weighted price across the two subgroups? Is there sufficient information from 1510.1 to inform this advice?	There is limited information to support the approach used by the applicant and so ESC can provide only limited advice regarding the proposal for weighted pricing (see also ESC advice to MSAC on the resubmission for Application 1510.1).

ESC discussion

Application 1579 is for National Product Listing of emicizumab for use in patients with moderate to severe haemophilia A (HMA; also called congenital factor VIII deficiency) without factor VIII (FVIII) inhibitors. There is a separate application for patients with FVIII inhibitors (see related Application 1510.1).

ESC noted that patients can develop and lose inhibitors, so patients can be in flux between the two subgroups throughout their life.

ESC noted that the main trial used for evidence was HAVEN 3 (N=152), an open-label randomised controlled trial in adult patients with severe HMA without inhibitors. Treatment with emicizumab showed reduced bleeding rates and acceptable safety. However, due to the open-label nature of HAVEN 3, patients may have underreported adverse events (AEs).

ESC considered that a major advantage of emicizumab compared with FVIII is that emicizumab treatment does not lead to the development of FVIII inhibitors. However, across HAVEN trials 1-4, 3/398 patients developed anti-emicizumab antibodies (0.75%), not all of which were neutralising.

ESC noted that the trial data do not support modelling of any gains in survival or quality of life (QoL). ESC considered that the clinical evidence presented in the application conservatively suggests non-inferiority of emicizumab versus FVIII prophylaxis in severe HMA without inhibitors.

ESC considered the following translation issues from HAVEN 3:

- whether population characteristics are likely to be similar for non-disease related demographics
- whether results in adolescents and adults can be extrapolated to paediatric patients, and results for severe HMA can be extrapolated to moderate HMA
- whether compliance rates are likely to be similar across disease subgroups
- whether results against FVIII prophylaxis in patients with severe HMA without inhibitors from the before-and-after study (from Arm D) are broadly consistent with results against on-demand FVIII in this type of patient from the randomised trial (Arms A, B and C)
- whether supplementary dosage and pharmacokinetics data are supportive, including the single-arm HAVEN 4 study in support of dosing with emicizumab every 4 weeks
- whether the annualised bleeding rate calculations are appropriate.

ESC noted the issue of potential leakage from the relatively small population of moderate–severe HMA patients to the relatively large population of mild HMA patients given the broader TGA-approved indication, the comparative effectiveness of emicizumab on bleeding rates, greater convenience of subcutaneous administration, and the desirability of avoiding FVIII inhibitors. The proportion of mild HMA patients who receive any FVIII treatment is reported to be approximately 20% per year. The application is for emicizumab as prophylaxis, and mild patients are generally treated with FVIII on-demand, not as prophylaxis. ESC considered that haematologists are inherently conservative and are properly self-regulated, which decreases the likelihood of inappropriate emicizumab prescribing. ESC queried the possibility of the National Blood Authority (NBA) restricting patient eligibility for NPL-funded emicizumab. The NBA advised that it does not hold statutory powers to do this, but clinicians do need to make a declaration stating a patient’s requirement for certain treatment. There is also a precedent from the NPL funding of immunoglobulins for the Jurisdictional Blood Committee to establish a framework outlining appropriate usage of blood and blood products.

ESC noted that the economic evaluation was a cost-consequence analysis in patients with severe and moderate HMA comparing prophylaxis with emicizumab and prophylaxis with FVIII estimates of cost offsets from differences in bleeds from the before-and-after study (from Arm D of HAVEN 3). Costs due to adverse events were not included. The applicant used a 1-year time horizon (starting after the titration phase) and annual treatment costs are per kilogram of body weight. The evaluation emphasised this scenario where emicizumab prophylaxis was priced to be slightly less than FVIII prophylaxis. The applicant assumed high compliance to emicizumab, which ESC considered to be appropriate, as emicizumab is a highly desirable treatment option for patients.

ESC noted the net financial costs were estimated to be from \$3.95 million in year 1 to \$3.59 million in year 5, with a peak in year 2 of \$6.15 million (due to a spike in uptake). The costs were sensitive to the proportions of patients with different severity of HMA (mild, moderate, severe), the proportions of FVIII use for prophylaxis and on-demand, and the proportions of emicizumab as weekly, 2-weekly, and 4-weekly treatment.

The combined sensitivity analysis, which ESC considered to be the most appropriate, had the lowest budget impact.

ESC noted the weighted costs for the non-inhibitor subgroup were varied in the resubmission for Application 1510.1, and queried whether the information provided in both applications was enough to determine which approach was most appropriate.

ESC accepted the high clinical need for emicizumab. ESC noted the high consumer support for this application, and noted the request for compassionate access.

ESC advised that a risk sharing arrangement should be further explored, and that measures should be considered to minimise the likelihood of leakage to the mild HMA subgroup. To provide more confidence in the basis of this arrangement, ESC requested more information on the numbers and proportions of mild HMA patients who currently receive FVIII as on-demand and as prophylaxis. ESC noted that this risk sharing arrangement would need to be considered in the context of the broader arrangement offered in the resubmission for Application 1510.1 encompassing both with and without inhibitor subgroups.

15. Other significant factors

Nil.

16. Applicant's comments on MSAC's Public Summary Document

While Roche welcomes MSAC's support for funding of emicizumab, Roche contends the alternative pricing methodology advised by MSAC is inappropriate and contains multiple inaccuracies and erroneous assumptions. Roche has worked for several years with the haemophilia community to validate the assumptions and inputs used in our pricing approach. Roche will continue to work with the Department to enable access to emicizumab as a matter of priority, and is confident that agreement on fair pricing can be reached. This will ensure that all eligible Australian patients are able to realise the benefits associated with emicizumab treatment and that the government does not forego the savings offered by listing emicizumab across the inhibitor and non-inhibitor populations

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)