NATIONAL BLOOD AUTHORITY
AUSTRALIA

NOVOSEVEN RT
EPTACOG ALFA

Utilisation Analysis from the Integrated Data Management System (IDMS) and the Australian Bleeding Disorder Registry (ABDR)

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Introduction

Eptacog alfa, sold as NovoSeven RT in Australia, is a room temperature stable, activated recombinant coagulation Factor VII (rFVIIa) derived from baby hamster kidney (BHK) cells. Eptacog alfa is supplied by NovoNordisk as a powder in single-use vials to be reconstituted with the sterile solvent provided in a pre-filled syringe.

Scope of the preliminary utilisation review

This preliminary review examined usage trends for NovoSeven RT to assess whether the product is being used in a manner consistent with criteria for NBA funded access.

Conditions treated using NovoSeven RT

NovoSeven RT is funded under the national blood arrangements for the control of bleeding and prophylaxis in patients with a range of bleeding disorders (described below), however use in these patient groups is restricted to those with:

- Inhibitors (antibodies) to coagulation Factor VIII or Factor IX including patients with Haemophilia A or B.
- Congenital Factor VII deficiency.
- Glanzmann's Thrombasthenia, with antibodies to glycoprotein IIb (GPIIb) and/or human leukocyte antigens (HLA), and with past or present refractoriness to platelet transfusions.

NovoSeven RT is used to bypass inhibited coagulation factors in these disorders to restore the body's ability to prevent or stop bleeding.

Haemophilia A and B

Haemophilia is a disorder that mostly affects males, and results in uncontrolled bleeding, usually into the joints or muscles. These bleeding episodes may occur spontaneously, without an obvious cause, or because of trauma or injury. Haemophilia A (HMA) is the deficiency of coagulation Factor VIII (FVIII) that can be inherited or acquired, while Haemophilia B (HMB) is the deficiency of coagulation Factor IX (FIX). Treatment for Haemophilia includes the administration of missing coagulation factors.

The major complication of clotting factor replacement therapy is that patients may develop antibodies (inhibitors) against the replacement factors. These inhibitors develop in up to 35% of patients with severe HMA, in 3-13% of patients with moderate-mild HMA and in 1-4% of patients with severe HMB. Inhibitors can develop at any time over a patient's treatment, generally in line with the intensity of the treatment. As a result, severe haemophiliac patients typically develop inhibitors around 2 years of age, while moderate-mild haemophiliacs develop inhibitors after the fourth decade (Abdi, et al., 2021).

Factor VII deficiency

Factor VII (FVII) deficiency is a rare inherited bleeding disorder affecting approximately 1:500,000 people. Patients with low FVII levels (<1%) can experience severe nosebleeds, bleeding of the gums, easy bruising and prolonged or excessive bleeding after surgery or physical trauma. FVII deficient patients with FVII levels of >5% experience more moderate symptoms (Australian Haemophilia Centre Director's Organisation and National Blood Authority, 2016).

Glanzmann's Thrombasthenia

Glanzmann thrombasthenia is a rare inherited disorder caused by a lack of two platelet surface proteins. Absence of these proteins reduces the ability of platelets to form a clot when the patient is bleeding. This can result in severe bleeding of nose and gums, easy bruising and sporadic gastrointestinal bleeds. (Botero, et al., 2020).

NovoSeven RT on the National Price Product List

NovoSeven has been available in Australia since 1999. In May 2008, the Jurisdictional Blood Committee (JBC) agreed to add NovoSeven RT (a room-temperature stable form) on to the National Product Price List (NPPL). The range of NovoSeven RT presentations currently available on the NPPL is summarised in **Table 1**.

Table 1 – NovoSeven-RT Presentations available on the NPPL.

Product	ARTG Number
NovoSeven RT 1mg, powder for injection	ARTG ID 206194
NovoSeven RT 2mg, powder for injection	ARTG ID 206195
NovoSeven RT 5mg, powder for injection	ARTG ID 206196
NovoSeven RT 8mg, powder for injection	ARTG ID 206197

NovoSeven RT data used to inform the review

The two sources of data the NBA uses to track the use of rFVIIa are the Australian Bleeding Disorders Registry (ABDR) and the Integrated Data Management System (IDMS).

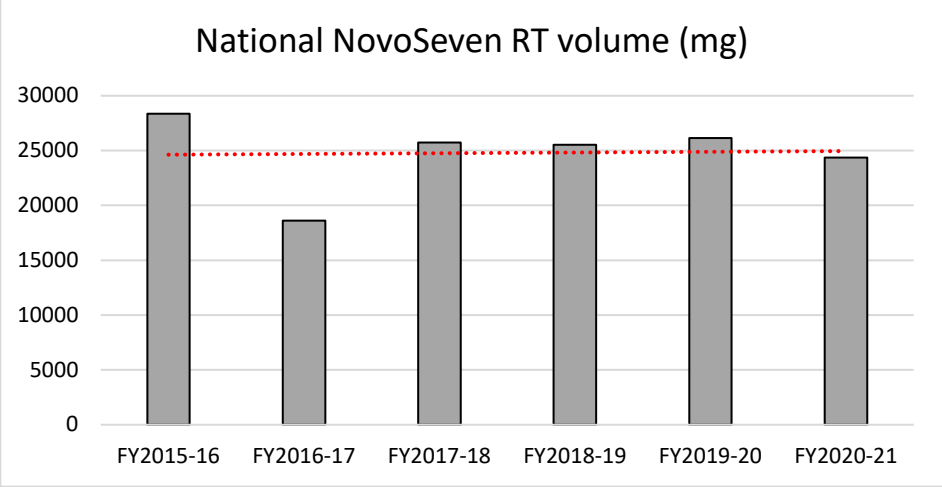
Data from the IDMS system provides an accurate accounting of the volumes and costs of utilisation, but does not capture the reasons for use, or patient level information. Patient level information is captured in the ABDR data and is derived from the treatment plans and product orders recorded by Haemophilia Treatment Centre (HTC) staff. This data can be limited by patients withholding consent to have this information captured by the database.

Annual reports from the ABDR between 2009 and 2020 are publicly available on the NBA website. These reports provide a comprehensive analysis of NovoSeven RT use, including the number of patients receiving the product, for which conditions, usage across jurisdictions, on-demand against prophylaxis use, and adult against paediatric patients.

Analysis of utilisation trends

The total volume of NovoSeven RT used across Australia for the past 6 financial years is illustrated in **Figure 1** and over that period has been relatively stable and has been relatively reflective of forecasted usage in the National Supply Plan and Budget. This indicates that usage has been predictable and consistent over the period it has been funded by the national blood arrangements.

Figure 1 – NovoSeven RT issued 2015-16 to 2020-21 compared to the National Supply Plan and Budget (red line)



NovoSeven RT use by indication

Use of NovoSeven RT by individual patients is influenced by the severity of disease, response levels of inhibitors, number and magnitude of spontaneous bleeding events patients suffer, if patients are on a prophylactic regimen or if patients undergo elective surgery. As recorded in the ABDR 2019-20 Annual Report, there were up to 4381 patients in Australia with bleeding disorders potentially eligible for NovoSeven treatments. This number includes 2449 with haemophilia A, 585 with haemophilia B and 93 with acquired haemophilia. Of the potentially eligible patient population, 1330 patients received blood and/or blood related products. The number of patients who received NovoSeven RT in the same period was just 74 - see **Table 2**.

Table 2 - Volume (mg) of NovoSeven RT utilised 2017/18 - 2019/20 per bleeding disorder from ABDR annual reports

Bleeding Disorder	2017/18		2018/19		2019/20	
	Total Vol.	# pts	Total Vol.	# pts	Total Vol.	# pts
FVIII deficiency – Haemophilia A	9186	43	9918	39	7943	42
FVIII deficiency – Haemophilia A (acquired)	5178	12	4291	11	3515	9
FIX deficiency – Haemophilia B	1940	≤5*	4454	≤5*	5480	≤5*
FVII deficiency	1930	8	1430	12	2043	12
FXI deficiency	70	≤5*	15	≤5*	-	-
FV deficiency	19	≤5*	-	-	-	-
Platelet dysfunction – Glanzmann's Thrombasthenia	315	7	257	6	2053	≤5*
Platelet dysfunction – Bernard-Soulier	-	-	7	≤5*	12	≤5*
Von Willebrand Disease – Uncharacterised (acquired)	-	-	-	-	36	≤5*
Von Willebrand Disease Type 2 – Uncharacterised (acquired)	-	-	30	≤5*	-	-
Other (acquired)	318	≤5*	78	≤5*	-	-
TOTAL	18956	74	20480	73	21082	74

*In order to maintain the anonymity of individual patients and health providers, data showing less than five (5) may be suppressed or aggregated if there is a potential to re-identify or exceptions are agreed between national and state/territory data custodians – 2019-20 ABDR annual report.

The ABDR 2019-20 Annual Report states that NovoSeven RT was only given to patients with existing inhibitors, which is in accordance with the criteria for access.

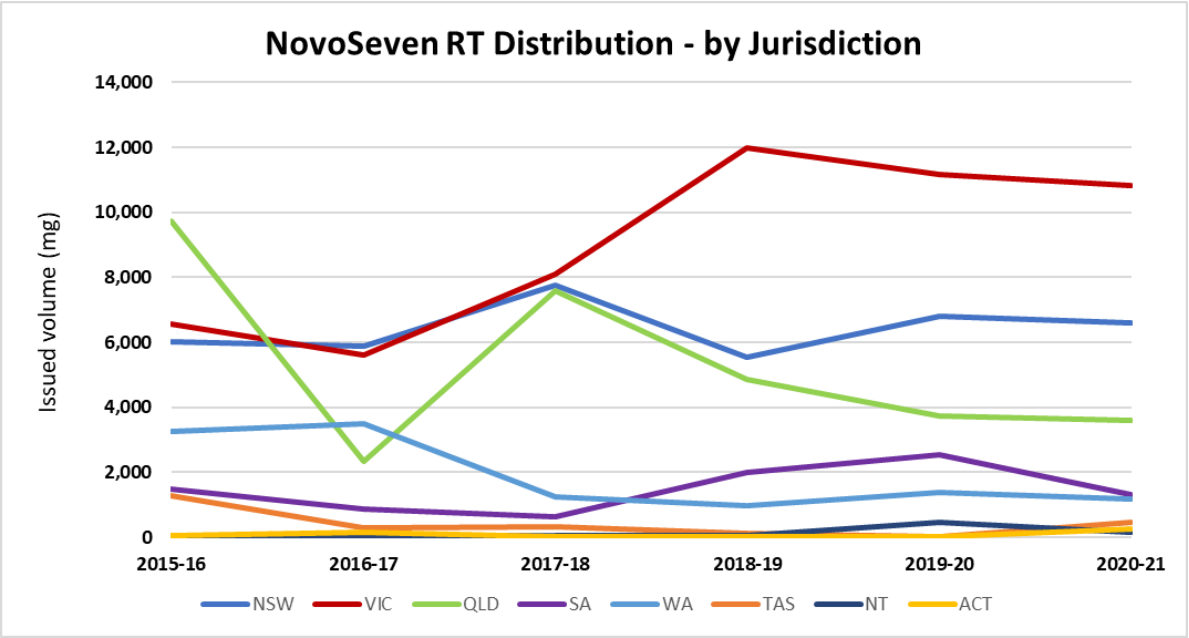
As shown in **Table 2**, NovoSeven RT was given predominantly to patients with Haemophilia A or B (with inhibitors), congenital FVII deficiency, or Glanzmann's Thrombasthenia. Use in other conditions accounts for a small proportion of the total NovoSeven RT use recorded in the ABDR. In 2017-18 this was 2.15% of total use, decreasing to 0.63% in 2018-19, and 0.23% in 2019-20.

Jurisdictional trends

Figure 2 show the jurisdictional trends of NovoSeven RT distribution between 2015 and 2021. This data shows some fluctuation in usage, most notably in the volume issued in Queensland which had an 80% decrease between 2015-16 and 2016-17, and then a rise again in 2017-18. Since this time the volume of NovoSeven RT issued in Queensland has steadily declined. In contrast, NovoSeven RT issued to Victoria rose between in 2017-18 and 2018-19, however since that time the issued volume has remained stable.

Further work could be done to investigate the reasons for changes to demand for NovoSeven RT in each jurisdiction. Such analysis could include examining the number of patients accessing NovoSeven RT in each jurisdiction, and any changes that have occurred to the patient population. However, given that the volume of NovoSeven RT distributed nationally is consistent from year to year (**Figure 1**), and the apparently stable national patient population who access this treatment (**Table 2**), these jurisdictional fluctuations do not appear to be reason for concern.

Figure 2 – NovoSeven RT distribution by Jurisdiction



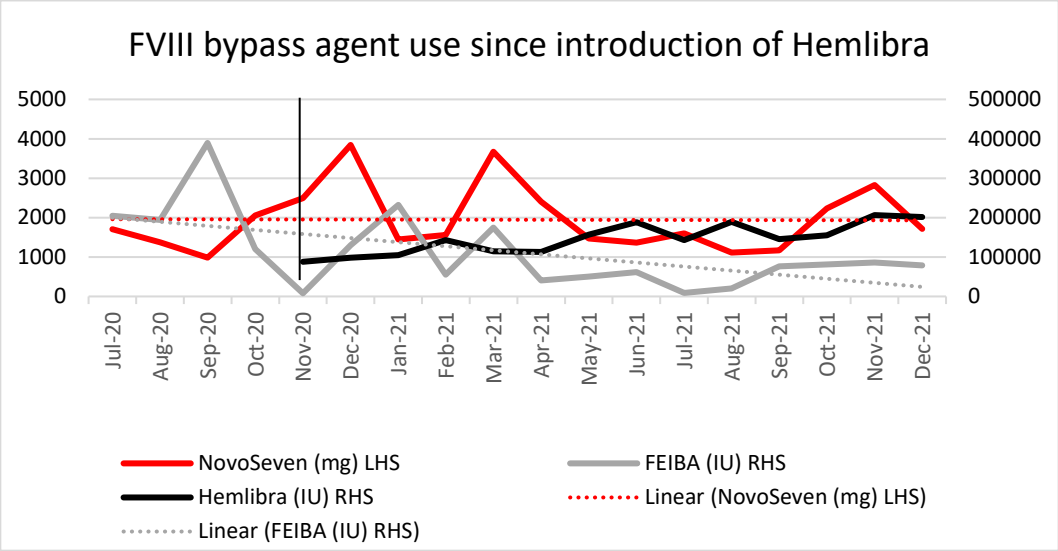
Comparative therapies funded on the NPPL

There are two products on the NPPL that are potential comparators to NovoSeven RT and may influence demand. Factor eight inhibitor bypassing activity (FEIBA) is a plasma-derived activated prothrombin complex concentrate. Like NovoSeven RT, FEIBA is used to treat patients who have developed inhibitory antibodies to FVIII. Studies have demonstrated that NovoSeven RT and FEIBA have similar efficacy as bypass reagents to FVIII inhibitors (Astermark, et al., 2007).

Hemlibra (emicizumab) was added to the NPPL in November 2020. It is used as a prophylaxis for adult and paediatric patients with moderate to severe HMA. Its effectiveness as a prophylaxis for HMA patients with FVIII inhibitors was expected to influence the demand for NovoSeven RT and FEIBA.

Initial analysis of data from NBA Distribution Reports (**Figure 3**) suggests that FEIBA utilisation has been more significantly influenced by Hemlibra than NovoSeven RT in the short period since it became available. One explanation for this could be the possible therapeutic benefit of using rFVIIa in combination with Hemlibra for patients with FVIII inhibitors (Meeks & Leissinger, 2019).

Figure 3 - Usage of NovoSeven RT, FEIBA and Hemlibra July 2020-December 2021



Vertical line indicates the introduction of Hemlibra in November 2020

Future influences on use of NovoSeven RT

By providing competition in the market, the introduction of additional new therapies could have a substantial impact on the demand and cost for NovoSeven RT. Below is a brief summary of upcoming therapies that have been identified through NBA horizon scanning (**Table 3**).

Table 3 - Emerging alternative therapeutics to rFVIIa (NovoSeven RT) adapted from (Franchini & Mannucci, 2018)

	Marzeptacog Alfa	Concizumab	Fitusiran	Etranacogene Dezaparvovec
Manufacturer	Catalyst Bioscience	NovoNordisk	Sanofi/Alnylam	CSL Behring
Technology	Engineered SC rFVIIa	Humanised monoclonal antibody	siRNA	Gene therapy
Mechanism of action	SC rFVIIa on-demand and prophylaxis	TFPI inhibition	Antithrombin inhibition	Gene replacement
Dosing frequency	TBD	TBD	Monthly	Single dose
Route of administration	Subcutaneous	Subcutaneous	Subcutaneous	Intravenous
Stage of development	Phase II/III	Phase III	Phase III	Phase III

Catalyst Biosciences has developed marzeptacog alfa, a subcutaneous form of rFVIIa, intended for both on demand use and for prophylaxis. Horizon scanning has identified three additional non-factor replacement therapeutics. Concizumab, a NovoNordisk product, is a monoclonal antibody currently in Phase 3 trials that binds to tissue factor pathway inhibitor (TFPI) and is expected to be equally effective in prophylaxis against haemophilia A and B (HMA and HMB) regardless of inhibitor status (Shapiro, 2021). Etranacogene dezaparovec, is a gene replacement therapy for HMB intended to restore patient's ability to produce Factor IX.

Conclusions

Key findings from the preliminary review are that:

- The volume of NovoSeven RT distributed between 2015-16 to 2020-21 is consistent and predictable.
- The volume issued to patients is consistent with a stable patient population.
- Significant use of a less expensive alternative bypass agent, FEIBA, demonstrates that NovoSeven RT is used only where it is the preferred clinical option.
- There is no discernible impact of Hemlibra on NovoSeven RT at this stage.

These findings support the view that NovoSeven RT is being appropriately used in the treatment of bleeding disorders. The NBA recommends that no further review or investigation is required given it is being appropriately used.