

An addendum to this minute has been included at the end of the document.

5.17 ADRENALINE

I.M injection 150 micrograms in 0.3 mL single dose syringe auto-injector, Anapen 150 Junior[®],

I.M injection 300 micrograms in 0.3 mL single dose syringe auto-injector, Anapen 300[®],

I.M injection 500 micrograms in 0.3 mL single dose syringe auto-injector, Anapen 500[®],

Allergy Concepts Pty Ltd

1 Purpose of Application

- 1.1 The minor submission requested the General Schedule, Authority Required listing of adrenaline auto-injectors Anapen 300[®], Anapen 500[®] and Anapen 150 Junior[®] (Anapen Junior) for treatment of acute allergic reaction with anaphylaxis.
- 1.2 Listing was requested on a cost-minimisation basis with existing adrenaline auto-injectors (EpiPen, EpiPen Junior, Adrenaline Mylan, Adrenaline Junior Mylan).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	As per the current PBS listing for adrenaline auto-injector brands to treat acute allergic reaction with anaphylaxis. Eligible patients have been: <ul style="list-style-type: none"> Assessed to be at significant risk of anaphylaxis; or Discharged from hospital or an emergency department after treatment with adrenaline (epinephrine) for acute allergic reaction with anaphylaxis; or Previously issued with an authority prescription for adrenaline auto-injector
Intervention	ANAPEN and ANAPEN Junior as a new brand of single dose adrenaline auto-injector pre-filled syringes presented in three strengths: <ul style="list-style-type: none"> ANAPEN Junior 150 containing adrenaline (epinephrine) 150mcg/0.3mL ANAPEN 300 containing adrenaline (epinephrine) 300mcg/0.3mL ANAPEN 500 containing adrenaline (epinephrine) 500mcg/0.3mL The 500mcg strength will be new to the PBS as only 150mcg and 300 mcg strengths have ever been listed.
Comparator	Currently listed PBS brands of adrenaline (epinephrine) auto-injector 150mcg (EpiPen® Jr, Adrenaline Jr Mylan) and 300mcg (EpiPen®, Adrenaline Mylan).
Outcomes	Prevention of death from anaphylaxis and preservation of quality of life are the patient relevant outcomes. However, it is beyond the scope of this minor submission to explore these outcomes further in requesting an alternative brand of adrenaline auto-injector be listed on the PBS. Another patient relevant outcome is the appropriate use of ANAPEN and ANAPEN Junior versus existing comparator brands as auto-injector administration techniques differs among brands.
Clinical claim	ANAPEN and ANAPEN Junior brands are non-inferior to currently listed brands of adrenaline auto-injector in efficacy, safety and ease of use as an emergency treatment for acute allergic reactions with anaphylaxis.

Source: Table 1.1.1, p18 of the submission.

2 Background

Registration status

- 2.1 Anapen Junior, Anapen 300 and Anapen 500 are not registered with the TGA: the submission was made while undergoing TGA evaluation. The requested indication is “emergency treatment for acute allergic reactions (anaphylaxis) caused by peanuts or other foods, drugs, insect bites or stings, and other allergens as well as exercise-induced or idiopathic anaphylaxis”. This is broader than the indication for EpiPen, which does not include the treatment of exercise-induced or idiopathic anaphylaxis.
- 2.2 At the time of PBAC consideration no TGA documents were available. The TGA Delegate’s Overview is expected on 1 March 2021. In light of the ongoing supply issues for PBS listed brands of adrenaline PFS auto-injectors, this submission was accepted prior to receiving the Delegate’s Overview.
- 2.3 Anapen 300 and Anapen Junior were previously registered but removed from the Australian Register of Therapeutic Goods (ARTG) in January 2017.

Previous PBAC consideration for adrenaline auto-injectors

- 2.4 Anapen Junior and Anapen 300 were previously recommended for listing by the PBAC in March 2010. Both items were listed on the PBS but removed in January 2017 at the request of the former sponsor.

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2.5 A summary of prior PBAC considerations relevant is provided below.

Table 2: Previous PBAC considerations

Meeting date	Brand	Form	Request	Outcome	Detail
March 2010	Anapen 300 & Anapen Junior	Pre-filled syringe (PFS) auto-injector	The submission requested listing of two strengths of a new form of adrenaline auto-injector.	Recommend	The PBAC recommended listing on a cost-minimisation basis with EpiPen. The equi-effective doses are were described as one Anapen and one EpiPen.
March 2011	Anapen 500	PFS auto-injector	The submission requested listing of a new strength of adrenaline auto-injector.	Recommend	The PBAC recommended listing for patients where a 300 mcg adrenaline dose may not be sufficient as the patient has a mean body weight greater than 60kg or has been assessed to be at high risk of severe anaphylaxis. The recommendation was on a cost-minimisation basis with adrenalin 300 mcg / 0.3 mL auto-injector.
July 2016	AdrenaJect®	PFS auto-injector	The submission requested listing of a new adrenaline auto-injector under the same conditions as EpiPen.	Recommend	<p>The PBAC recommended listing under the same conditions as existing adrenaline auto-injectors on the basis that AdrenaJect is bioequivalent to EpiPen. (para 6.1, adrenaline Public Summary Document (PSD), July 2016 PBAC Meeting)</p> <p>The PBAC considered that the various brands of adrenaline auto-injectors should not be considered equivalent for the purposed of substitution (i.e. a-flagged), due to varying administration techniques. (para 6.2, adrenaline PSD, July 2016 PBAC Meeting)</p>
March 2018	AdrenaJect®	PFS auto-injector	The submission requested the PBAC to reconsider its recommendation that AdrenaJect not be considered equivalent to EpiPen for the purposes of brand substitution. Additionally, the submission requested a change to the authority level from Authority Required to Authority Required (STREAMLINED).	Deferred	<p>The PBAC deferred making a recommendation and requested further information from the Sponsor regarding their education plan.</p> <p>The PBAC also requested the Department to consider options that may support safe uptake of a new device. (para 5.1, adrenaline (AdrenaJect) PSD, March 2018 PBAC Meeting)</p>

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Meeting date	Brand	Form	Request	Outcome	Detail
March 2018	Emerade®	PFS auto-injector	The submission requested a temporary listing as an alternative to EpiPen, to address a supply shortage of adrenaline products.	Recommended	The PBAC recommended a temporary listing to address shortage supply issues with EpiPen. (para 5.1, adrenaline (Emerade) PSD, March 2018 PBAC Meeting). Emerade was subsequently delisted in September 2018 following the lapse of the TGA Section 19A (1) approval.

2.6 Further information is available in the Committee in Confidence Section.

For more detail on PBAC's view, see section 6 PBAC outcome.

3 Requested listing

3.1 The submission requested an almost identical listing for adrenaline (Anapen 300, 500 and Anapen Junior) as the current PBS brands of adrenaline auto-injector. The submission proposed additional wording for Anapen 500.

3.2 The submission stated that the Anapen branded products are not interchangeable or substitutable with any current PBS listed or potential future competitor brands that may enter the Australian market, due to the different device activation or administration technique among product brands by different sponsors.

3.3 The requested listings are shown below. Secretariat suggested additions are in italics and deletions are in strikethrough.

MEDICINAL PRODUCT Medicinal Product Pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands (trade products)
ADRENALINE (EPINEPHRINE)					
adrenaline (epinephrine) 150 microgram/0.3 mL injection, 0.3 mL pen device	8679R	1	1	0	^a Adrenaline Jr Mylan ^a EpiPen Jr.
adrenaline (epinephrine) 150 microgram/0.3 mL injection, 0.3 mL pen device	NEW	1	30 1	0	Anapen Junior
adrenaline (epinephrine) 300 microgram/0.3 mL injection, 0.3 mL pen device	8698T	1	1	0	^a Adrenaline Jr Mylan ^a EpiPen Jr.
adrenaline (epinephrine) 300 microgram/0.3 mL injection, 0.3 mL pen device	NEW	1	1	0	Anapen

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Initial treatment: Restriction Summary 7371 edited / Treatment of Concept: 4909 edited
Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Restriction Type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online)
Caution: ANAPEN has a different administration technique from other adrenaline auto-injector brands. It is important that ANAPEN is prescribed to patients with the appropriate training for its use.
<i>Non-Anapen and Anapen products have different administration techniques and should not be prescribed to the same patient without training in their use.</i>
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
Administrative Advice: The auto-injector should be provided in the framework of a comprehensive anaphylaxis prevention program and an emergency action plan including training in recognition of the symptoms of anaphylaxis and the use of the auto-injector device. (For further information see the Australasian Society of Clinical Immunology and Allergy website at www.allergy.org.au .)
Administrative Advice: Authority approvals will be limited to a maximum quantity of 2 auto-injectors at any one time.
Administrative Advice: No applications for repeats will be authorised.
Indication: Acute allergic reaction with anaphylaxis
Treatment Phase: Initial sole PBS-subsidised supply for anticipated emergency treatment
Clinical criteria:
Patient must have been assessed to be at significant risk of anaphylaxis by, or in consultation with a clinical immunologist; or
Patient must have been assessed to be at significant risk of anaphylaxis by, or in consultation with an allergist; or
Patient must have been assessed to be at significant risk of anaphylaxis by, or in consultation with a paediatrician; or
Patient must have been assessed to be at significant risk of anaphylaxis by, or in consultation with a respiratory physician
Prescribing Instructions: The name of the specialist consulted must be provided at the time of application for initial supply.

Initial treatment (upon hospital discharge) Restriction Summary 8695 edited / ToC: 8734 edited

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Restriction Type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online)
Caution: ANAPEN has a different administration technique from other adrenaline auto-injector brands. It is important that ANAPEN is prescribed to patients with the appropriate training for its use.
<i>EpiPen Non-Anapen and Anapen products have different administration techniques and should not be prescribed to the same patient without training in their use.</i>
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
Administrative Advice: The auto-injector should be provided in the framework of a comprehensive anaphylaxis prevention program and an emergency action plan including training in recognition of the symptoms of anaphylaxis and the use of the auto-injector device. (For further information see the Australasian Society of Clinical Immunology and Allergy website at www.allergy.org.au .)
Administrative Advice: Authority approvals will be limited to a maximum quantity of 2 auto-injectors at any one time.
Administrative Advice: No applications for repeats will be authorised.
Indication: Acute allergic reaction with anaphylaxis
Treatment Phase: Initial sole PBS-subsidised supply for anticipated emergency treatment
Clinical criteria:
Patient must have been discharged from hospital or an emergency department after treatment with adrenaline (epinephrine) for acute allergic reaction with anaphylaxis

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Continuing treatment Restriction Summary 7351 edited/ ToC: 4947 edited

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Restriction Type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online)
Caution: ANAPEN has a different administration technique from other adrenaline auto-injector brands. It is important that ANAPEN is prescribed to patients with the appropriate training for its use.
EpiPen Non-Anapen and Anapen products have different administration techniques and should not be prescribed to the same patient without training in their use.
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
Administrative Advice: The auto-injector should be provided in the framework of a comprehensive anaphylaxis prevention program and an emergency action plan including training in recognition of the symptoms of anaphylaxis and the use of the auto-injector device. (For further information see the Australasian Society of Clinical Immunology and Allergy website at www.allergy.org.au .)
Administrative Advice: Authority approvals will be limited to a maximum quantity of 2 auto-injectors at any one time.
Administrative Advice: No applications for repeats will be authorised.
Indication: Acute allergic reaction with anaphylaxis
Treatment Phase: Continuing sole PBS-subsidised supply for anticipated emergency treatment
Clinical criteria:
Patient must have previously been issued with an authority prescription for this drug

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ADRENALINE (EPINEPHRINE)					
adrenaline (epinephrine) 500 microgram/0.3 mL injection, 0.3 mL pen device	NEW	1	1	0	Anapen

Restriction Summary [new – based on 7371 edited] / Treatment of Concept: [new - based on 4909 edited]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Restriction Type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online)
Administrative Advice: <i>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.</i>
Administrative Advice: The auto-injector should be provided in the framework of a comprehensive anaphylaxis prevention program and an emergency action plan including training in recognition of the symptoms of anaphylaxis and the use of the auto-injector device. (For further information see the Australasian Society of Clinical Immunology and Allergy website at www.allergy.org.au .)
Administrative Advice: Authority approvals will be limited to a maximum quantity of 2 auto-injectors at any one time.
Administrative Advice: No applications for repeats will be authorised.
Indication: Acute allergic reaction with anaphylaxis
Treatment Phase: Initial sole PBS-subsidised supply for anticipated emergency treatment
Clinical criteria:
Patient must have been assessed to be at significant risk of anaphylaxis by, or in consultation with a clinical immunologist; or
Patient must have been assessed to be at significant risk of anaphylaxis by, or in consultation with an allergist; or
Patient must have been assessed to be at significant risk of anaphylaxis by, or in consultation with a paediatrician; or
Patient must have been assessed to be at significant risk of anaphylaxis by, or in consultation with a respiratory physician
AND
Clinical criteria:
Patient must have a mean body weight of 60 kg for whom a 300 microgram adrenaline dose may not be sufficient; or
Patient must have been assessed to be at high risk of severe anaphylaxis for whom a 300 microgram adrenaline dose may not be sufficient.
Prescribing Instructions: The name of the specialist consulted must be provided at the time of application for initial supply.
Caution: ANAPEN has a different administration technique from other adrenaline auto-injector brands. It is important that ANAPEN is prescribed to patients with the appropriate training for its use. EpiPen Non-Anapen and Anapen products have different administration techniques and should not be prescribed to the same patient without training in their use.

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Restriction Summary [new – based on 8695 edited] / Treatment of Concept: [new – based on 8734 edited]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Restriction Type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online)
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
Administrative Advice: The auto-injector should be provided in the framework of a comprehensive anaphylaxis prevention program and an emergency action plan including training in recognition of the symptoms of anaphylaxis and the use of the auto-injector device. (For further information see the Australasian Society of Clinical Immunology and Allergy website at www.allergy.org.au .)
Administrative Advice: Authority approvals will be limited to a maximum quantity of 2 auto-injectors at any one time.
Administrative Advice: No applications for repeats will be authorised.
Indication: Acute allergic reaction with anaphylaxis
Treatment Phase: Initial sole PBS-subsidised supply for anticipated emergency treatment
Clinical criteria: Patient must have been discharged from hospital or an emergency department after treatment with adrenaline (epinephrine) for acute allergic reaction with anaphylaxis.
AND
Clinical criteria: Patient must have a mean body weight of 60 kg for whom a 300 microgram adrenaline dose may not be sufficient
OR
Clinical criteria: Patient must have been assessed to be at high risk of severe anaphylaxis for whom a 300 microgram adrenaline dose may not be sufficient.
Caution: ANAPEN has a different administration technique from other adrenaline auto-injector brands. It is important that ANAPEN is prescribed to patients with the appropriate training for its use.
EpiPen Non-Anapen and Anapen products have different administration techniques and should not be prescribed to the same patient without training in their use.

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Restriction Summary [new – based on 7351 edited] / Treatment of Concept: [new – based on 4947 edited]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Restriction Type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online)
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
Administrative Advice: The auto-injector should be provided in the framework of a comprehensive anaphylaxis prevention program and an emergency action plan including training in recognition of the symptoms of anaphylaxis and the use of the auto-injector device. (For further information see the Australasian Society of Clinical Immunology and Allergy website at www.allergy.org.au .)
Administrative Advice: Authority approvals will be limited to a maximum quantity of 2 auto-injectors at any one time.
Administrative Advice: No applications for repeats will be authorised.
Indication: Acute allergic reaction with anaphylaxis
Treatment Phase: Continuing sole PBS-subsidised supply for anticipated emergency treatment
Clinical criteria: Patient must have previously been issued with an authority prescription for this drug.
AND
Clinical criteria: Patient must have a mean body weight of 60 kg for whom a 300 microgram adrenaline dose may not be sufficient
OR
Clinical criteria: Patient must have been assessed to be at high risk of severe anaphylaxis for whom a 300 microgram adrenaline dose may not be sufficient.
Caution: ANAPEN has a different administration technique from other adrenaline auto-injector brands. It is important that ANAPEN is prescribed to patients with the appropriate training for its use. <i>EpiPen Non-Anapen and Anapen products have different administration techniques and should not be prescribed to the same patient without training in their use.</i>

- 3.4 The sponsor supported the proposed changes to the restriction (p1, pre-PBAC response), but reaffirmed its position that Anapen should not be substitutable (i.e. a-flagged) with any other brand of adrenaline.

For more detail on PBAC’s view, see section 6 PBAC outcome.

4 Comparator

- 4.1 The minor submission nominated EpiPen and EpiPen Junior 150 as the main comparator for Anapen 300 and Anapen Junior, respectively.
- 4.2 The submission stated that Anapen 500 is a new strength that will replace standard medical management of 2 X 300 mcg adrenaline auto-injectors for patients weighing 60 kg or more. No comparator was nominated.

For more detail on PBAC’s view, see section 6 PBAC outcome.

5 Consideration of the evidence

- 5.1 As a minor submission, the clinical evidence, economic analysis and financial estimates were not independently evaluated.

Sponsor hearing

5.2 There was no hearing for this item as it was a minor submission.

Consumer comments

5.3 The PBAC noted and welcomed the input from individuals (13), health care professional (1) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with Anapen including the availability of an alternative brand of adrenaline to address stock shortages issue, and the need for a 500 mcg strength to meet currently unmet clinical need for patients greater than 60 kg.

Clinical trials

5.4 The minor submission did not present any new clinical evidence for Anapen 300 and Anapen Junior.

5.5 A study not considered by the PBAC in its previous consideration of Anapen 500 was presented. The study (P15-09) assessed the pharmacokinetic (PK)/ pharmacodynamic (PD) cardiovascular profile of a single 500 mcg adrenaline injection in healthy normal weight males and otherwise healthy overweight or obese females.

5.6 The study reported that:

- Anapen 500 produces rapid PK and PD changes in normal weight, overweight and obese subjects, irrespective of intramuscular or subcutaneous injection, and is well tolerated.
- The results confirm those of the equivalent Anapen 300 study (P14-04) that showed a high correlation between PK and PD parameters.
- For the first 20 minute post-injection period, which would be the most relevant for a prompt reversal of the cardiovascular manifestations of anaphylactic shock (i.e. fall in blood pressure and heart depression), the Tmax and Cmax (or Emax) are similar for normal weight male subjects and overweight and obese female subjects, and Tmax is similar for PK and PD parameters.
- Total exposure to adrenaline in overweight/obese women is even higher than in normal weight men, reflecting an enhanced protection duration potentially of high interest in the anaphylactic shock treatment period.
- Compared with Anapen 300, there is a nearly proportional increase in responses that is well tolerated, which indicates the dose increase should result in an enhanced efficacy associated with similar tolerance. The interpretation of the clinical evidence is best captured by this conclusion of Study P15-09.

Clinical claim

5.7 The submission claimed non-inferior comparative effectiveness of Anapen 300 and Anapen Junior compared with EpiPen. The submission referred to the PBS therapeutic relativity statement to support this claim.

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- 5.8 The submission claimed that Anapen 500 is non-inferior in comparative effectiveness to the current PBS listed brands of 300 mcg auto-injector, as supported by the PBAC recommendation in November 2011 and based on the similarities in PK/PD changes in Study 15-09 and 14-04.
- 5.9 The submission claimed non-inferior comparative safety of Anapen 300, Anapen 500 and Anapen Junior compared with EpiPen.
- 5.10 The PBAC considered that the claim of non-inferior comparative effectiveness and safety could not be confirmed before the finalisation of the TGA approval.

Economic Analysis

- 5.11 The minor submission presented a cost-minimisation analysis of Anapen 500, Anapen 300 and Anapen Junior against currently listed adrenaline auto-injectors.
- 5.12 The PBAC previously recommended listing Anapen 300 and Anapen Junior on a cost-minimisation basis with EpiPen (March 2010 PBAC Meeting); and recommended Anapen 500 on a cost-minimisation basis with adrenaline 300 mcg (November 2011 PBAC Meeting).

Estimated PBS usage & financial implications

- 5.13 The sponsor proposed the same price for Anapen 500, Anapen 300 and Anapen Junior as the currently listed adrenaline auto-injector brands (DPMQ \$84.26).
- 5.14 The submission claimed that Anapen is not expected to grow the market because the brand will be prescribed in place of other adrenaline auto-injectors. The PBAC previously accepted this argument (para 7.5, adrenaline Public Summary Document, March 2016 PBAC Meeting).
- 5.15 The minor submission estimated there to be no financial implications to the PBS or changes in PBS usage as the submission expected Anapen Junior and Anapen 300 to substitute for EpiPen Jr/Adrenaline Jr Mylan and EpiPen/Adrenaline Mylan 300 mcg respectively. Anapen 500 is expected to substitute adrenaline use for individuals weighing at least 60 kg per the draft PI.
- 5.16 If Anapen 500 were to replace usage of two 300 mcg strength auto-injectors, then a net save would be expected. However, it is unclear how many patients are using two 300 mcg auto-injectors as per guidelines and therefore the sponsor has taken a conservative approach in the financial estimates.
- 5.17 The submission did not state the equi-effective doses of one Anapen 500. The PBAC previously recommended Anapen 500 on a cost-minimisation basis with adrenaline 300 mcg at its November 2011 meeting.

Quality Use of Medicines

- 5.18 The sponsor stated that the listing of Anapen would increase the availability of adrenaline auto-injectors to treat anaphylaxis and address the concerns of stock shortages due to one supplier in Australia.
- 5.19 The submission claimed that there is a clinical need for Anapen 500 to address under dosing and/or repeated 300 mcg auto-injector usage issues in the treatment of anaphylaxis in individuals weighing 60 kg or more.
- 5.20 The submission stated that the versions of Anapen proposed for listing have been upgraded to ensure optimal effectiveness and safety with ease of use and simple, timely administration and delivery of adrenaline.
- 5.21 The sponsor raised concerns over the potential for confusion regarding the administration of different adrenaline auto-injector devices. The risk minimisation plan for Anapen submitted to the TGA includes risk minimising activities to address this. The PBAC may wish to request NPS MedicineWise educate prescribers on the different auto-injector devices if Anapen is recommended for listing.
- 5.22 The sponsor stated that it would be supporting ASCIA and Allergy & Anaphylaxis Australia in the provision of various anaphylaxis education/training resources and initiatives, as well as other stakeholders within the allergy and anaphylaxis community. This includes ASCIA and/or company specific materials for healthcare professionals, patients and carers.

For more detail on PBAC's view, see section 6 PBAC outcome.

6 PBAC Outcome

- 6.1 The PBAC deferred making a recommendation to list adrenaline auto-injectors, Anapen Junior, Anapen 300 and Anapen 500, as the TGA Delegate's Overview was not available at the time of consideration. However, the PBAC was of a mind to recommend the General Schedule, Authority Required listing of adrenaline auto-injectors Anapen 300, Anapen 500 and Anapen Junior for treatment of acute allergic reaction with anaphylaxis.
- 6.2 The PBAC noted that consideration of medicines in parallel with the TGA is usually restricted to major submissions, however in light of the ongoing supply issues for PBS listed brands of adrenaline PFS auto-injectors, this submission was accepted prior to receiving the Delegate's Overview.
- 6.3 The PBAC noted that consumer comments referred to the shortages of availability of PBS listed brands of adrenaline and the benefits of a 500 mcg strength to meet the unmet clinical for patients greater than 60 kg.
- 6.4 The PBAC noted that the issues of brand substitution ('a' flagging) and shortage of supply of adrenaline products in its previous considerations of adrenaline auto-injectors remained a consideration for this submission. While the PBAC noted the

differences in administration techniques of Anapen, EpiPen and Adrenaline Mylan, it considered that patients with sufficient anaphylaxis education/training resources would be able to administer different devices appropriately. The PBAC noted that the sponsor requested that Anapen not be considered equivalent to other adrenaline auto-injector brands for the purposes of substitution. However, the PBAC considered that the substitutability of Anapen and EpiPen would assist in the timely dispensing of adrenaline during the shortages of other PBS listed brands. The PBAC requested that the Department discuss the option of ‘a’ flagging Anapen with other brands of adrenaline with the sponsor.

- 6.5 The PBAC noted that the proposed restrictions for Anapen, in particular the NOTE that Anapen and non-Anapen products should not be prescribed to the same patient without training, placed emphasis on the prescriber to highlight the differences in the administration techniques. The PBAC advised that the NOTE should also state that pharmacists ensure patients are educated on these differences.
- 6.6 The PBAC considered that the listing of Anapen 300 and Anapen Junior would not grow the current market. The PBAC noted that it was unclear how many patients were using two 300 mcg auto-injectors as per guidelines although the availability of a 500 mcg adrenaline auto-injector would benefit some patients.
- 6.7 The PBAC noted that the requested PBS listing for Anapen 500 included additional restrictions to limit treatment to patients with a mean body weight of 60 kg or more, or patients who have been assessed to be at high risk of severe anaphylaxis, where a 300 mcg dose of adrenaline may not be sufficient. The PBAC noted that the initial prescribing criteria restricts prescribing by, or in consultation with, a clinical immunologist, an allergist, a paediatrician or a respiratory physician, and therefore advised that the additional clinical criteria was not required. The PBAC considered that the removal of the requested additional clinical criteria would allow prescribers flexibility in dosing.
- 6.8 The PBAC noted that the sponsor planned to implement a range of quality use of medicines activities. The PBAC advised that these activities should be targeted at all prescribers as well as pharmacists.
- 6.9 The PBAC advised in principle that the Early Supply Rule should not apply to Anapen, as it does not apply to EpiPen, because it is used for recurrent episodic use and there is a clinical imperative to ensure ongoing supply.
- 6.10 The PBAC advised in principle that Anapen is suitable for prescribing by nurse practitioners, in line with the recommendation for EpiPen.

Outcome:
Deferred

Addendum to the November 2020 PBAC Minutes:

NEW LISTINGS

Between its **November 2020** and **March 2021** meetings, the PBAC decided to recommend to the Minister (under section 101(3) of the *National Health Act 1953* (“the Act”)) that adrenaline auto-injectors, Anapen 300[®], Anapen 500[®] and Anapen 150 Junior[®] be made available as pharmaceutical benefits under Part VII of the Act, under certain circumstances specified in accordance with section 101(3C) of the Act.

SCHEDULE EQUIVALENTS

Between its **November 2020** and **March 2021** meetings, the PBAC decided to advise the Minister (under section 101(4AACD) of the Act) that Anapen 300[®] should be treated as equivalent to EpiPen and Adrenaline Mylan; and that Anapen 150 Junior[®] should be treated as equivalent to EpiPen Jr and Adrenaline Jr Mylan.

A note of the PBAC’s advice follows.

7 Background

- 7.1 At its November 2020 meeting, the PBAC deferred making a recommendation regarding the General Schedule, Authority Required listing of adrenaline auto-injectors, Anapen 300[®], Anapen 500[®] and Anapen 150 Junior[®] (Anapen Junior) for treatment of acute allergic reaction with anaphylaxis, as the TGA Delegate’s Request for ACM Advice (Delegate’s Overview) or indicative TGA outcome was not available at the time of consideration. The PBAC was of a mind to recommend adrenaline pending provision of the TGA Delegate’s overview or other such advice supportive of the TGA registration.
- 7.2 The sponsor provided the positive TGA Delegate’s Summary on 23 December 2020. ARTG registration is expected at the end of February 2021.
- 7.3 In its previous considerations of adrenaline auto-injectors, the PBAC noted the issues of brand substitution (‘a’ flagging) and shortage of supply of adrenaline products. While the PBAC noted the differences in administration techniques of Anapen, EpiPen and Adrenaline Mylan, it considered that patients with sufficient anaphylaxis education/training resources would be able to administer different devices appropriately.
- 7.4 The PBAC previously noted that the sponsor requested that Anapen not be considered equivalent to other adrenaline auto-injector brands for the purposes of substitution (‘a’ flagged). However, the PBAC considered that the substitutability of Anapen and EpiPen would assist in the timely dispensing of adrenaline during shortages.

8 TGA advice

- 8.1 The TGA Delegate's Overview (p5) stated that the evaluator has no objections to the registration of Anapen 150/300/500 adrenaline (epinephrine) 0.3 mL injection solution syringe based on the two PK/PD studies in healthy volunteers: Study P14-04 and Study P15-09 and Periodic Safety Update Report (PSUR) covering 1 June 2010 – 4 September 2018.
- 8.2 The TGA Delegate's Overview (pp10-11) noted that the sponsor has made a commitment to work with key bodies (ASCIA and Allergy Australia) to develop treatment and care plans and instructional videos about how to use this device which will be made available to doctors (GPs, paediatricians, immunologists), nurses, and the community.
- 8.3 The TGA Delegate's Overview (p10) also noted that a routine risk minimisation plan was proposed in the TGA submission. The TGA Delegate's Overview also noted that the sponsor should continue to review the data regarding device failure, which was an important identified risk that should be clearly described in the PSUR.

9 PBAC Outcome

- 9.1 The PBAC recommended the General Schedule Authority Required listing of adrenaline auto-injectors Anapen 300®, Anapen 500® and Anapen 150 Junior® (Anapen Junior) for the treatment of acute allergic reaction with anaphylaxis.
- 9.2 The PBAC recommended Anapen 300 and Anapen 500 on a cost-minimisation basis to Epipen; and Anapen Junior to Epipen Jr. The PBAC maintained that the listing of Anapen 300 and Anapen Junior would not grow the current market. The PBAC reiterated that it was unclear how many patients were using two 300 mcg auto-injectors as per guidelines although the availability of a 500 mcg adrenaline auto-injector would benefit some patients. Overall, the PBAC considered the listing of Anapen should result in no net cost to the Government.
- 9.3 The PBAC advised that the equi-effective doses should be consistent with PBAC's previous recommendation of Anapen 300 and Anapen Junior at its March 2010 meeting; and Anapen 500 at its November 2011 meeting. The PBAC advised that the equi-effective doses are:
 - one Anapen 300 and one Anapen 500 and one Epipen 300 and one Adrenaline Mylan 300
 - one Anapen Junior and one Epipen Jr and one Adrenaline Jr Mylan
- 9.4 The PBAC considered that the claim of non-inferior comparative effectiveness and safety was acceptable based on the advice in the TGA Delegate's Overview. The TGA Delegate's Overview stated that the evaluator had no objections to the TGA registration of Anapen. The PBAC also noted that there is a long history of use of this

product internationally and similarity between the formulation for Anapen and EpiPen (p5, TGA Delegate's Overview).

- 9.5 The PBAC advised that under Section 101(4AACD) of the *National Health Act 1953*, in the Schedule of Pharmaceutical Benefits, Anapen 300 should be treated as equivalent at the pharmacy level (i.e. 'a' flagged in the Schedule) for the purpose of substitution for the treatment of acute allergic reaction with anaphylaxis with EpiPen 300 and Adrenaline Mylan 300; and Anapen Junior should be treated as equivalent at the pharmacy level (i.e. 'a' flagged in the Schedule) for the purpose of substitution for the treatment of acute allergic reaction with anaphylaxis with EpiPen Jr and Adrenaline Jr Mylan. The PBAC was satisfied that the differences in administration techniques of Anapen, EpiPen and Adrenaline Mylan would be appropriately managed based on the clinical, safety and risk management information in the TGA Delegate's Overview. The PBAC advised that Anapen 500 should not be treated as equivalent at the pharmacy level (i.e. 'a' flagged in the Schedule) for the purpose of substitution for the treatment of acute allergic reaction with anaphylaxis with other adrenaline auto injectors as there are no other adrenaline auto injector products on the PBS with this strength.
- 9.6 The PBAC reiterated that the substitutability of Anapen, EpiPen and Adrenaline Mylan would assist in the timely dispensing of adrenaline during shortages.
- 9.7 The PBAC noted in the TGA Delegate's Overview that the sponsor was committed to working with key bodies (Australasian Society of Clinical Immunology and Allergy (ASCIA) and Allergy Australia) to develop education and training resources around how to use Anapen. The PBAC reiterated its advice that educational activities should be targeted at all prescribers as well as pharmacists. The PBAC requested the sponsor and the Department work together with NPS MedicineWise and the Pharmaceutical Society of Australia to ensure pharmacists are educated on the product differences of adrenaline auto-injector devices.
- 9.8 The PBAC reiterated the following advice regarding the restrictions for Anapen:
- A NOTE should be included to note that Anapen and non-Anapen products should not be prescribed to the same patient without training from the prescriber and that pharmacists should ensure patients are educated on the product differences.
 - The additional clinical criteria for Anapen 500 in the requested listing regarding limiting treatment to patients with a mean body weight of 60 kg or more, or patients who have been assessed to be at high risk of severe anaphylaxis, where a 300 mcg dose of adrenaline may not be sufficient should not be included. The PBAC considered that the removal of the requested additional clinical criteria would allow prescribers flexibility in dosing.
- 9.9 The PBAC advised that Anapen is suitable for prescribing by nurse practitioners, in line with the recommendation for EpiPen.

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9.10 The PBAC advised that the Early Supply Rule should not apply to Anapen, as it does not apply to EpiPen, because it is used for recurrent episodic use and there is a clinical imperative to ensure ongoing supply.

9.11 The PBAC noted that this submission is not eligible for an Independent Review, as it received a positive recommendation.

Outcome:

Recommended

10 Recommended listing

10.1 Add new adrenaline brand (Anapen) listing as follows; and add restriction flow on of maximum quantity of 2 for EpiPen, EpiPen Jr, Adrenaline Mylan and Adrenaline Jr Mylan:

MEDICINAL PRODUCT Medicinal Product Pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands (trade products)
ADRENALINE (EPINEPHRINE)					
adrenaline (epinephrine) 150 microgram/0.3 mL injection, 0.3 mL pen device	8679R	1	1	0	^a Adrenaline Jr Mylan ^a EpiPen Jr.
adrenaline (epinephrine) 150 microgram/0.3 mL injection, 0.3 mL pen device	NEW	1	1	0	Anapen Junior
adrenaline (epinephrine) 300 microgram/0.3 mL injection, 0.3 mL pen device	8698T	1	1	0	^a Adrenaline Jr Mylan ^a EpiPen Jr.
adrenaline (epinephrine) 300 microgram/0.3 mL injection, 0.3 mL pen device	NEW	1	1	0	Anapen

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Initial treatment: Restriction Summary 7371 edited / Treatment of Concept: 4909 edited	
Concept ID	Category / Program: GENERAL – General Schedule (Code GE)
(for internal Dept. use)	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
	Restriction Type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online)
14061 edited	Caution: Non-Anapen and Anapen products have different administration techniques. These products should not be prescribed to the same patient without training in their use. Pharmacists should ensure that patients are educated regarding the product differences upon dispensing.
25796	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
14062	Administrative Advice: The auto-injector should be provided in the framework of a comprehensive anaphylaxis prevention program and an emergency action plan including training in recognition of the symptoms of anaphylaxis and the use of the auto-injector device. (For further information see the Australasian Society of Clinical Immunology and Allergy website at www.allergy.org.au .)
21431	Administrative Advice: Authority approvals will be limited to a maximum quantity of 2 auto-injectors at any one time.
13287	Administrative Advice: No applications for repeats will be authorised.
14054	Indication: Acute allergic reaction with anaphylaxis
	Treatment Phase: Initial sole PBS-subsidised supply for anticipated emergency treatment
14079	Clinical criteria:
14075	Patient must have been assessed to be at significant risk of anaphylaxis by, or in consultation with a clinical immunologist; or
14076	Patient must have been assessed to be at significant risk of anaphylaxis by, or in consultation with an allergist; or
14077	Patient must have been assessed to be at significant risk of anaphylaxis by, or in consultation with a paediatrician; or
14078	Patient must have been assessed to be at significant risk of anaphylaxis by, or in consultation with a respiratory physician
13830	Prescribing Instructions: The name of the specialist consulted must be provided at the time of application for initial supply.

Initial treatment (upon hospital discharge) Restriction Summary 8695 edited / ToC: 8734 edited

Concept ID	Category / Program: GENERAL – General Schedule (Code GE)
(for internal Dept. use)	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
	Restriction Type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online)
Insert 14061 edited	Caution: Non-Anapen and Anapen products have different administration techniques. These products should not be prescribed to the same patient without training in their use. Pharmacists should ensure that patients are educated regarding the product differences upon dispensing.
Insert 25796	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
14062	Administrative Advice: The auto-injector should be provided in the framework of a comprehensive anaphylaxis prevention program and an emergency action plan including training in recognition of the symptoms of anaphylaxis and the use of the auto-injector device. (For further information see the Australasian Society of Clinical Immunology and Allergy website at www.allergy.org.au .)
21431	Administrative Advice: Authority approvals will be limited to a maximum quantity of 2 auto-injectors at any one time.
13287	Administrative Advice: No applications for repeats will be authorised.
14054	Indication: Acute allergic reaction with anaphylaxis
	Treatment Phase: Initial sole PBS-subsidised supply for anticipated emergency treatment
23753	Clinical criteria:
23754	Patient must have been discharged from hospital or an emergency department after treatment with adrenaline (epinephrine) for acute allergic reaction with anaphylaxis

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Continuing treatment Restriction Summary 7351 edited/ ToC: 4947 edited

Concept ID	Category / Program: GENERAL – General Schedule (Code GE)
(for internal Dept. use)	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
	Restriction Type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online)
Insert 14061 edited	Caution: Non-Anapen and Anapen products have different administration techniques. These products should not be prescribed to the same patient without training in their use. Pharmacists should ensure that patients are educated regarding the product differences upon dispensing.
Insert 25796	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
14062	Administrative Advice: The auto-injector should be provided in the framework of a comprehensive anaphylaxis prevention program and an emergency action plan including training in recognition of the symptoms of anaphylaxis and the use of the auto-injector device. (For further information see the Australasian Society of Clinical Immunology and Allergy website at www.allergy.org.au .)
21431	Administrative Advice: Authority approvals will be limited to a maximum quantity of 2 auto-injectors at any one time.
13287	Administrative Advice: No applications for repeats will be authorised.
14054	Indication: Acute allergic reaction with anaphylaxis
	Treatment Phase: Continuing sole PBS-subsidised supply for anticipated emergency treatment
7738	Clinical criteria:
7737	Patient must have previously been issued with an authority prescription for this drug

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ADRENALINE (EPINEPHRINE)					
adrenaline (epinephrine) 500 microgram/0.3 mL injection, 0.3 mL pen device	NEW	1	1	0	Anapen

Restriction Summary [new – based on 7371 edited] / Treatment of Concept: [new - based on 4909 edited]

Concept ID (for internal Dept. use)	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
	Restriction Type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online)
Insert 14061 edited	Caution: Non-Anapen and Anapen products have different administration techniques. These products should not be prescribed to the same patient without training in their use. Pharmacists should ensure that patients are educated regarding the product differences upon dispensing.
Insert 25796	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
14062	Administrative Advice: The auto-injector should be provided in the framework of a comprehensive anaphylaxis prevention program and an emergency action plan including training in recognition of the symptoms of anaphylaxis and the use of the auto-injector device. (For further information see the Australasian Society of Clinical Immunology and Allergy website at www.allergy.org.au .)
21431	Administrative Advice: Authority approvals will be limited to a maximum quantity of 2 auto-injectors at any one time.
13287	Administrative Advice: No applications for repeats will be authorised.
14054	Indication: Acute allergic reaction with anaphylaxis
	Treatment Phase: Initial sole PBS-subsidised supply for anticipated emergency treatment
14079	Clinical criteria:
14075	Patient must have been assessed to be at significant risk of anaphylaxis by, or in consultation with a clinical immunologist; or
14076	Patient must have been assessed to be at significant risk of anaphylaxis by, or in consultation with an allergist; or
14077	Patient must have been assessed to be at significant risk of anaphylaxis by, or in consultation with a paediatrician; or
14078	Patient must have been assessed to be at significant risk of anaphylaxis by, or in consultation with a respiratory physician
13830	Prescribing Instructions: The name of the specialist consulted must be provided at the time of application for initial supply.

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Restriction Summary [new – based on 8695 edited] / Treatment of Concept: [new – based on 8734 edited]

Concept ID (for internal Dept. use)	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
	Restriction Type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online)
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21431	Administrative Advice: Authority approvals will be limited to a maximum quantity of 2 auto-injectors at any one time.
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14054	Indication: Acute allergic reaction with anaphylaxis
	Treatment Phase: Initial sole PBS-subsidised supply for anticipated emergency treatment
23753	Clinical criteria:
23754	Patient must have been discharged from hospital or an emergency department after treatment with adrenaline (epinephrine) for acute allergic reaction with anaphylaxis.

Restriction Summary [new – based on 7351 edited] / Treatment of Concept: [new – based on 4947 edited]

Concept ID (for internal Dept. use)	Category / Program: GENERAL – General Schedule (Code GE)
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	Restriction Type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online)
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14054	Indication: Acute allergic reaction with anaphylaxis
	Treatment Phase: Continuing sole PBS-subsidised supply for anticipated emergency treatment
7738	Clinical criteria:
7737	Patient must have previously been issued with an authority prescription for this drug.

11 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about

other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

12 Sponsor's Comment

The sponsor had no comment.