ABOUT THE AUTHORS

Harold Kim, MD, FRCPC

Dr. Harold Kim is an allergist practicing in Kitchener and London, Ontario, and serving as Chief of the Division of Clinical Immunology and Allergy at University of Western Ontario He holds Associate and Assistant Professorships at University of Western Ontario and McMaster Universities respectively. Dr. Kim has contributed to a number of national guidelines documents. He is a past president of the Canadian Society of Allergy and Clinical Immunology, and he is Editor-in-Chief of Allergy, Asthma, and Clinical Immunology.

Affiliations:
University of Western Ontario, London, Ontario
McMaster University, Hamilton, Ontario

Graham Walter, MD, FRCPC

Graham Walter is a community-based allergist practicing in Winnipeg, Manitoba. He completed his Internal Medicine residency at the University of Manitoba, followed by Clinical Immunology & Allergy subspecialty training at Western University Ontario.

Affiliations:
University of Manitoba, Winnipeg, Manitoba

EPINEPHRINE AUTO-INJECTORS IN CANADA: A REVIEW OF AVAILABLE PRODUCTS AND CLINICAL PROPOSALS

Background

Anaphylaxis is a severe reaction with significant associated morbidity and mortality that necessitates prompt on-demand management for patients. Epinephrine administered intramuscularly at a dose of 0.01 mg/kg of body weight, up to a maximum single dose of 0.5 mg at one time, is the first-line treatment for anaphylaxis.[1,2] Epinephrine auto-injectors (EAIs) are devices designed to deliver a predetermined dose of epinephrine rapidly and reliably into the vastus lateralis muscle of the mid-anterolateral thigh for treatment of anaphylaxis.[3,4] All commercially available auto-injectors in Canada are fixed-dose delivery systems, therefore titration of epinephrine dose based on patient weight is not possible.[5-7]

In Canada, there are several manufacturers of EAIs, providing treating physicians and patients with a variety of options to treat anaphylaxis in the community. However, as these devices all contain the same medication, physicians may not realize that specific EAIs may be of greater utility in certain clinical circumstances. This scientific review aims to describe all currently available EAIs in Canada, with detailed discussion on the differences between products and the nuances of a patient-centred approach to prescription in a market filled with seemingly "one size fits all" devices.

Epinephrine Dosing and Needle Length

Canadian Society of Allergy and Clinical Immunology (CSACI) Recommendations

The CSACI recommends the use of a 0.15 mg EAI for children weighing 15 kg-25 kg, a 0.3 mg EAI for adults and children weighing 25-45kg, and a 0.5 mg EAI for adults and adolescents weighing 45 kg or greater.[8,9]

Although recommendations are not explicitly made regarding needle length, the recommendation for a 0.5 mg EIA in patients greater than 45 kg acts as a de facto recommendation, as there is only one 0.5 mg EIA on the market in Canada, and it is manufactured with a 24 mm needle.[8] The longer needle length when compared to competitors was largely developed based on data demonstrating differences in anterolateral thigh subcutaneous adipose tissue depth and skin-to-muscle distance (STMD) in patients with higher body mass indices.[10]

Conversely, care should be taken when counselling regarding pediatric patients under 15 kg body weight, as the 0.15 mg EIAs available may have needle lengths exceeding the STMD, potentially resulting in inadvertent intraosseous administration.[11]

Other Society Recommendations

ecommendations from other societies, including the American Academy of Allergy, Asthma, & Immunology (AAAAI), the American College of Allergy, Asthma, & Immunology (ACAAI), and the European Academy of Allergy & Clinical Immunology (EAACI) are largely the same as the Canadian recommendations, with major differences in recommendations based upon commercial availability of various EIA products, needle lengths and dosages.[9]

Epinephrine Auto-injectors Commercially Available in Canada

EpiPen®

EpiPen® is a widely recognized epinephrine auto-injector on the Canadian market. It is available in two different needle lengths and dosages: EpiPen Jr® and EpiPen. The Product Monograph for EpiPen Jr and EpiPen **(Figure 1)** recommends the use of EpiPen Jr for pediatric patients weighing 15-30 kg and EpiPen for pediatric and adult patients weighing 30 kg or more. The EpiPen Jr delivers a single dose of 0.15 mg epinephrine[5] with a needle length of approximately 12.7 mm, whereas EpiPen delivers a single fixed dose of 0.3 mg epinephrine with a needle length of approximately 16 mm **(Table 1)**.[3]

Although the product monograph for EpiPen Jr limits its use to those pediatric patients weighing <15 kg, as discussed above, most experts agree that off-label prescription of this product for patients weighing <15 kg is appropriate in areas where the 0.1 mg version of this auto-injector is not available (including in Canada).[3,9] Further to this, it should be noted that the 30 kg Product Monograph weight cut-off is different from the 25 kg cut-off suggested by North American allergy societies.[8] This discrepancy reflects the notion that patients weighing 25-30 kg should be administered 0.3 mg instead of 0.15 mg of epinephrine as this higher dose is closer to the internationally accepted dosing at 0.01 mg/kg.[9,12,13]

Practically speaking, therefore, if clinicians prescribe the EpiPen or EpiPen Jr products, the CSACI recommendations are for EpiPen Jr in patients weighing 0-25 kg (vs 30 kg listed by the product monograph), and the regular EpiPen product for those weighing 25-45 kg.[8] Once a patient exceeds this weight, consideration should be made to switch to a product available in 0.5 mg dosing.

As EpiPen has been available on the Canadian market for the longest period of time (and had been the sole EAI on the market on multiple occasions), it likely benefits from both provider and patient name recognition. Further to this, the EpiPen name has also become somewhat of a proprietary eponym, perhaps further driving prescribing practices. From a strictly scientific perspective, other benefits of EpiPen include a moderate-length needle and lower dosing for smaller-sized adults and children.[9] Drawbacks of this device include limited dosing options for patients >45 kg, and short needle length, which may be an issue in patients with a greater degree of subcutaneous tissue.

Based on a growing body of clinical evidence, there is a clear need for the 0.1 mg EpiPen Jr auto-injector in Canada, as well as a higher dose of 0.5 mg, similar to that available with other devices.[9,13,14]

*Emerade™**

Emerade™ **(Figure 1)** is a relatively novel EAI available in Canada.* Each auto-injector delivers a fixed dose of epinephrine into the anterolateral muscle of the thigh, similar to EpiPen. However, Emerade is unique as it is available in both 0.3 mg and 0.5 mg doses, as well as in a longer needle length of approximately 24 mm (23-25 mm listed depending on the resource).[3,6] The Product Monograph suggests the 0.3 mg dose for patients weighing 30-60 kg, with either the 0.3 mg or 0.5 mg dose recommended for those weighing over 60 kg, depending on "clinical judgement" which is not further defined **(Table 1)**.[6]

Figure 1: *Commercially available epinephrine auto-injectors in Canada[17-19] ; courtesy of Harold Kim, MD and Graham Walter, MD*

CSACI recommendations regarding Emerade suggest the use of the 0.3 mg device in patients weighing 25-45 kg, with an increase to the 0.5 mg dose in all patients >45 kg.[8] This implies a switch from a 0.3 mg EAI (of any manufacturer) to the 0.5 mg Emerade EAI in all patients weighing more than 45 kg.

As mentioned above, the major benefits of the Emerade EAI lie in its dosing and needle length. Emerade 0.5 mg EAI is also the only product with a 24 mm needle length, which theoretically ensures more appropriate intramuscular dosing of epinephrine in patients with relatively more adipose tissue.[10] Further to this, the increase in epinephrine dosing available from the Emerade 0.5 mg auto-injector is likely more evidence-based in the majority of patients weighing >45 kg (and certainly in those weighing ≥ 60 kg as recommended by the product monograph).[9,13,14]

The drawbacks of this device are actually rooted in these same features, namely the concern for epinephrine overdose and accidental intraosseous injection due to a needle length that exceeds skin-to-bone distance (STBD).[3,15] These risks can be mitigated by proper patient phenotyping and discussion regarding which patients might benefit from this longer needle length and higher dosing. This patient population typically consists of patients weighing

>45-60 kg with an STMD similar to said needle length, which can be determined by point-of-care (POC) ultrasound in clinics equipped with such technology.[15] Further drawbacks include the lack of a 0.15 mg product on the Canadian market. In addition, this may affect patient comfort with said EAI, as patients and parents anecdotally seem to feel more comfortable continuing use of the same product when increasing dose for weight (i.e., transitioning from the 0.15 mg EpiPen Jr to the 0.3 mg EpiPen when their child reaches 25 kg, rather than altering both the dose and the device).

Allerject®
Allerject® **(Figure 1)** is an additional brand of EAI on the Canadian market. These EAIs have the identical intended use as EpiPen and Emerade, with several unique features. Allerject is available in two different doses and needle lengths: 0.15 mg (12.7 mm) and 0.3 mg (16 mm).[7] Its product monograph suggests identical dosing to that of EpiPen/ EpiPen Jr, with the 0.15 mg EAI recommended in children weighing 15 kg-30 kg, and the 0.3 mg EAI used in those weighing ≥ 30 kg **(Table 1)**.

The recommendations by the CSACI are therefore identical to those for EpiPen/ EpiPen Jr, i.e.; Allerject 0.15 mg is recommended in patients weighing 0-25 kg, and Allerject 0.3 mg is recommended in patients 25-45 kg. Again, once a patient exceeds this weight, consideration should be made to switch to a product available in 0.5 mg dosing (Emerade 0.5 mg EAI).

Allerject auto-injectors offer a unique, compact design, likely making this product easier to carry in a pocket when compared to other available products on the Canadian market. Another distinguishing feature of this device is its voice assistance, with real-time instructions provided aloud when the auto-injector is removed from its sheath to assist patients with epinephrine administration. Not only can this be helpful for pediatric patients, but it may theoretically also hold an advantage in patients with disabilities.

The drawbacks of this product are the same as those for the EpiPen given the similarity in available needle lengths and dosages. They include limited evidence-based dosing options for patients >45 kg, and short needle length, which may be an issue in patients with a greater amount of subcutaneous tissue.

Recommendations

Patients Weighing <25 kg
Based on available EAIs and local recommendations, we would suggest the use of either the EpiPen Jr or Allerject 0.15 mg product in all patients weighing less than 25 kg in the absence of a 0.1 mg product in any device currently on the market. There exist no head-to-head clinical trials to assist in deciding which product might be best for your patient. As both these EAIs contain the identical medication and dose, prescribers should consider their respective product-specific benefits such as unique features, product dimension and patient comfort when deciding between them. Patients may also have a personal preference for one product over another based on prior experience

Patients Weighing 25-45 kg
Recommendations in this weight class are for the EpiPen, Allerject 0.3 mg or Emerade 0.3 mg* device. When deciding between these EAIs, we offer similar guidance to that provided above regarding the 0.15 mg devices.

Patients Weighing >45 kg
In agreement with the CSACI recommendations, we propose use of the Emerade 0.5 mg product*. Given that the product monograph does not recommend this product until patient weight reaches 60 kg, we also suggest some caution in the 45-60 kg patient population with small body habitus and less adipose tissue.

Special Populations

All of the above proposals are weight-based, rather than based on metrics that may encompass more relevant patient attributes such as body mass index (BMI). Therefore, we recommend gross assessment of adiposity by all clinicians prescribing EAIs for patients who meet the weight criteria suggested but have a lower BMI or less adipose tissue. Further to this, POC ultrasonographic assessment of the STMD in centres equipped with this technology adds a greater degree of specificity to this assessment and is recommended.[15]

Conversely, some patients may not meet the weight criteria, but have a higher degree of adiposity which may necessitate a longer needle length. Additionally, we recommend these patients undergo assessment of adiposity either clinically or, more optimally, by ultrasound. It is unlikely that many patients have an STMD that would necessitate the 24 mm needle while weighing <45 kg.

In the pediatric population <15, kg, care should be taken to review EAI use with caregivers, in particular that the anterolateral thigh muscle may need to be laterally compressed between the caregiver's hand before the EAI is deployed, in order to prevent intraosseous administration.

***As of May 5, 2023, Bausch Health has recalled all lots of Emerade auto-injectors in Canada due to possible device failure. Our recommendations have been left unchanged to emphasize the need for a device with more adequate needle length and dosing for many patients.**

CELEBRATING 5 YEARS IN CANADA AND WORLDWIDE
500,000 PATIENTS TREATED WORLDWIDE ACROSS 3 INDICATIONS*

HAVE CONFIDENCE IN DUPIXENT®

Indicated in patients aged 6+ years with moderate-to-severe atopic dermatitis (AD) inadequately controlled with topical prescription therapies[1]

DUPIXENT® (dupilumab injection) is indicated:

Since 2017

- for the treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable
  - DUPIXENT® can be used with or without topical corticosteroids

Since 2020

- as an add-on maintenance treatment in patients aged 6 years and older with severe asthma with a type 2/eosinophilic phenotype or oral corticosteroid-dependent asthma
  - **DUPIXENT® is not indicated for relief of acute bronchospasm or status asthmaticus**

Since 2020

- as an add-on maintenance treatment with intranasal corticosteroids in adult patients with severe chronic rhinosinusitis with nasal polyposis (CRSwNP) inadequately controlled by systemic corticosteroids and/or surgery

Please consult the Product Monograph at http://products.sanofi.ca/en/dupixent-en.pdf for contraindications, warnings, precautions, adverse reactions, interactions, dosing, and conditions of clinical use.

The Product Monograph is also available by calling 1-800-589-6215.

* Comparative clinical significance unknown.

The #1 dispensed interleukin inhibitor indicated in AD in Canada[1,3*]

10,000 treated patients in Canada across 3 indications[4]

Reference: 1. DUPIXENT® Product Monograph, sanofi-aventis Canada Inc., March 25, 2022. **2.** Data on file, sanofi-aventis Canada Inc., August 1, 2022. **3.** IQVIA. Geographic Prescription Monitor Total Prescription Share. May 2022. **4.** Data on file, sanofi-aventis Canada Inc., July 13, 2022.

sanofi | REGENERON®

MEMBER OF INNOVATIVE MEDICINES CANADA

REVIEWED BY PAAB

Pr DUPIXENT® (dupilumab) Injection

Device	Manufacturer	Approximate Cost in Canadian Dollars per device (ON)[16]	Doses Available	Needle-length	Weight Indication (monograph)	Weight Indication (CSACI) (monograpgh)	Approximate Product Dimensions In(Out) of Package (cm)	Other Features
EpiPen / EpiPen Jr	Pfizer	$94.44-$108.61	0.15 mg	12.7 mm	15-30 kg	<25 kg	16 (14) x 3.5 (2.9)	
			0.3 mg	16.0 mm	>30 kg	25-45 kg		
Emerade	Bausch Health	$85.54-$98.37	0.3 mg	16.0 mm	30-60 kg	25-45 kg	18 (17) x 2.9 (2.1)	
			0.5 mg	24.0 mm	>60 kg**	>45 kg		
Allerject	Valeo Pharma	$93.35-$108.50	0.15 mg	12.7 mm	>30 kg	>25 kg	5.2 (5) x 8.5 (8.5)	Voice-assisted instructions on administration
			0.3 mg	16.0 mm	>30 kg	25-45 kg		

Table 1: *Comparison of epinephrine auto-injector features and recommendations ; courtesy of Harold Kim, MD and Graham Walter, MD mg = milligrams, mm = millimetres, cm = centimetres, kg = kilograms*
***Recommendation in monograph applies to adult patients only*

Correspondence:
Dr. Graham Walter
Email: grahamwalter91@gmail.com

Financial Disclosures:
Graham Walter: None declared

Harold Kim: **Medical lecturer and/or advisory board participant:** ALK, AstraZeneca, Bausch Health, CSL Behring, GSK, Miravo, Novartis, Medexus, Pfizer, Sanofi, Takeda.

References:

1. *Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report - Second National Institute of Allergy and Infectious Disease/ Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391–7.*
2. *Shaker MS, Wallace D V., Golden DBK, Oppenheimer J, Bernstein JA, Campbell RL, et al. Anaphylaxis—a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol. 2020;145(4):1082–123.*
3. *Kim H, Alizadehfar R, Alqurashi W, Ellis AK, Fischer DA, Roberts H, et al. Epinephrine autoinjectors: individualizing device and dosage to optimize anaphylaxis management in the community setting. Allergy Asthma Proc. 2023;44(1):45–50.*
4. *Fischer D, Vander Leek TK, Ellis AK, Kim H. Anaphylaxis. Allergy, Asthma Clin Immunol. 2018;14(Suppl 2).*
5. *Mylan Specialty L.P. Prescribing Information EpiPen® [Internet]. 2017. p. 1–22. Available from: https://pdf.hres.ca/dpd_pm/00039519.PDF*
6. *Bausch Health CI. Emerade Prescribing Information [Internet]. 2020. Available from: https://www.emerade.ca/resources/assets/pdf/en/about/emerade-product-monograph.pdf*
7. *Kaleo Inc. Allerject Prescribing Information [Internet]. European Journal of Haematology. 2019. Available from: https://pdf.hres.ca/dpd_pm/00054258.PDF*
8. *Li LDX, Abrams EM, Lavine E, Hildebrand K, Mack DP. CSACI position statement: transition recommendations on existing epinephrine autoinjectors. Allergy, Asthma Clin Immunol [Internet]. 2021;17(1):1–6. Available from: https://doi.org/10.1186/s13223-021-00634-2*
9. *Dreborg S, Walter G, Kim H. International recommendations on epinephrine auto-injector doses often differ from standard weight-based guidance: a review and clinical proposals. Allergy, Asthma Clin Immunol [Internet]. 2022;18(1):1–11. Available from: https://doi.org/10.1186/s13223-022-00736-5*
10. *Song TT, Nelson MR, Chang JH, Engler RJM, Chowdhury BA. Adequacy of the epinephrine autoinjector needle length in delivering epinephrine to the intramuscular tissues. Ann Allergy, Asthma Immunol [Internet]. 2005;94(5):539–42. Available from: http://dx.doi.org/10.1016/S1081-1206(10)61130-1*
11. *Kim H, Dinakar C, McInnis P, Rudin D, Benain X, Daley W, et al. Inadequacy of current pediatric epinephrine autoinjector needle length for use in infants and toddlers. Ann Allergy, Asthma Immunol [Internet]. 2017;118(6):719-725.e1. Available from: http://dx.doi.org/10.1016/j.anai.2017.03.017*
12. *Sicherer SH, Simons FER, Mahr TA, Abramson SL, Dinakar C, Fleisher TA, et al. Epinephrine for first-aid management of anaphylaxis. Pediatrics. 2017;139(3).*
13. *Dreborg S, Kim H. The pharmacokinetics of epinephrine/adrenaline autoinjectors. Allergy, Asthma Clin Immunol [Internet]. 2021;17(1):1–11. Available from: https://doi.org/10.1186/s13223-021-00511-y*
14. *Patel N, Isaacs E, Duca B, Nagaratnam N, Donovan J, Fontanella S, et al. Optimal dose of adrenaline auto-injector for children and young people at risk of anaphylaxis: A phase IV randomized controlled crossover study. Allergy Eur J Allergy Clin Immunol. 2023;(January):1–10.*
15. *Jeimy S, Wong-Pack A, Veettil S, Kim H. Point-of-care ultrasonography in the allergy and immunology clinic. Ann Allergy, Asthma Immunol [Internet]. 2019;123(1):42–7. Available from: https://doi.org/10.1016/j.anai.2019.02.010*
16. *1Prescribe Smart.*
17. *Mylan Specialty L.P. How EpiPen Works [Internet]. [cited 2023 Apr 27]. Available from: https://www.epipen.ca/how-epipen-works*
18. *Bausch Health CI. Emerade : Designed for Simplicity [Internet]. [cited 2023 Apr 27]. Available from: https://www.emerade.ca*
19. *Kaleo Inc. Why Allerject? [Internet]. [cited 2023 Apr 27]. Available from: https://www.allerject.ca/why-allerject.html#voice*