Common Drug Review
Pharmacoeconomic Review Report

January 2018

Drug	icatibant (Firazyr, subcutaneous)
Indication	For the treatment of acute attacks of hereditary angioedema (HAE) in adults with C1 esterase inhibitor deficiency.
Listing request	As per indication.
Manufacturer	Shire Human Genetics Therapies Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in allergy and immunology who provided input on the conduct of the review and the interpretation of findings.

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

C1-INH	C1 esterase inhibitor
HAE	hereditary angioedema
ITC	indirect treatment comparison
IV	intravenous
SC	subcutaneous

SUMMARY

Icatibant (Firazyr) is indicated in Canada for the treatment of acute hereditary angioedema (HAE) attacks in adults with C1 esterase inhibitor deficiency.[1] It is available as 3 mL (10 mg/mL) single-dose, single-use, pre-filled syringes, at a confidential price of $[redacted] per 30 mg syringe. The manufacturer is requesting listing as per the Health Canada indication.

The manufacturer submitted a cost-minimization analysis in which similar clinical effectiveness for icatibant versus its comparator, a plasma-derived C1 esterase inhibitor (Berinert), was assumed based on the results of a manufacturer-funded indirect treatment comparison (ITC). The analysis was conducted from the Canadian public-payer perspective. Unit cost for Berinert was calculated from Canadian Blood Services annual reports.[2,3] Unit costs for non-drug resources were derived from standard reference lists (Ontario Schedule of Benefits, Canadian Institute for Health Information Patient Cost Estimator), while costs for supportive medications were sourced from the Ontario Drug Benefit Formulary. Resource utilization for hospitalizations, supportive care, drug self-administration, and related training was derived from expert opinion.[4] The time horizon for the analysis was the duration of one attack of HAE (estimated at 96 hours), which was expected to encompass the onset of symptom relief for all attacks (the primary end point of the majority of relevant trials).[4] The manufacturer's base-case analysis assumed that one subcutaneous (SC) injection of icatibant would be required per attack. Berinert dosing was based on patient weight using the weight distribution of patients in the FAST-1 and FAST-2 trials.[5,6]

When only drug costs are considered, results of the manufacturer's base case suggest that icatibant is more expensive than Berinert by $[redacted] HAE attack ($[redacted] versus $2,569). Due to its more convenient route of administration (SC for icatibant versus intravenous [IV] for Berinert), the manufacturer assumed that self-administration at home would be more frequent with icatibant than Berinert, and that Berinert would generally be administered in a hospital setting. Consequently, the costs of training, administration, monitoring, and supportive care are assumed to be lower with icatibant than Berinert ($132 versus $515), The manufacturer reports that the average total cost of icatibant per HAE attack ($[redacted]) is less than that of Berinert ($3,084), resulting in expected cost savings of $[redacted] per HAE attack.

The CADTH Common Drug Review (CDR) identified a number of limitations with the submitted analysis. The ITC was limited by significant heterogeneity between trials, which generates uncertainty regarding the comparative effectiveness of icatibant and Berinert. The manufacturer did not consider weight variation in the determination of the number of vials of Berinert per HAE attack. In addition, although icatibant is likely to be associated with lower costs for training, administration, monitoring, and supportive care compared with Berinert, based on clinical experts' feedback, the manufacturer may have underestimated the percentage of patients self-administrating Berinert. Given the uncertainty regarding drug use and actual administration costs, there is uncertainty with respect to the cost impact of icatibant, which could range from a cost saving of $564 per attack (in patients who weigh from 75 kg to 100 kg) to an additional cost of $159 per attack (in patients who weigh from 50 kg to 75 kg), when compared with Berinert.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

Icatibant (Firazyr) is a synthetic peptide that is a selective competitive antagonist of the bradykinin B2 receptor. Icatibant is indicated in Canada for the treatment of acute attacks of hereditary angioedema (HAE) in adults with C1 esterase inhibitor deficiency.[1] Icatibant is available as 3 mL (10 mg/mL) single-dose, single-use, pre-filled syringes. Icatibant is administered by slow subcutaneous (SC) injection in the abdominal area at a recommended dose of 30 mg. Additional doses may be administered at intervals of at least six hours if response is inadequate or if symptoms recur, with no more than three doses administered within a 24-hour period. The manufacturer submitted a confidential price of $[redacted] per 30 mg syringe.

1.1 Cost Comparison Table

The comparator treatments presented in Table 1 have been deemed the appropriate comparators by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified.

TABLE 1: COST COMPARISON TABLE FOR ICATIBANT FOR ACUTE HAE ATTACKS

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose Per Acute Attack	Drug Cost Per Acute Attack($)
Icatibant (Firazyr)	**30 mg/3 mL**	**Pre-filled SC syringe**	[redacted][a]	**Usually one injection; no more than 3 doses per 24 hours.**	[redacted]
C1 esterase inhibitor (Berinert)	500 IU	Single-use vial and 10 mL diluent	722.94[b]	20 IU/kg by slow IV injection	2,169[c,d]

HAE = hereditary angioedema; IU = international units; IV = intravenous; SC = subcutaneous.
Prices do not include administration costs.
[a] Manufacturer's confidential submitted price.
[b] Cost calculated using Canadian Blood Services 2011–2012 and 2012–2013 annual reports, and inflated to the 2014–2015 estimate.
[c] Based on a patient weight of 75 kg.
[d] Assumes wastage of excess medication in vial.

2. SUMMARY OF PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-minimization analysis[4] comparing icatibant to Berinert, a plasma-derived C1 esterase inhibitor (C1-INH) concentrate for the treatment of acute HAE attacks. The analysis is from the Canadian ministry of health perspective. Because no head-to-head trials were available comparing icatibant with Berinert, the manufacturer performed an indirect treatment comparison (ITC) to compare the effects of each drug in terms of time to onset of symptom relief (TOSR) using three end points: time to onset of primary symptom relief; time to initial symptom improvement (as assessed by the patient); and TOSR based on a composite visual analogue scale. The manufacturer's ITC included one placebo-controlled phase 3 trial investigating the use of icatibant (FAST-3), two active-controlled phase 3 trials investigating the efficacy of icatibant compared with tranexamic acid (FAST-1 and FAST-2),[5-7] and five placebo-controlled trials investigating other comparators including Cinryze, Ruconest (recombinant C1-INH) and Kalbitor (ecallantide). Cinryze is not indicated for treatment of acute HAE attacks, and neither Ruconest nor ecallantide are approved for sale in Canada. The results of the ITC on TOSR (Table 2) suggested there was no statistically significant difference between icatibant and Berinert.

TABLE 2: INDIRECT TREATMENT COMPARISON SUMMARY

Indirect Comparison (Icatibant versus comparator)	Number of HR Estimates[a] < 1 / ≥ 1	Mean HR	Median HR	Minimum HR	Maximum HR	Icatibant Sig. Better/Worse[b]
Berinert 20 IU/kg	8 / 37	1.381	1.387	0.717	2.099	2 / 0
Berinert 10 IU/kg	0 / 45	2.169	2.192	1.069	3.387	29 / 0

HR = hazard ratio; international unit; sig = significantly; TOSR = time to onset of symptom relief.
Source: Manufacturer pharmacoeconomic submission (Table 4, page 26).[4]
[a] HR estimates greater than 1 imply a result in favour of icatibant, while HR estimates less than 1 favour the comparator.
[b] "Sig. better" is the number of comparisons (out of 45) where the entire 95% confidence interval for the HR lies above 1 (favours icatibant); whereas, "Sig. worse" is the number of comparisons (out of 45) where the 95% confidence interval for the HR lies below 1 (favours comparator).

The analysis was conducted from the Canadian public payer perspective. The time spent in two health states — "during an attack" (the period of time before the onset of symptom relief) and "after recovery" (after onset of symptom relief) — was estimated for each intervention over a 96-hour period by combining data for the TOSR (the primary end point of the majority of relevant trials).[4]

Unit cost for the plasma-derived C1-INH concentrate Berinert was not readily available and was calculated from Canadian Blood Services annual reports.[2,3] Unit costs for non-drug resources were derived from standard reference lists (Schedule of Benefits, Canadian Institute for Health Information Patient Cost Estimator), while costs for supportive medications were sourced from the Ontario Drug Benefit Formulary (Table 3). The manufacturer's base-case analysis assumed that one SC injection of icatibant would be required per attack. Berinert dosing was based on patient weight using the weight distribution of patients in the FAST-1 and FAST-2 trials.[5,6]

The economic report stated that resource utilization was primarily derived from expert opinion.[4] The experts provided advice for hospitalization and supportive care and drugs, and provided input on self-administration and training. Based on expert opinion, the manufacturer assumed that for icatibant, self-administration training would be conducted by a nurse and require a 30-minute session, while for Berinert, the manufacturer assumed four hours of total training would be required due to the

complexity of intravenous administration and the requirement for aseptic techniques.[4] Finally, the manufacturer assumed that 95% of patients with a non-laryngeal attack would self-administer icatibant, while no patients receiving Berinert would self-administer. In cases of laryngeal attacks, 50% of patients on icatibant may self-administer at home; however, no patients on Berinert may self-administer in the case of laryngeal attacks.[4]

TABLE 3: MANUFACTURER-SUBMITTED UNIT COSTS

Item/Unit	Unit Cost	Source
Icatibant (Firazyr)	$[redacted]	Manufacturer[4]
C1-INH (Berinert)	$722.94	Canadian Blood Services annual reports, adjusted to 2014–2015[2,3]
SC injection by health care practitioner	$3.89	Ontario Schedule of Benefits[8]
IV infusion by health care practitioner	$6.15	
Physician visit	$157.00	
Emergency room visit	$77.20	
Hospital in-patient stay	$909.38	Canadian Institute for Health Information[9]
Morphine 20 mg	$3.22	Ontario Drug Benefit e-formulary[10]
Metoclopramide 10 mg	$0.06	
Ondansetron 4 mg	$3.27	
Nurse hourly wage	$49.23	Ontario Nurses Association[11]

C1-INH = C1 esterase inhibitor; IV = intravenous; SC = subcutaneous.
Source: Manufacturer's pharmacoeconomic submission (Table 5, page 30).[4]
[a] Manufacturer-submitted confidential price.

For the base-case analysis, the manufacturer reported that the mean total cost of an HAE attack treated with icatibant was $[redacted] compared with $3,084.35 when treated with Berinert. Treatment of an acute attack with icatibant would be associated with expected cost savings of $[redacted] per episode (Table 4).

TABLE 4: MANUFACTURER BASE-CASE RESULTS FOR ICATIBANT

	Estimated Costs (Mean Per Attack, $)		Mean Incremental Cost Per Attack, $ (Savings)
	Icatibant	C1-INH (Berinert)	
Drug	$[redacted]	$2,569.20	$[redacted]
Administration, monitoring, and supportive care	$107.57	$318.23	($210.66)
Self-administration training	$24.61	$196.91	($172.30)
Adverse events	$0.00	$0.00	$0.00
Total costs	**$[redacted]**	**$3,084.35**	**($[redacted])**

Adapted from manufacturer's pharmacoeconomic submission (tables 9 and 10, page 35).[4]

The manufacturer conducted one-way sensitivity analyses to test the robustness of the results and assess the uncertainty around the parameters. The results suggested the treatment of an acute HAE attack with icatibant was associated with cost savings, except when the number of icatibant injections was increased (Table 5).

TABLE 5: MANUFACTURER-SUBMITTED SENSITIVITY ANALYSIS RESULTS

Variable	Sensitivity Analysis Value	Incremental Cost (Savings) for Icatibant Versus C1-INH
Base-case result	Not applicable	($[redacted])
Icatibant injections	Clinical trial injection distribution	$44.84
Berinert infusions	Expert opinion	($68.65)
	3 to 4 vials	($213.23)
Self-administration	100% for all therapies	($40.84)
	0% for all therapies	($334.50)
	100% for icatibant, 0% for infusions	($277.30)
Attacks leading to hospitalization	100% for all therapies	($41.50)
	0% for all therapies	($41.50)
Nurse training	Removed from model	($79.86)
	Cost decreased 50%	($166.01)
	Cost increased 50%	($424.46)

Adapted from manufacturer's pharmacoeconomic submission (tables 13, page 36).[4]

3. INTERPRETATIONS AND KEY LIMITATIONS

Lack of Evidence to Support Equivalent Efficacy and Safety

Similar efficacy was assumed based on an ITC that compared icatibant to Berinert, Cinryze, Rocunest, and ecallantide in terms of TOSR. The ITC was limited by significant heterogeneity between trials in the patient population, the definition of end points, and arrangements for using rescue medication (which rescue medication was permitted, type of medication permitted, extent of use of rescue medication in each study group, and the analyses performed to adjust for imbalances in the use of rescue medications between study groups). These limitations raise substantial uncertainty on the level of inference that may be drawn from the indirect comparison (CDR *Clinical Review Report* for more details).

Dosing of Berinert

The Berinert-recommended dose is 20 IU/kg. The number of vials of Berinert used in the base-case analysis was 3.55 vials per HAE attack. The manufacturer states that this number was derived from the patient weight distributions in the FAST-1 and FAST-2 trials. According to its product monograph, Berinert is provided in single-use vials that do not include preservatives.[12] This points to the potential for wastage of the unused portion of the Berinert vial, which was not included in the manufacturer's base-case analysis. The number of vials of Berinert required per attack will likely vary from three vials ($2,169, for a patient weight > 50 kg and ≤ 75 kg) to four vials ($2,892, for a patient weight > 75 kg and ≤ 100 kg). In CDR reanalyses using three vials of Berinert per attack, icatibant was associated with *additional costs* of $148 per HAE attack. Using four vials of Berinert per attack, icatibant was associated with *cost savings* of $575 per HAE attack.

Cost Per Unit for Berinert

The unit cost for the plasma-derived C1 esterase inhibitor (C1-INH) concentrate Berinert was calculated from Canadian Blood Services annual reports based on utilization data and expenditure on plasma-derived C1-INH products for the period from April 2011 to March 2012.[2] The data was extrapolated and adjusted accordingly, based on historical data to derive the anticipated April 2014 to March 2015 unit price for Berinert.[3] The unavailability of a public commercial cost for Berinert and the extrapolation required to estimate a cost raises uncertainty around the true cost per unit for Berinert. CDR reanalyses of the manufacturer-estimated cost for Berinert showed that when reducing the cost by 10%, icatibant becomes associated with *additional total costs* of $5 per HAE attack.

Self-administration of Berinert

The manufacturer's base case assumed that no patients on Berinert would self-administer the medication during a non-laryngeal attack due to Berinert requiring intravenous (IV) administration. This is considered a challenging process requiring skill during an HAE attack, as the attack may affect the patient's dexterity and ability to prepare the IV treatment. This assumption may be biasing the results in favour of icatibant by overestimating the costs associated with hospital administration of Berinert. Clinical experts indicated that self-administration of Berinert by patients during an HAE attack is seen in clinical practice; therefore, the cost savings associated with icatibant may be overestimated in the manufacturer's base-case analysis. CDR reanalyses of Berinert self-administration percentages showed that when the percentage of Berinert self-administration for non-laryngeal attacks increases, icatibant becomes associated with *decreasing cost savings* per HAE attack (Table 6).

TABLE 6: CDR REANALYSIS OF BERINERT SELF-ADMINISTRATION VERSUS ICATIBANT

	Berinert Self-administration, Mean Incremental Cost Per Attack (Savings)					
Self-administration for Non-laryngeal Attacks	**Base Case 0%**	**5%**	**10%**	**50%**	**75%**	**95%**
Drug	$[redacted]					
Self-administration training	($172.30)					
Adverse events	$0.00					
Administration, monitoring, and supportive care	($210.66)	($[redacted])	($[redacted])	($[redacted])	($[redacted])	($[redacted])
Cost (savings) with icatibant	**($[redacted])**	**($241.09)**	**($230.01)**	**($141.41)**	**($86.04)**	**($41.73)**

A final CDR reanalysis was conducted that revised the assumptions on the dosing and self-administration of Berinert: the CDR "most likely" scenario estimated that three or four vials of Berinert would be used per HAE attack, and that 5% of patients using Berinert would be able to self-administer the treatment for non-laryngeal attacks. This scenario was based on feedback from clinical expert opinion on this review. Results of this reanalysis show icatibant to be associated with additional costs of $159.31 per HAE attack for patients weighing > 50 kg and ≤ 75 kg, and with cost savings of $563.65 per HAE attack for patients weighing > 75 kg and ≤ 100 kg (Table 7).

TABLE 7: RESULTS OF CDR MOST LIKELY SCENARIOS

	Base Case, Mean Incremental Cost Per Attack	CDR Most Likely Scenario 1: 3 Vials of Berinert[a] and 5% Self-administrating Berinert, Mean Incremental Cost (Savings) Per Attack	CDR Most Likely Scenario 2: 4 Vials of Berinert[b] and 5% Self-administrating Berinert, Mean Incremental Cost (Savings) Per Attack
Drug	$[redacted]	$[redacted]	($[redacted])
Administration, monitoring, and supportive care	($210.66)	($199.59)	($199.59)
Self-administration training	($172.30)	($172.30)	($172.30)
Adverse events	$0.00	$0.00	$0.00
Incremental costs (savings) with Icatibant versus Berinert	**($[redacted])**	**$159.31**	**($563.65)**

[a] Weight ranging from > 50 to ≤ 75 kg.
[b] Weight ranging from > 75 to ≤ 100 kg.

4. ISSUES FOR CONSIDERATION

The manufacturer's analysis assumed one SC injection of icatibant would be used per HAE attack. The product monograph for icatibant states that in cases of insufficient relief or recurrence of symptoms, a second injection of icatibant can be administered after six hours. If the second injection produces insufficient relief or a recurrence of symptoms is observed, a third injection of icatibant can be administered after a further six hours. No more than three doses may be administered in any 24-hour period.[1] Evidence from the FAST-3 open-label extension study (see CDR *Clinical Review Report*) indicates that about 5% of HAE patients would require a second dose of icatibant before symptoms begin to improve. Increased icatibant doses per HAE attack will make it more expensive than Berinert and may be associated with additional costs ranging from $[redacted] to $[redacted] per attack.

5. CONCLUSIONS

At a confidential price of $[redacted] per 30 mg syringe, when only drug costs per HAE attack are considered, icatibant is more expensive than three vials of Berinert ($2,169, for a patient weighing > 50 kg and ≤ 75 kg) but less expensive than four vials of Berinert ($2,892, for a patient weighing > 75 kg and ≤ 100 kg).

The comparative effectiveness of icatibant and Berinert is uncertain. Due to its more convenient route of administration (SC for icatibant versus IV for Berinert), icatibant is likely to be associated with lower costs of training, administration, monitoring, and supportive care compared with Berinert, but the true cost difference is unknown.

CDR reanalyses varying the number of vials of Berinert required per attack and the proportion of patients self-administering Berinert suggest that the cost impact of icatibant could range from a cost saving of $564 per attack (for patients who weigh from 75 kg to 100 kg), to an additional cost of $159 per attack (for patients who weigh from 50 kg to 75 kg), when compared with Berinert.

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