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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

abobotulinumtoxinA (Dysport Therapeutic)

(Ipsen Biopharmaceuticals Canada, Inc.)

Indication: For the symptomatic treatment of focal spasticity affecting the upper limbs in adults

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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

aboBoNTA	abobotulinumtoxinA
BoNTA	botulinum neurotoxin A
CDR	CADTH Common Drug Review
ITC	indirect treatment comparison
incoBoNTA	incobotulinumtoxinA
LU	Limited Use
MAS	Modified Ashworth Scale
ODB	Ontario Drug Benefit
onaBoNTA	onabotulinumtoxinA
RCT	randomized controlled trial
U	units
ULIS-III	Upper Limb International Spasticity-III study
ULS	upper limb spasticity
95% range	The range which includes 95% of samples

Drug	AbobotulinumtoxinA (Dysport Therapeutic)
Indication	For the symptomatic treatment of focal spasticity affecting the upper limbs in adults
Reimbursement Request	For the symptomatic treatment of focal spasticity including of the upper limbs in adults
Manufacturer	Ipsen Biopharmaceuticals Canada, Inc.

Summary

Background

AbobotulinumtoxinA (aboBoNTA, Dysport Therapeutic) is a botulinum neurotoxin subtype indicated for the symptomatic treatment of focal spasticity affecting the upper limbs in adults (upper limb spasticity, ULS), and is available in single-use vials of 300 Units (U) and 500 U, at submitted prices of $428.40 and $714.00, respectively. The recommended initial dose of aboBoNTA is individually tailored depending on the size, number, and location of muscles involved. In the pivotal trial, 500 U or 1,000 U were used intramuscularly, divided among selected muscles, at a given treatment session. Repeat treatment should be administered when the effect of a previous injection has diminished, but no sooner than 12 weeks after the previous injection, with a majority of study patients being re-treated between 12 and 16 weeks.[1] The manufacturer is requesting that aboBoNTA be reimbursed for the treatment of adults with focal spasticity, including spasticity of the upper limbs.

CADTH Common Drug Review (CDR) previously reviewed aboBoNTA for the treatment of cervical dystonia; CADTH Canadian Drug Expert Committee recommended aboBoNTA be reimbursed in a manner similar to other botulinum neurotoxin A (BoNTA) therapies, and with a price reduction.[2]

Summary of the Economic Analysis Submitted by the Manufacturer

The manufacturer submitted a cost comparison, presented as a budget impact analysis, estimating total drug costs based on claims for onabotulinumtoxinA (onaBoNTA) and incobotulinumtoxinA (incoBoNTA) from April 2015 to March 2016.[3] Claims from Ontario Drug Benefit (ODB) were obtained based on Limited Use (LU) Code 412 ("for the management of focal spasticity, due to stroke or spinal cord injury in adults"). Clinical similarity was assumed on the basis of an unpublished indirect treatment comparison (ITC) submitted by the manufacturer,[4] comparing aboBoNTA to onaBoNTA and incoBoNTA. Costs were obtained from ODB list prices and the manufacturer;[3] where partially used vials were assumed to be wasted. All other costs, such as administration and monitoring, were assumed equal. For the base case, the manufacturer assumed that all claims reimbursed for the comparators (onaBoNTA and incoBoNTA) were replaced by aboBoNTA. Determination of dose per claim for aboBoNTA was in line with a 3:1 or lower ratio as observed in clinical trials for cervical dystonia, with some alteration to minimize wastage of

aboBoNTA (Table 3).[3] The manufacturer estimated the total cost reimbursed by ODB from April 2015 through March 2016 for onaBoNTA and incoBoNTA for ULS was $8.65 million. Should these claims have been instead for aboBoNTA, the total cost to ODB would have been $8.43 million, leading to an estimated savings of approximately $116,000 for ODB for that year (1.3% for amount spent on patients with ULS receiving botulinum toxin). The manufacturer also submitted a scenario where the relative doses of aboBoNTA, onaBoNTA, and incoBoNTA were assumed the same, while the duration of effect was estimated using preliminary data from the Upper Limb International Spasticity (ULIS)-III observational study.[5] This resulted in an estimated savings of $1.10 million, or 12.7% should aboBoNTA replace all claims for onaBoNTA and aboBoNTA prescribed for ULS.

Key Limitations

Uncertainty in assumption of clinical similarity: The ITC submitted by the manufacturer[4] included a total of 18 placebo-controlled trials. The analysis reported a lack of statistically significant differences between the botulinum neurotoxin A (BoNTA) treatments for all measured outcomes which included change in Modified Ashworth Scale at week 4 to week 6, and week 12; change in Disability Assessment Score at week 4 to week 6, and week 12; and rates of adverse events at week 12 (see CDR Clinical Report, Appendix 8). Despite a comprehensive search, only limited data were available for some outcome measures. Additionally, potential methodological and clinical heterogeneity may exist across trials. For example, baseline characteristics, doses used, treatment experience, and outcome measure definitions were not sufficiently reported. Variation in the placebo responses across trials suggests important heterogeneity may exist among the trials. As such, the assumption of clinical similarity is uncertain, particularly at any specific dose ratio, in the ULS population.

Inappropriate analysis type: The manufacturer conducted a budget impact analysis, rather than a cost comparison, considering a scenario where 100% of claims for botulinum toxin for the treatment of ULS are replaced by aboBoNTA. The analysis inflates the manufacturer's results. Even if the conclusion of cost savings is accurate, a 100% market share is not plausible in a real-world setting. Additionally, as the number of ODB beneficiaries has not been provided and is not possible to derive from the data set, it is difficult to assess the results for individual patients. It is also difficult to generalize the results to other jurisdictions. CDR used the means and standard deviations of the provided claims data to model distributions for a probabilistic analysis to estimate relative mean costs per patient.

Inappropriate dosing conversion: The manufacturer's use of claims data were helpful in establishing the substantial variation in the dose for botulinum toxin for ULS in clinical practice relative to that expected based on monograph-recommended doses. The assumption that claims for aboBoNTA would be limited to the maximum dose used in trials while comparators are reimbursed at doses far beyond those outlined in their respective product monographs or used in trials: a) is unlikely to reflect clinical practice given what is observed in the claims data, b) undermines the dose equivalency ratios on which the assumption of clinical similarity is based, and c) artificially lowers the relative cost of aboBoNTA. CDR's probabilistic analysis was based on an assumed ratio of 2.5:1 (for aboBoNTA to onaBoNTA or incoBoNTA) cited in the manufacturer's submission as the most appropriate (and the most widely cited ratio)[3] for all analyses, and included wastage for all comparators.

Inappropriately conducted extended duration scenario: The interim results from the Upper Limb International Spasticity (ULIS)-III study[5] suggest that aboBoNTA may be used less frequently than onaBoNTA, which may be used less frequently than incoBoNTA. However, the manufacturer has extrapolated a single re-treatment interval (the second) in a small group of patients to a full year for all patients in Ontario. Additionally, the manufacturer was unable to provide dosing or clinical outcome information for the ULIS-III data upon request, highlighting that though injections may be being given at different frequencies; it is not possible to compare costs or patient outcomes (i.e., cost-effectiveness) from these data at this time. CDR was unable to conduct an alternate extended duration scenario analysis for patients with ULS given the paucity of data.

Issues for Consideration

Potential extended duration may be preferred by patients: Preliminary data from the ULIS-III observational study suggests that it may be possible to extend the time between re-treatments for aboBoNTA relative to its comparators, although no information is available to suggest costs would be reduced. However, should re-treatment time be extended without increased adverse events or loss of efficacy, this may be preferred by patients as potentially more convenient, time saving, and less painful.

Per unit costing: The submitted price of aboBoNTA per unit is equivalent to that of onaBoNTA when a 2.5:1 ratio is assumed. If vial sizes for aboBoNTA were available to account for this dose ratio (i.e., if aboBoNTA came in 125 U, 250 U, and 500 U sizes to match the available 50 U, 100 U, and 200 U onaBoNTA vials), the cost of treatment with both drugs would be identical if dosed at a 2.5:1 ratio. As only 300 U and 500 U vial single-use sizes of aboBoNTA are available, the increased wastage of excess medication is the main driver of the additional cost for aboBoNTA when compared with onaBoNTA (see CDR reanalyses). This effect may be mitigated in clinical practice if clinicians alter dosing to minimize vial wastage, but is unlikely to be eliminated. Furthermore, the per-dose equivalent unit cost of aboBoNTA is 8% more than that of incoBoNTA at a 2:5 to 1 ratio (500 U is $714 for aboBoNTA compared with 200 U at $660 for incoBoNTA, see Table 1). Thus, both the higher price per equivalent unit and the increased wastage of medication drive the increased cost of aboBoNTA.

Results / Conclusions

Based on a 2.5:1 dosing ratio for aboBoNTA relative to comparators (onaBoNTA and incoBoNTA) and a 12-week duration of effect; when considering observed use of onaBoNTA from claims data, CDR estimated that aboBoNTA maintenance therapy ($5,971 per patient per year) was on average $297 more expensive than that of onaBoNTA ($5,674 per patient per year). Similarly, based on observed use of incoBoNTA from claims data, aboBoNTA maintenance therapy ($6,828 per patient per year) was estimated to be on average $669 more expensive than incoBoNTA ($6,158). Under these assumptions, the cost per unit of aboBoNTA would need to be reduced by 4.9% to be cost neutral to onaBoNTA, and by 9.8% to be cost neutral to incoBoNTA. Claims data suggests incoBoNTA may be used in clinical practice at higher doses than onaBoNTA, which may also impact the dose ratio of aboBoNTA to incoBoNTA used in clinical practice.

CDR considered there to be insufficient data available to estimate costs based on possible differences in duration of effect among comparators.

AboBoNTA is priced to be equivalent to the cost of onaBoNTA when a 2.5:1 dosing ratio is assumed, but is 8% more expensive than incoBoNTA at the same 2.5:1 dose-equivalent unit. The absence of an equivalent vial size to the smallest available size of onaBoNTA and incoBoNTA may result in increased wastage of aboBoNTA.

Cost Comparison Table

Clinical experts have deemed the comparator treatments presented in Table 1 to be appropriate. 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. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 1: Cost Comparison Table for Drug Class, Disease, etc.

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Cost per Treatment ($)[a]	Average Annual[b] Drug Cost ($)[a]
abobotulinumtoxinA (Dysport Therapeutic)	**300 U 500 U**	**Vial for injection**	**428.4000[c] 714.0000[c]**	**Initially 500 U to 1,000 U IM divided among affected muscles Re-treatment should not occur in intervals of less than 12 weeks**	**714 to 1,428**	**3,570 to 7,140**
IncobotulinumtoxinA (Xeomin)	50 U 100 U	Vial for injection	165.0000 330.0000	Dosing should not exceed 400 U IM divided among affected muscles. Initial dose should be at lowest recommended range and titrated up. The period between re-treatments is recommended to be at least 12 weeks.	Up to 1,320	Typically up to 6,600
OnabotulinumtoxinA (Botox)	50 U 100 U 200 U	Vial for injection	178.5000 357.0000 714.0000	Usual doses in trials ranged from 200 U to 240 U, and up to 360 U divided among affected muscles. Repeat doses should be administered when clinical effect diminishes but not more than every 12 weeks.	714 to 1,428[d]	3,570 to 7,140[d]

IM = intramuscular.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed July 2017), unless otherwise indicated, and do not include dispensing fees.

a Cost per treatment includes wastage of excess medication in vials.

b Annual drug cost assumes initial dose and subsequent treatments at weeks 12, 24, 36, and 48.

c Manufacturer's submitted price.

d Assumes product monograph's reported dose range in clinical practice of 200 U to 360 U.

Appendix 1: Reviewer Worksheets

Table 2: Summary of Manufacturer's Submission

Drug Product	**AbobotulinumtoxinA (Dysport Therapeutic)**
Treatment	AbobotulinumtoxinA (aboBoNTA)
Comparator(s)	OnabotulinumtoxinA (onaBoNTA) IncobotulinumtoxinA (incoBoNTA)
Study Question	If all onaBoNTA and incoBoNTA claims reimbursed were instead reimbursed for aboBoNTA, what would be the additional cost or savings to a provincial drug plan?
Type of Economic Evaluation	Cost comparison presented as a budget impact analysis
Target Population	Indication: For the symptomatic treatment of focal spasticity affecting the upper limbs in adults. Listing Request: For the treatment of adults with focal spasticity, including spasticity of the upper limbs.
Perspective	Canadian public drug payer
Outcome Considered	Drug costs
Key Data Sources	
Cost	Manufacturer's submitted price for aboBoNTA ODB list prices for onaBoNTA and incoBoNTA
Clinical Efficacy	Unpublished ITC submitted by manufacturer[4]
Harms	Unpublished ITC submitted by manufacturer[4]
Utilization Data	Unpublished IMS Brogan (RxDynamics) data set on all onaBoNTA and incoBoNTA claims reimbursed by ODB between April 2015 and March 2016 under the LU Code 412 for focal spasticity due to stroke or spinal cord injury in adults.
Time Horizon	One year
Results for Base Case	The manufacturer concluded that if all claims for onaBoNTA or incoBoNTA reimbursed for focal spasticity by ODB between April 2015 and March 2016 had instead been reimbursed for an equivalent dose of Dysport Therapeutic, ODB would have saved $155,755 (1.3%) during that year.

aboBoNTA = abobotulinumtoxinA; ITC = indirect treatment comparison; incoBoNTA = incobotulinumtoxinA; LU = Limited Use; ODB = Ontario Drug Benefit; onaBoNTA = onabotulinumtoxinA.

Source: Manufacturer's pharmacoeconomic repor [3]

Manufacturer's Results

The manufacturer submitted a cost comparison, presented as a budget impact analysis, and estimated total drug costs using IMS Brogan data for all claims reimbursed by Ontario Drug Benefit (ODB) for onabotulinumtoxinA (onaBoNTA) and incobotulinumtoxinA (incoBoNTA) under LU Code 412 ("For the management of focal spasticity, due to stroke or spinal cord injury in adults") between April 2015 and March 2016. Costs per vial were ODB list prices for comparators and provided by the manufacturer for abobotulinumtoxinA (aboBoNTA).[3] All other costs, such as administration and monitoring, were assumed similar between comparators. The manufacturer then calculated costs for a hypothetical scenario in which *all claims* reimbursed for the comparators are instead reimbursed for aboBoNTA. Conversions from claims for comparators to aboBoNTA were done according to Table 3,

based on the less than 3:1 ratio demonstrated in clinical trials for patients with cervical dystonia and altered to minimize vial wastage. Any claim for more than 3,000 U of onaBoNTA or incoBoNTA was excluded, although at this setting no claims were excluded. The maximum dose of aboBoNTA dispensed in the base case was 1,500 U while comparator maximum dosing was not artificially constrained.

Table 3: Manufacturer's Assumed Dose Conversion for Base-Case Cost Comparison

onaBoNTA or incoBoNTA Dose Dispensed	# of aboBoNTA 300 U Vials Dispensed	# of aboBoNTA 500 U Vials Dispensed	Corresponding aboBoNTA Dose Dispensed	Approximate aboBoNTA Ratio (Dispensed Not Necessarily Injected)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

= number; aboBoNTA = abobotulinumtoxinA; incoBoNTA = incobotulinumtoxinA; onaBoNTA = onabotulinumtoxinA; U = units.

Source: Adapted from Table 5-4 in manufacturer's pharmacoeconomic submission.[3]

The manufacturer estimated that the total cost reimbursed by ODB from April 2015 through March 2016 for onaBoNTA and incoBoNTA as $8.65 million and that equivalent claims reimbursed for aboBoNTA would have cost $8.43 million, leading to an estimated savings of approximately $116,000 or 1.3% for the reimbursement of botulinum toxin for upper limb spasticity (ULS) by ODB for that year, see Table 4.

Table 4: Manufacturer's Base-Case Analysis Results

Scenario	Total Drug Cost
Current Scenario (without aboBoNTA)	
onaBoNTA	$7,462,549.50
incoBoNTA	$1,187,505.00
Total [A]	$8,650,054.50
Hypothetical Scenario (with aboBoNTA)	
aboBoNTA [B]	$8,428,912.80
Incremental Cost [B-A]	–$115,755.30
% Difference [(B-A)/A]	–1.3%

aboBoNTA = abobotulinumtoxinA; incoBoNTA = incobotulinumtoxinA; onaBoNTA = onabotulinumtoxinA.

Source: Adapted from Table 5-5 in Manufacturer's pharmacoeconomic submission.[3]

The manufacturer then conducted an "extended duration scenario analysis," where interim data from the currently underway ULIS-III observational study[5] were used to estimate the relative durations of effect between botulinum neurotoxin A (BoNTA) products (see Table 5). The manufacturer used the mean number of weeks between the first and second re-treatment for all products to estimate the mean number of injections used for each per year, calculated a ratio of injections per year between aboBoNTA and each comparator, and then multiplied the base case cost results for aboBoNTA by this ratio.

Table 5: Mean Time to Re-Treatment Based on ULIS-III Data

	aboBoNTA		onaBoNTA		incoBoNTA	
	n	**Mean weeks ± SD**	**n**	**Mean weeks ± SD**	**n**	**Mean weeks ± SD**
Re-Treatment Interval 1	203	22.1 ± 8.4 (154.9 ± 58.6 days)	94	19.7 ± 8.6 (137.8 ± 60.5 days)	38	17.8 ± 6.6 (124.4 ± 41.0 days)
Re-Treatment Interval 2	110	20.9 ± 6.9 (146.4 ± 48.5 days)	48	18.8 ± 5.3 (131.8 ± 36.9 days)	19	16.6 ± 4.6 (116.3 ± 32.3 days)

aboBoNTA = abobotulinumtoxinA; incoBoNTA = incobotulinumtoxinA; onaBoNTA = onabotulinumtoxinA; SD = standard deviation; ULIS-III = Upper Limb International Spasticity-III Study.

Source: Adapted from Table 5-6 in Manufacturer's pharmacoeconomic submission.[3]

Under these assumptions, the manufacturer calculated that the use of aboBoNTA for all BoNTA treatment for ULS from April 2015 to March 2016 would have cost ODB approximately $1.10 million or 12.7% less than onaBoNTA and incoBoNTA (see Table 6).

Table 6: Manufacturer's Extended Duration Analysis Results

Scenario	Total Drug Cost
Current Scenario (without aboBoNTA)	
onaBoNTA	$ 7,462,549.50
incoBoNTA	$1,187,505.00
Total [A]	$8,650,054.50
Hypothetical Scenario (with aboBoNTA)	
aboBoNTA [B]	$7,553,949.99
Incremental Cost [B-A]	–$1,096,104.51
% Difference [(B-A)/A]	–12.7%

aboBoNTA = abobotulinumtoxinA; incoBoNTA = incobotulinumtoxinA; onaBoNTA = onabotulinumtoxinA.

Source: Adapted from Table 5-5 and 5-8 in Manufacturer's pharmacoeconomic submission.[3]

The manufacturer also conducted a sensitivity analysis varying the maximum dose dispensed for aboBoNTA, finding additional savings when the dose was limited to 1,000 U (12.1% less than comparators), but additional costs when the dose was limited to 1,900 U (0.8% more than comparators). Comparator maximum dosing remained the same as in the base case. In a subsequent analysis submitted by the manufacturer, when all onaBoNTA and incoBoNTA claims greater than the maximum recommended dose of 400 U were excluded, thus limiting all three BoNTA doses to recommended ranges, replacing the remaining claims with aboBoNTA would cost 3.2% more than comparators.

CADTH Common Drug Review Results

Trial-based dose range

While the manufacturer's economic analysis was based entirely around ODB claims data, CADTH Common Drug Review (CDR) explored the costs of comparators if they were used in a manner similar to the clinical trials used in the indirect treatment comparison (ITC) to inform the assumption of clinical similarity. CDR also wished to explore relative costs per patient or per claim, rather than per population.

Dosing instructions in BoNTA product monographs[1,6,7] for the treatment of ULS are based on doses used in clinical trials. The manufacturer's ITC[4] included a total of 18 trials: seven onaBoNTA, eight aboBoNTA, and three incoBoNTA. Doses in these trials ranged from 75 U to 500 U for onaBoNTA, 150 U to 400 U for incoBoNTA, and 500 U to 1,500 U for aboBoNTA. Drug costs per treatment, including wastage of excess medication, for doses across the full range of those used in the trials included in the ITC are presented in Table 7, assuming a dose ratio of 2.5 to 1 for aboBoNTA compared with both onaBoNTA and incoBoNTA. Whether aboBoNTA was more or less expensive than onaBoNTA depended on the dose being prescribed, while aboBoNTA was almost always more expensive than incoBoNTA.

Table 7: Cost per Dose of aboBoNTA Compared with onaBoNTA and incoBoNTA Across Full Range of Doses Used in Clinical Trials Included in ITC, Assuming a 2.5:1 Ratio

aboBoNTA Dose (U)	onaBoNTA/ incoBoNTA Dose (U) (2.5:1)	aboBoNTA Cost per Dose ($)	onaBoNTA Cost per Dose ($)	Additional Cost (Savings) aboBoNTA vs onaBoNTA($)	incoBoNTA Cost per Dose ($)	Additional Cost (Savings) aboBoNTA vs incoBoNTA ($)
200	80	428.40	357.00	71.40	330.00	98.40
250	100	428.40	357.00	71.40	330.00	98.40
300	120	428.40	535.50	(107.10)	495.00	(66.60)
350	140	714.00	535.50	178.50	495.00	219.00
400	160	714.00	714.00	0	660.00	54.00
450	180	714.00	714.00	0	660.00	54.00
500	200	714.00	714.00	0	660.00	54.00
550	220	856.80	892.50	(35.70)	825.00	31.80
600	240	856.80	892.50	(35.70)	825.00	31.80
650	260	1,142.40	1,071.00	71.40	990.00	152.40
700	280	1,142.40	1,071.00	71.40	990.00	152.40
750	300	1,142.40	1,071.00	71.40	990.00	152.40
800	320	1,142.40	1,249.50	(107.10)	1,155.00	(12.60)
850	340	1,285.20	1,249.50	35.70	1,155.00	130.20
900	360	1,285.20	1,428.00	(142.80)	1,320.00	(34.80)
950	380	1,428.00	1,428.00	0	1,320.00	108.00
1,000	400	1,428.00	1,428.00	0	1,320.00	108.00
1,050	420	1,713.60	1,606.50	107.10	1,485.00	228.60
1,100	440	1,713.60	1,606.50	107.10	1,485.00	228.60
1,150	460	1,713.60	1,785.00	(71.40)	1,650.00	63.60
1,200	480	1,713.60	1,785.00	(71.40)	1,650.00	63.60
1,250	500	1,856.40	1,785.00	71.40	1,650.00	206.40
1,300	520	1,856.40	1,963.50	(107.10)	1,815.00	41.40
1,350	540	1,999.20	1,963.50	35.70	1,815.00	184.20
1,400	560	1,999.20	2,142.00	(142.80)	1,980.00	19.20
1,450	580	2,142.00	2,142.00	0	1,980.00	162.00
1,500	600	2,142.00	2,142.00	0	1,980.00	162.00

aboBoNTA = abobotulinumtoxinA; incoBoNTA = incobotulinumtoxinA; onaBoNTA = onabotulinumtoxinA; U = units.

Average claim – probabilistic analysis based on ODB claims data

The manufacturer used ODB data provided by IMS Brogan for all onaBoNTA and incoBoNTA claims reimbursed between April 2015 and March 2016 for CD (LU:412), and assumed a hypothetical situation where all such claims were instead reimbursed for aboBoNTA. In order to do so, the manufacturer assumed the units per claim conversion amounts outlined in Table 3. However, assuming that all claims above 600 U of the comparators (401 of 6,588 claims, the largest of which was for 1,050 U of onaBoNTA) would be dispensed as 1,500 U of aboBoNTA is unlikely to reflect whatever practice is driving the prescription and reimbursement of such high doses, undermines the equivalency

ratios in the assumption of clinical similarity, and artificially lowers the relative cost of aboBoNTA. When this constraint is removed and the 2.5:1 ratio is maintained without a maximum limit set for aboBoNTA, and keeping all other manufacturer assumptions, the cost to ODB in the same time period would have been $164,561 or 1.9% *more* if aboBoNTA had been substituted for onaBoNTA and incoBoNTA.

In the reanalysis submitted by the manufacturer, where all onaBoNTA and incoBoNTA claims greater than 400 U were excluded, the manufacturer concluded that reimbursement with aboBoNTA would cost 3.2% more than the comparators. However, CDR considers it more suitable to substitute 900 U of aboBoNTA for 350 U of either of the comparators (350 U * 2.5 ratio = 875U), rather than the 800 U used by the manufacturer (see Table 3); this alteration increases the cost of aboBoNTA to 3.9% more than its comparators.

Additionally, comparing the cost of a 100% market share of aboBoNTA to the 87% onaBoNTA/13% incoBoNTA seen in the April 2015 through March 2016 ODB claims data assumes that this market share is both stable over time and across jurisdictions, which seems unlikely. The substitution of aboBoNTA for all incoBoNTA claims for this time period would have cost ODB $33,292 (2.8%) more than the $1,187,505 reimbursed for incoBoNTA; aboBoNTA is more expensive than incoBoNTA under all of the manufacturer's assumptions, including the maximum dose cap on aboBoNTA.

In order to explore the uncertainty around cost per patient dose, as well as to adjust for the bias incurred when comparators are assumed to be dispensed at doses substantially higher than their monograph ranges while aboBoNTA was not, while still incorporating all the available data, CDR conducted probabilistic analyses mapping the claims data for onaBoNTA and incoBoNTA using the mean and standard deviation of claims reimbursed for each drug to gamma distributions. These distributions were then used to make 10,000 random draws, representing 10,000 hypothetical patients who were assigned a dose of both aboBoNTA and onaBoNTA. The cost of those doses were calculated using the available vial sizes and assuming wastage of additional medication, resulting in an average cost per claim for each drug being calculated for each comparison.

Results for this analysis are outlined in Table 8. The mean cost of aboBoNTA ($1,378 per claim) was $68 more than onaBoNTA ($1,309 per claim) using onaBoNTA claims data, while when incoBoNTA claims data were used, the mean cost of aboBoNTA ($1,576 per claim) was $155 more than that of incoBoNTA ($1,421 per claim). Assuming 4.3 claims per year (52/12 weeks), the average annual cost per patient of aboBoNTA is $297 more expensive than onaBoNTA (using onaBoNTA data) and $669 more expensive than incoBoNTA (using incoBoNTA data). In order to be cost neutral, the cost of aboBoNTA would need to be reduced by 9.8% to equal the cost of incoBoNTA, and 4.9% to be equal to the cost of onaBoNTA. Results were similar when alternate analyses were conducted using ODB claims data from January 2013 through March 2016, also provided by the manufacturer.

Table 8: CDR-Modelled Mean Dose and Cost of aboBoNTA, onaBoNTA, and incoBoNTA Using ODB Claims Data

Parameter	onaBoNTA ODB Claims Data	incoBoNTA ODB Claims Data
ODB April 2015 to March 2016 utilization data parameters	N: 5,760 Mean: 350 U SD: 168 U	N: 828 Mean: 405 U SD: 190 U
10,000 draws from gamma distributions with above parameters	Mean: 350 U SD: 168 U Mean Cost: $1,309 (95% range,$536 to $2,321)	Mean: 404 U SD: 191 U Mean Cost: $ 1,421 (95% range, $495 to $2,970)
Same 10,000 draws if aboBoNTA reimbursed instead (ratio 2.5:1)	Mean: 874 U SD: 420 U Mean Cost: $1,377 (95% range, $428 to $2,713)	Mean: 1,011 U SD: 477 U Mean Cost: $ 1,576 (95% range, $428 to $3,284)
Mean additional cost per claim with aboBoNTA vs. comparator	**$68.43**	**$154.54**
Costs per year assuming an average of 52/12 mean claims per year	aboBoNTA: $5,971 (95% range, $1,856 to $11,757) onaBoNTA: $5,674 (95% range, $2,321 to $10,056) **Difference (aboBoNTA – onaBoNTA): $297**	aboBoNTA: $6,828 (95% range,$1,856 to $14,232) incoBoNTA: $6,158 (95% range,$2,145 to $12,870) **Difference (aboBoNTA – incoBoNTA): $669**

aboBoNTA = abobotulinumtoxinA; incoBoNTA = incobotulinumtoxinA; SD = standard deviation; ODB = Ontario drug benefit; onaBoNTA = onabotulinumtoxinA; U = units; vs. = versus.

The mean dose of onaBoNTA derived using the ODB claims data are approximately 50 U lower than that of incoBoNTA for the same time period, leading to a higher mean cost per claim despite its lower per unit price. This suggests that despite the 1:1 dose ratio typically assumed, incoBoNTA is being used at slightly higher doses than onaBoNTA in patients with focal spasticity.

CDR therefore conducted a probabilistic sensitivity analysis comparing aboBoNTA to incoBoNTA using the onaBoNTA claims data as the source of the distribution for aboBoNTA while the incoBoNTA distribution was derived from incoBoNTA data. This effectively assumes that aboBoNTA will be used at a 2.5 to 1 ratio to onaBoNTA, but at a lower ratio to incoBoNTA. This resulted in the average cost per aboBoNTA claim being $41.50 less than that of incoBoNTA, or $180 less per patient per year if both products are used every 12 weeks. Of note, incoBoNTA claims represented only 13% of BoNTA claims reimbursed by ODB from April 2015 through March 2016.

Table 9: CDR-Modelled Mean Dose and Cost of aboBoNTA, onaBoNTA, and incoBoNTA Using ODB Claims Data

Parameter	onaBoNTA ODB Claims Data Used for aboBoNTA	incoBoNTA ODB Claims Data
ODB April 2015 to March 2016 utilization data parameters	N: 5,760 Mean: 350 U converted to 876 U aboBoNTA SD: 168 U converted to 421 U aboBoNTA	N: 828 Mean: 405 U SD: 190 U
10,000 draws from gamma distributions with above parameters	Mean: 874 SD: 418 Mean cost: $1,377 (95% range, $428 to $2,713)	Mean: 404 U SD: 188 U Mean Cost: $ 1,418 (95% range, $495 to $2,805)
Mean additional cost (savings) per claim with aboBoNTA versus incoBoNTA	**($41.50)**	
Costs per year assuming an average of 52/12 mean claims per year	aboBoNTA: $5,965 (95% range,$1,856 to $11,757) incoBoNTA: $6,145 (95% range,$2,145 to $12,155) **Difference (aboBoNTA – incoBoNTA): ($179.82)**	

aboBoNTA = abobotulinumtoxinA; incoBoNTA = incobotulinumtoxinA; SD = standard deviation; ODB = Ontario drug benefit; onaBoNTA = onabotulinumtoxinA; U = units.

Extended duration

The interim results of the ULIS-III observational study appear to support a longer duration of effect for aboBoNTA than onaBoNTA, which may be longer than incoBoNTA. However, with only two time points and a rapidly decreasing number of patients, it is not yet possible to determine if this difference will be sustained over time. Additionally, when requested, the manufacturer was unable to provide data on the doses of each comparator being used at each time point, nor any information on clinical or patient-relevant outcomes. As such, neither the cost nor relative effectiveness of the three BoNTA therapies as used in the ULIS-III study can be used to inform cost-effectiveness analyses at this time.

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