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WHAT DOES THE NEW ONTARIO PHARMACARE PLAN OFFER CHILDREN AND YOUNG ADULTS WITH RARE DISORDERS?

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Abstract

A publicly-funded pharmacare program (OHIP+) was announced in the 2017 Ontario budget for all children and young adults that will begin in January 2018 and cover drugs in the Ontario Public Drug Programs formulary. In this commentary, drugs indicated for rare disorders commonly occurring in childhood that were reviewed by the Common Drug Review (CDR) between 2004 and 2016 are examined to assess the Ontario reimbursement situation. Although 72% of the drugs are reimbursable, the eligibility criteria are unavailable for >50% of them. The criteria for others are onerous. Providing reimbursement for rare disorder drugs that received a positive CDR recommendation not already covered would likely cost <25% of OHIP+'s projected cost. Children who will benefit most from OHIP+ are those with common conditions whose parents do not presently have access to provincial or private insurance. Children with rare disorders deserve accessible provincial financial support for potentially life-transforming drugs.

In their 2017 budget, the governing Liberals announced a publicly-funded pharmacare system for Ontario's 4 million children and young adults under the age of 25 that will begin in January 2018.[1] The new program, called OHIP+, will cover all children.

Parents of children diagnosed with rare disorders who need access to expensive drugs that are becoming available for such disorders often cannot afford them and insurance does not cover them. Will OHIP+ help these children and their families?

OHIP+ AND THE ONTARIO PUBLIC DRUG PROGRAMS (OPDP)

OHIP+ will cover prescription drugs in the OPDP formulary, which includes almost 4,000 products (a "product" is any medication formulation/dosage combination) on a "General Benefit" unrestricted use list and 940 "Limited Use" products that have criteria restricting access to patients with specific disease characteristics or a defined treatment period.

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Although the number of products is large, fewer than 700 unique drugs are reimbursed. OPDP pay less than $5 per product item for 87.1% of the General Benefit products. Only 1.6% cost more than $100 per item. The corresponding figures for Limited Use products are 76.7% and 5.9%.[2]

In addition to the General Benefit and Limited Use lists, the Government of Ontario also has an Exceptional Access Program (EAP) and an Inherited Metabolic Diseases Program (IMDP). There is no single, comprehensive, publicly available list of drugs reimbursed under the EAP that includes their access criteria.[3,4] Nevertheless, the eligibility criteria, which are often extensive and complex, are available for 127 "frequently requested" EAP drugs.[4] In a list dated March 2016, the IMDP includes 45 "drugs and supplements" that may be reimbursed,[5] but the eligibility criteria are only detailed for a few drugs. Other drugs have been added subsequently.[6] The costs of drugs in the EAP and IMDP programs are not reported, but many are biotechnological products, which are often expensive.

The drugs most commonly dispensed to children under 12 are antibiotics, analgesics, cough/cold remedies, anti-asthma drugs, anti-allergens and attention-deficit hyperactive disorder (ADHD) drugs.[7] In older children and young adults, they are antibiotics, anti-asthma drugs, ADHD drugs, antidepressants, antidiabetic drugs and contraceptives. Most of these drugs are available as generic products so that the Government of Ontario's estimated annual cost for OHIP+ of $465 million[8] will increase the OPDP annual $5 billion budget[9] by less than 10%. The overall annual budget of the Ministry of Health and Long-Term Care[10] will increase by a tiny fraction.

RECENT DRUGS FOR RARE DISORDERS OCCURRING IN CHILDHOOD REVIEWED BY THE COMMON DRUG REVIEW

In a recent analysis of 55 CDR recommendations for 42 rare disorder drugs submitted between 2004 and February 2016,[11,12] 18 reimbursement recommendations pertained to 16 drugs for rare disorders that commonly manifest during childhood (Table 1). Of the 18 reimbursement recommendations, 12 were negative. However, resubmissions for 2 drugs, elosulfase alfa and sapropterin, led to revised CDR assessments later in 2016 so that 8 submissions (44%) now have positive recommendations.

All 16 drugs are for the treatment of lifetime disorders requiring continuous therapy. Nine are indicated for lysosomal storage disorders (Fabry, Gaucher and Pompe diseases and mucopolysaccharidoses), which are inherited metabolic diseases characterized by an abnormal build-up of various toxic materials in the body's cells as a result of enzyme deficiencies.[13] The onset of these disorders usually occurs in childhood. They impact different parts of the body, including the skeleton, brain, heart and central nervous system, and often lead to children dying at a young and unpredictable age after much suffering, such as severe skeletal deformities that are among the health problems that can be caused by mucopolysaccharidosis IVA.

The other drugs are for cystic fibrosis (CF) due to particular gene mutations,[14] tuberous sclerosis complex-associated benign brain tumours which can result in intellectual disability,[15] Dravet syndrome (a severe form of epilepsy with a high mortality rate[16]), phenylketonuria (PKU) which can lead to intellectual disability,[17] cryopyrin-associated periodic syndrome (auto-inflammatory disease that may cause hearing and vision loss, mental impairment, significant bone deformities and renal failure),[18] atypical hemolytic uremic syndrome (aHUS) which causes damage of the lining of blood vessels resulting in clotting that impacts various vital organs (particularly the kidneys),[19] and homozygous familial hypercholesterolemia which can lead to severe cardiovascular disease.[20]

Of the 8 drugs with a positive CDR recommendation, 5 — velaglucerase alfa, alglucosidase alfa, ivacaftor for G551D mutation CF, stiripentol and sapropterin — are on the EAP list; the eligibility criteria of the latter 3 are available from the "frequently requested" EAP list. Five of the 10 drugs with a negative CDR recommendation — miglustat, idursulfase, everolimus, canakinumab and eculizumab — are also on the EAP list, but the eligibility criteria are on the "frequently requested" list only for everolimus and eculizumab. In addition, 3 other drugs — agalsidase alfa, agalsidase beta, and laronidase — that received a negative CDR recommendation are on the IMDP list; their access criteria are not available. Overall,

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TABLE 1 Common Drug Review Recommendations and OPDP Coverage for 16 drugs For Rare Disorders Manifesting in Childhood

Generic Name	Brand Name	Disorder Treated	Reimbursement Recommendation	OPDP Coverage
agalsidase alfa	Replagal	Fabry disease	Negative	IMDP
agalsidase beta	Fabrazyme	Fabry disease	Negative	IMDP
taliglucerase alfa	Elelyso	Gaucher disease	Negative	No
velaglucerase alfa	Vpriv	Gaucher disease	Positive[b]	EAP
miglustat	Zavesca	Gaucher disease	Negative	EAP
alglucosidase alfa	Myozyme	Pompe disease	Positive[b]	EAP
laronidase	Aldurazyme	Mucopolysaccharidosis I	Negative	IMDP
idursulfase	Elaprase	Mucopolysaccharidosis II	Negative	EAP[c]
elosulfase alfa[a]	Vimizim	Mucopolysaccharidosis IVA	Positive[b]	No
ivacaftor	Kalydeco	G551D CF mutation	Positive[b]	EAP[d]
ivacaftor	Kalydeco	CFTR gating mutations	Positive[b]	No
ivacaftor	Kalydeco	R117H CFTR mutation	Positive[b]	No
everolimus	Afinitor	Tuberous sclerosis complex-associated subependymal giant cell astrocytoma	Negative	EAP[d]
stiripentol	Diacomit	Dravet syndrome	Positive[b]	EAP[d]
sapropterin[a]	Kuvan	Phenylketonuria	Positive[b]	EAP[d]
canakinumab	Ilaris	Cryopyrin-associated periodic syndrome	Negative	EAP
eculizumab	Soliris	Atypical hemolytic uremic syndrome	Negative	EAP[d]
lomitapide	Juxtapid	Homozygous familial hypercholesterolemia	Negative	No

CF = cystic fibrosis; CFTR = CF transmembrane conductance regulator; EAP = Exceptional Access Program; IMDP = Inherited Metabolic Diseases Program; OPDP = Ontario Public Drug Program.

[a]*Resubmission;* [b]*With criteria and/or conditions;* [c]*Criteria available in a separate document;* [d]*Criteria specified in EAP "frequently requested" list.*

72% of the rare disorder drugs reviewed by the CDR between 2004 and 2016 are reimbursable under the EAP or the IMDP.

LISTING DOES NOT GUARANTEE ACCESS

Drugs may be listed, but access to them varies depending on the complexity or harshness of the criteria that must be met before reimbursement can be obtained. The EAP reimbursement criteria for ivacaftor and stiripentol are consistent with CDR recommendations (Table 2) and patients satisfying the criteria usually obtain coverage.

In contrast, OPDP require PKU patients who are suitable candidates for sapropterin to qualify for a six-month manufacturer-funded trial of the drug after which EAP coverage may be accessible for patients with a demonstrated response to the trial. The EAP eligibility criteria are similar to but more extensive than the CDR criteria. However, both sets of criteria are complex and stringent and have been criticized by Ontario PKU physicians as lacking clinical sense. According to a 2015 presentation,[21] no PKU patient has obtained reimbursement in Ontario; the situation has not changed subsequently.

Everolimus for tuberous sclerosis complex-associated subependymal giant cell astrocytoma is normally reimbursed only after surgical resection has been tried, unless surgery is contraindicated (Table 3). The

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TABLE 2 Clinical Criteria Recommended by the Common Drug Review and Used in the Ontario Exceptional Access Program*

Drug	Common Drug Review Recommendation	Ontario Exceptional Access Program Criteria
Ivacaftor (Kalydeco)	For CF patients aged 6 years or more who have G551D CFTR gene mutation, if clinical criteria for the discontinuation of treatment in patients who fail to demonstrate a meaningful response are developed in consultation with CF treatment clinics.	For CF patients aged 6 years or more who have G551D CFTR gene mutation. Initial treatment for 1 year. Renewal based on a documented response to treatment and measurements of patient's sweat chloride and FEV1 levels.
Stiripentol (Diacomit)	For use in combination with clobazam and valproate for refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (Dravet syndrome), whose seizures are inadequately controlled with clobazam and valproate alone, if the patient is under the care of a neurologist.	For the treatment of patients with severe myoclonic epilepsy in infancy (Dravet syndrome) who meet all the following criteria; ■ Has refractory generalized tonic-clonic seizures. ■ Seizures inadequately controlled with clobazam and valproate alone. ■ Requires Diacomit for use in combination with clobazam and valproate. ■ Request submitted by neurologist or pediatrician.
Sapropterin (Kuvan)	For use in conjunction with a Phe-restricted diet to reduce blood Phe levels in patients with hyperphenylalaninemia due to tetrahydrobiopterin-responsive PKU with the following criteria: ■ Demonstrated response to initial 6-month trial. ■ Compliance with low protein diet, formulas, and treatment. ■ Achievement of 1 or more of the following (each based on 2 or more levels measured ≥1 month apart): ➢ Normal sustained Phe levels (<360 μmol/L). ➢ Sustained Phe reduction of ≥30% if baseline is <1200 μmol/L. ➢ Sustained Phe reduction of ≥50% if baseline is >1200 μmol/L. ■ Demonstrated increase of dietary protein tolerance based on targets set between clinician and patient. ■ Managed by physician specialized in metabolic/biochemical diseases.	Initial funding for 6 months considered by the manufacturer for PKU patients who meet all the following criteria: ■ Compliance with a low protein diet and formulas. ■ Baseline Phe levels of >360 μmol/L despite compliance with low protein diet (2 or more levels measured during 3–6 month time frame). ■ Baseline protein intake assessment by a dietitian. ■ Ability to comply with medication regimen. ■ Managed by physician specialized in metabolic/biochemical diseases. Continued EAP-funding considered for patients with demonstrated response to the initial 6-month trial who meet all the following criteria: ■ Compliance with low protein diet, formulas, and treatment. ■ Based on 2 or more levels measured ≥1 month apart, normal sustained Phe levels (>120 and <360 μmol/L), or sustained Phe reduction of ≥30% if baseline is <1200 μmol/L, or sustained Phe reduction of ≥50% if baseline is >1200 μmol/L. ■ Demonstrated increase of dietary protein tolerance based on targets set between clinician and patient. ■ Managed by physician specialized in metabolic/biochemical diseases. ■ Clinically meaningful age-appropriate improvement in neuro-behavioural or neuro-cognitive function or impairment for patients as determined by peer-reviewed clinically validated scales, or demonstrated improvement in quality of life using peer-reviewed validated scales.

CF = Cystic fibrosis; CFTR = CF transmembrane conductance regulator; Phe = phenylalanine; PKU = phenylketonuria.

**Criteria have been moderately edited to reduce repetition and verbosity, but the meaning remains.*

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mortality risk of surgery is more than 1%,[22] which is 3 orders of magnitude higher than the mortality risk of most drugs (≤1 in 100,000).[23]

The EAP eligibility criteria for reimbursement for eculizumab for aHUS are extensive, complex and stringent (Table 4). They lead to the drug usually being reserved for acute patients and those who have had a kidney transplant, but not all patients have access to the drug.

The reimbursement criteria for idursulfase are available in a separate document[24] and are relatively restrictive. The criteria for the other 7 drugs listed in the EAP or IMDP are not publicly available, but anecdotal evidence suggests that a majority of qualifying patients receive OPDP coverage.

The eligibility criteria are, therefore, not publicly available for more than half the reimbursable drugs and the criteria for some are onerous.

ESTIMATED COST OF COVERING THE RARE DISORDER DRUGS WITH POSITIVE CDR RECOMMENDATIONS

What would a less restrictive approach to access to the rare disorder drugs with positive CDR recommendations cost? To estimate annual costs of these drugs, the annual prevalence of each disorder was used to estimate the potential number of children and young adults in Ontario with the disease. These were combined with estimated annual costs to obtain estimates of the total costs.

Since access to stiripentol and ivacaftor is normally reasonably straightforward, these drugs were not included in the analysis. The number of estimated patients was arbitrarily reduced by 75% for velaglucerase alfa and alglucosidase alfa because anecdotal evidence suggests that a majority of patients seeking reimbursement for each of these drugs are successful. All potentially eligible sapropterin, everolimus and eculizumab patients were included due to their restrictive eligibility criteria and all potential elosulfase alfa patients were included because this drug is not currently reimbursed. Estimated annual costs for velaglucerase alfa, alglucosidase alfa, sapropterin, everolimus and eculizumab were obtained from their CDR recommendation reports (costs were commonly expressed as a range due to doses varying by body weight or surface area).[25–29] The estimated annual cost for elosulfase alfa was redacted in its CDR recommendation report; the cost for this drug was taken from price reported to be paid in Saskatchewan.[30]

Table 5 shows estimated numbers of patients aged less than 25 years and estimated costs of reimbursing the relevant drug for drugs with a positive CDR recommendation or on the frequently requested EAP list. The estimated additional cost of reimbursing these drugs ranges from $17.5 million to $108.0 million or 3.8% to 23.2% of the $465 million cost of OHIP+. However, the annual costs are most likely over-estimates because the higher costs are for adults which constitute about 25% of the OHIP+ population, some patients already have velaglucerase alfa, alglucosidase alfa, everolimus and eculizumab reimbursed, some children will not be appropriate candidates for the drug, and the costs provided in CDR recommendation reports are usually considerably higher than prices offered to or negotiated by prescription drug plans.

TABLE 3 Ontario Exceptional Access Program Clinical Criteria for Everolimus for Tuberous Sclerosis Complex-Associated Subependymal Giant Cell Astrocytoma*

Initial treatment of 1 year for patients for whom surgical resection cannot be considered for reasons such as: ■ Location, size, and/or distribution of tumour(s). ■ Subependymal giant cell astrocytoma progression despite previous surgical interventions. ■ Neurocognitive problems/ other complications secondary to previous surgical interventions.
Request must provide details outlining why the patient cannot be considered for surgical treatment.
Renewal considered in patients with documented stabilization of subependymal giant cell astrocytoma progression and improvement of symptoms.

**Criteria have been moderately edited to reduce repetition and verbosity, but the meaning remains.*

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Reimbursement for these drugs would, of course, require targeting large amounts of money to relatively few patients. This may be less appealing to voters than spreading resources to many patients regardless of need.

CONCLUSION

The introduction of OHIP+ may be a desire to improve children's health, a political strategy for the 2018 election, or both. Whatever the reason, parents, health policy analysts and the media have applauded OHIP+, with many viewing it as a first step to broader pharmacare.

Canadian provincial formularies chiefly include older, lower-cost generic products, while the relatively few newer expensive drugs that are listed are only accessible to patients satisfying specific, frequently complex and restrictive, clinical criteria. The listing of expensive drugs is commonly the result of patient support group advocacy, often led by families anxiously seeking access to medicines that have been prescribed by disease experts. Advocacy remains essential if patients requiring access to expensive drugs are to stand a chance at influencing bureaucrats and politicians to approve their coverage.[31]

TABLE 4 Ontario Exceptional Access Program Clinical Criteria for Eculizumab for Atypical Hemolytic Uremic Syndrome*

Treatment initiation: Patient must meet all the following criteria:

- Confirmed diagnosis of aHUS at initial presentation, defined by all the following:
  - ➢ Presence of an unexplained non-disseminated intravascular coagulation TMA.
  - ➢ Baseline ADAMTS-13 activity ≥10% on blood samples taken prior to plasma exchange or plasma infusion.
  - ➢ STEC-negative test in patients with a history of bloody diarrhea in the preceding 2 weeks.
  - ➢ Other diagnoses and causes of TMA must be ruled out.
- Evidence of ongoing active and progressing TMA as defined by:
  - ➢ Thrombocytopenia (platelet count <150 x 109/L) unexplained by another cause and hemolysis as indicated by documentation of 2 of the following: (a) red blood cell fragmentation (schistocytes) on a blood film, (b) low or absent haptoglobin, or (c) lactate dehydrogenase above normal, or
  - ➢ Tissue biopsy confirming TMA in patients who do not have evidence of platelet consumption and hemolysis.
- Evidence of at least 1 of the following documented clinical features of active organ damage or impairment:
  - ➢ Kidney impairment as demonstrated by 1 of the following:
    - o A decline in eGFR or a rise in serum creatinine of >20% in a patient with pre-existing renal impairment, or
    - o Serum creatinine > ULN for age or eGFR <60mL/min in patients who have no history of pre-existing renal impairment, or
    - o Serum creatinine > age-appropriate ULN in pediatric patients, or
    - o Renal biopsy.
  - ➢ Onset of neurological impairment related to TMA.

Continuation criteria at 6 months: A further 6-month of funding is considered if the patient demonstrates a response, defined as:

- Hematological normalization (platelet count, lactate dehydrogenase, haptoglobin).
- An improvement or stabilization of eGFR or serum creatinine.
- Stabilization of neurological or extra-renal impairment if these complications were originally present.

Continuation criteria at 12 months: Ongoing treatment response as defined in 6-month continuation criteria and the patient has limited organ reserve defined as:

- Significant cardiomyopathy, neurological, gastrointestinal or pulmonary impairment related to TMA, or
- Grade 4 or 5 chronic kidney disease (eGFR <30mL/min).

ADAMTS-13 = ADAM metallopeptidase with thrombospondin type 1 motif 13 gene; aHUS = atypical hemolytic uremic syndrome; eGFR = Estimated glomerular filtration rate; STEC = Shiga toxin-producing Escherichia coli; TMA = thrombotic microangiopathy; ULN = Upper limit of normal.

** Criteria have been edited to reduce repetition and verbosity, but the meaning remains.*

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In the news release about OHIP+, Premier Kathleen Wynne says the Liberals "are making sure that every young person across the province has access to the medications they need to stay healthy, feel better and live full lives" and that they "are easing parents' worries, while making life more affordable for them."[1] Minister of Health Eric Hoskins adds that access to medicines will be improved "by eliminating financial barriers to prescribed drugs."

Despite these assurances, the children who will benefit most from OHIP+ are those with common conditions whose parents do not presently have access to provincial or private insurance. Children with rare disorders will benefit from OHIP+ when they receive common medications to manage symptoms and associated conditions. However, their chance of receiving benefit for many new innovative rare disorder drugs already approved in Canada or that will become available in the near future is limited due to restrictive eligibility criteria and those who do will have their coverage stopped when they reach 25 years of age, which will result in discontinuation of care. Children with rare disorders and their families deserve accessible financial support for potentially life-transforming drugs.

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TABLE 5 Estimated costs Of Reimbursing the Drugs for Rare Disorders Manifesting in Childhood that have a Positive CDR Recommendation or are on the EAP List

Brand Name	Disorder Treated	Estimated Prevalence[a]	Estimated Children and Young Adults	Annual Cost[b]	Estimated Annual Cost
		Per 100,000	No.	x$1,000	x$1,000
Velaglucerase alfa	Gaucher disease	1	10[c]	51–610	510–6,100
Alglucosidase alfa	Pompe disease	0.8	8[c]	44–88	352–704
Elosulfase alfa	Mucopolysaccharidosis IVA	0.3	12	460[d]	5,520
Sapropterin	Phenylketonuria	10	400	12–169	4,800–67,600
Everolimus	Tuberous sclerosis complex-associated subependymal giant cell astrocytoma	0.8	32	70-105	2,240–3,360
Eculizumab	Atypical hemolytic uremic syndrome	0.85	34	121–728	4,114–24,752
Total					17,536–108,036

CDR = Common Drug Review; CFTR = CF transmembrane conductance regulator; EAP = Exceptional Access Program "frequently requested" list.

[a]*From Janoudi et al (2016),*[11] *with the following adjustments: (i) CFTR gating mutations only occur in about 3% of cystic fibrosis patients, (ii) Subependymal giant cell astrocytomas only occur in about 10% of tuberous sclerosis patients;* [b]*Annual cost taken from CDR recommendation reports;*[25–29] [c]*Estimated numbers reduced by 75%;* [d]*Annual cost not available from CDR report – cost taken from price reported to be paid in Saskatchewan.*[30]

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