Common Drug Review
Pharmacoeconomic Review Report

November 2016

Drug	Galsulfase (Naglazyme)
Indication	Long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome)
Reimbursement request	As per indication
Dosage form(s)	5 mg/5 mL (1 mg/mL) solution for intravenous infusion
NOC date	September 16, 2013
Manufacturer	BioMarin Pharmaceutical 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 inherited metabolic diseases who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary reimbursement recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

BIA	budget impact assessment
CDR	CADTH Common Drug Review
GAG	glycosaminoglycan
HTA	health technology assessment
MPS	mucopolysaccharidosis
MPS VI	mucopolysaccharidosis VI (Maroteaux-Lamy syndrome)
PBAC	Pharmaceutical Benefits Advisory Committee
SAE	serious adverse event
SMM	standard medical management

SUMMARY

Background

Galsulfase (Naglazyme) is available as a 5 mg/5 mL vial of solution for intravenous (IV) infusion at a cost of $1,535 per vial or $307 per mL[1] as long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of mucopolysaccharidosis VI (Maroteaux-Lamy syndrome) (MPS VI) (N-acetylgalactosamine-4-sulfatase [ASB] deficiency).

Mucopolysaccharidoses (MPS) are a group of inherited lysosomal storage disorders of disrupted glycosaminoglycan (GAG) metabolism.[1-3] Each MPS disorder is caused by a deficiency of a specific enzyme required for GAG degradation, which leads to accumulation of partially degraded GAGs.[1,2,4,5] The accumulation of GAGs causes progressive cellular, multi-system damage, organ failure, and reduced life expectancy. MPS VI is a rare, progressive, autosomal recessive disorder with multiple organ and tissue involvement.[1-3]

Currently, galsulfase is the only ERT indicated to treat patients with MPS VI. Prior to galsulfase, the management of MPS VI was generally supportive for complications. Standard medical management (SMM) differed based on patient characteristics (such as age, disease severity, and progression). As per the clinical trial identified,[6,7] galsulfase was assessed as a supplement to SMM in clinical practice.

Approach for this review

This review was initiated by the Formulary Working Group for the drug plans participating in the CADTH Common Drug Review (CDR) Program. As part of the CDR procedure, the manufacturer of galsulfase was invited to provide clinical and/or health economic evidence to support the CDR review process. The manufacturer provided Clinical Study Reports for galsulfase and a budget impact analysis (BIA) from the perspective of CDR-participating plans. To complement the limited health economic evidence shared by the manufacturer, CDR assessed the health economic evidence available in the public domain, and was supported by clinical expert inputs.

Cost assessment

Galsulfase was submitted at a marketed price of $307 per mL. The recommended dose is 1 mg per kg per week; therefore, the treatment cost per administration of galsulfase is $307 multiplied by the patient weight. Data from the pivotal clinical trial[6,7] indicated that patient age ranged from five to 29 years, and patient weight ranged from 14 kg to 47 kg; the mean patient weights in the trial were 24.6 kg for galsulfase and 20.8 kg for placebo. However, the patient weight was skewed to the low end due to patient age. The recently published long-term follow-up retrospective observational study of galsulfase[8] did not present an average weight, although the age ranges may suggest an average weight above the average weight in the pivotal study. Based on the available data on patient weight, CDR had to assume an average weight of 25 kg per patient (per the galsulfase trial treatment group). For an individual weighing 25 kg, at the recommended dose of 1 mg/kg of body weight administered once weekly (over at least four hours as an IV infusion),[9] the drug cost of galsulfase annually is $399,100. Based on the weight range in the study, for an individual weighing 14 kg, the drug cost of galsulfase decreases to $223,496; and for an individual weighing 47 kg, the drug cost of galsulfase annually increases to $750,308.

The CDR clinical expert indicated that if a five-year-old patient with typical MPS VI received galsulfase, it would be expected that, without a stopping rule applied, the patient would receive treatment for approximately 20 years. Over 20 years, considering the range in patient age (five to 29 years) and weight

(14 kg to 47 kg) from the pivotal study, it seems to be appropriate to assume an average weight of 25 kg over the 20-year period.[6] Based on this, the total average undiscounted lifetime drug cost of galsulfase per patient is approximately $8 million.

There is uncertainty regarding the number of patients who may receive galsulfase. Although the manufacturer estimated that there are approximately 15 to 20 potential patients with MPS VI in Canada,[10] a BIA was also provided by the manufacturer based on a patient population of [redacted] patients across Canada receiving galsulfase at baseline (year 0), which [redacted] patients at year 3.[11] The difference in patient numbers was not justified. Additionally, in the BIA provided by the manufacturer, the assumed patient weight of 22 kg was based on the average weight from the pivotal trial,[6,7] resulting in a budget impact of $[redacted] at baseline (year 0) [redacted] in year 3 (undiscounted). As MPS can range based on age at onset of the condition, CDR developed a scenario analysis increasing the average patient weight to 25 kg (as above). In addition, the CDR scenario considered that all 15 to 20 potential Canadian patients were able to receive treatment. CDR notes that the total cost depends substantially on the patient weight and number of patients, and thus created Table 1 for clarity.

TABLE 1: COST OF GALSULFASE DEPENDENT UPON WEIGHT AND PATIENT NUMBERS

Number of Patients	Weight (kg)						
	15	20	25	30	35	40	45
1	$239,460	$319,280	$399,100	$478,920	$558,740	$638,560	$718,380
10	$2,394,600	$3,192,800	$3,991,000	$4,789,200	$5,587,400	$6,385,600	$7,183,800
11	$2,634,060	$3,512,080	$4,390,100	$5,268,120	$6,146,140	$7,024,160	$7,902,180
12	$2,873,520	$3,831,360	$4,789,200	$5,747,040	$6,704,880	$7,662,720	$8,620,560
13	$3,112,980	$4,150,640	$5,188,300	$6,225,960	$7,263,620	$8,301,280	$9,338,940
14	$3,352,440	$4,469,920	$5,587,400	$6,704,880	$7,822,360	$8,939,840	$10,057,320
15	$3,591,900	$4,789,200	$5,986,500	$7,183,800	$8,381,100	$9,578,400	$10,775,700
16	$3,831,360	$5,108,480	$6,385,600	$7,662,720	$8,939,840	$10,216,960	$11,494,080
17	$4,070,820	$5,427,760	$6,784,700	$8,141,640	$9,498,580	$10,855,520	$12,212,460
18	$4,310,280	$5,747,040	$7,183,800	$8,620,560	$10,057,320	$11,494,080	$12,930,840
19	$4,549,740	$6,066,320	$7,582,900	$9,099,480	$10,616,060	$12,132,640	$13,649,220
20	$4,789,200	$6,385,600	$7,982,000	$9,578,400	$11,174,800	$12,771,200	$14,367,600

Review of the published economic literature

Embase and MEDLINE databases were searched with no date or language restrictions, with the initial search completed on September 28, 2015. Regular search updates were performed until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on January 20, 2016 (Appendix 3). The review did not identify any published economic literature on galsulfase for the treatment of MPS VI (Appendix 1).

Grey literature was identified by searching relevant websites, including those of health technology assessment (HTA) agencies (Appendix 1). An HTA review from Australia's Pharmaceutical Benefits Advisory Committee (PBAC) was identified. The PBAC Public Summary Document (PSD) reported that its health economic review was based on a trial-based cost-consequence analysis submitted by the manufacturer in which galsulfase in addition to SMM was compared with SMM alone (Appendix 2). Clinical data were based on the same pivotal study assessed in the CDR Clinical Review.[12] The cost-consequence evidence reported in the PSD indicated that patients receiving galsulfase in addition to

SMM could walk farther, climb more stairs, and had fewer hospitalizations and surgical or diagnostic procedures; and that this was associated with an additional annual cost of less than $10 million per patient compared with SMM alone. PBAC concluded that the preliminary economic evaluation suggested the resulting incremental cost-effectiveness ratio would be unacceptably high, but that the submission met the criteria for listing on Australia's Life Saving Drugs Programme (LSDP).

Health economic assessment

The CDR Clinical Review appraised the results of the identified randomized, double-blind, placebo-controlled clinical study[6,7] assessing the safety and efficacy of galsulfase in addition to SMM over a period of 24 weeks. The CDR clinical expert identified the need for hospitalization, surgical and diagnostic procedures, and wheelchair use as important outcomes that have an impact on health resource utilization, which may be informed by the study.

The following observations were seen in the pivotal study. Three patients (out of 19) in the galsulfase group and three patients (out of 20) in the SMM group were hospitalized during the time of the study, although patients receiving galsulfase plus SMM had fewer hospitalizations in total per patient than patients receiving SMM alone (there were about four times more hospitalizations in the placebo group than in the galsulfase group). Two patients required tracheostomy: one in the galsulfase group and one in the SMM group. Neither was determined to be study-related.[7] In total three patients in the galsulfase group and four patients in the SMM group had a serious adverse event (SAE) that required a surgical or diagnostic procedure, although patients receiving galsulfase had fewer surgical or diagnostic procedures.[7] The CDR Clinical Review indicates that wheelchair use was not reported in the study. Resource use was not well reported in the study, and the aforementioned evidence was sourced from SAE patient narratives in the Clinical Study Report.

Given the available data and the short-term nature of the study, it is difficult to make assumptions as to the extent to which health care resource utilization may be affected by the use of galsulfase in addition to SMM. The potential exists that there are cost implications for galsulfase that cannot be assessed given the paucity of data. It can be hypothesized that the introduction of galsulfase may reduce health care resource utilization, such as the potential for fewer hospitalizations, surgeries, and diagnostic procedures, and reduced wheelchair time. The CDR clinical expert did indicate that the use of galsulfase in patients with MPS VI is unlikely to affect the requirement for, or time to, bone marrow transplantation.

While no evaluation was provided to CDR assessing the relative health and economic implications of adding galsulfase to SMM in the Canadian situation, the general findings appear to be broadly similar to those identified by PBAC in its review of galsulfase. Galsulfase appears to be effective and well tolerated in patients with MPS VI (refer to CDR Clinical Review), but at a substantially greater total cost, driven by the cost of galsulfase ($399,100 per year for a 25 kg patient). The potential savings from other resource usage may not be enough to offset the high annual medication cost of adding galsulfase to SMM.

Patient input

Patient input was received as a single joint submission from two patient groups: the Isaac Foundation for Mucopolysaccharide (MPS) Treatment and Research, and the Canadian Society for Mucopolysaccharide and Related Diseases (the Canadian MPS Society). Information was obtained from a variety of sources, including patient interviews, an online survey, an internal review of a patient registry, and published literature.

Information was presented indicating the effect of MPS VI on the musculoskeletal system, leading to significant pain, loss of function, and reduced quality of life (QoL); affecting daily living activities and general enjoyment (e.g., bike riding, playing musical instruments, writing, drawing). Additionally, caregivers of patients with MPS VI are often required to miss work due to extensive care requirements, long hospital stays, multiple surgical interventions, and frequent medical appointments.

For patients without access to galsulfase, it was reported that a long-term palliative approach to managing the disease was taken, managing symptoms as they appeared. All interviewed patients who had received galsulfase, and their caregivers, reported stabilization of their condition and improvement in their QoL following initiation of galsulfase, although the previous impact of the disease persisted.

Patient input on treatment limitations focused on the access to galsulfase and infusion facilities. No serious or life-threatening infusion reactions were reported as a result of galsulfase, and it was reported that mild infusion-related reactions were tolerable and did not result in discontinuation of galsulfase. The weekly, four-hour galsulfase infusions were noted as a concern, as in some cases, two days of infusion per week were required.

Issues for consideration

- CDR was not able to assess the effects of implementing a treatment stopping rule based on efficacy and safety considerations.
- The assumption is that the manufacturer pays for the infusion. If the jurisdiction is required to fund the infusion, this would add further costs to treatment with galsulfase.
- MPS VI is a chronic condition; however, there is limited long-term natural history data to optimally inform the safety and efficacy of galsulfase. Further long-term data on galsulfase treatment and the natural history of the condition may assist decision-makers in their reimbursement policies.
- Patient input indicated that some patients may require more than one infusion per week, which would increase the annual cost of treatment with galsulfase.
- A 10-year cross-sectional follow-up study suggested that there is an association between treatment with galsulfase and prolonged survival; however, the CDR Clinical Review indicated that chance, confounding, or bias cannot be ruled out as alternative explanations for the results.

Conclusions

The annual acquisition cost of galsulfase for a patient weighing 25 kg at the recommended dosing regimen is $399,100. A typical five-year-old patient with MPS VI receiving galsulfase over 20 years would cost approximately $8 million (galsulfase drug cost only; undiscounted).

While no evaluation was provided to CDR assessing the relative health and economic implications of adding galsulfase to SMM in the Canadian situation, the general findings indicate treatment with galsulfase appears to lead to improvements on the 12-minute walk test (12MWT) with numerically fewer SAEs than SMM patients with MPS VI, but at a substantially greater total annual cost driven by galsulfase medication cost.

Cost comparison table

Galsulfase is the first treatment to be indicated for MPS VI, to be used as an add-on to SMM. Clinical experts have determined that there are no appropriate comparator treatments in this context (Table 2). 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 2: COST COMPARISON TABLE FOR GALSULFASE FOR THE TREATMENT OF MUCOPOLYSACCHARIDOSIS VI

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Weekly Drug Cost ($)	Average Annual Drug Cost ($)
Galsulfase	**5 mg/ 5 mL**	**Solution for intravenous infusion**	**1,535.0000[a]**	**1 mg/kg of body weight per week**	**4,298[b] 9,210[c] 14,429[d]**	**223,496[b] 399,100[c] 750,308[d]**

[a] Price is reported marketed price based on email correspondence with the manufacturer (August 2015); does not include markup or dispensing fees.[13]
[b] Assumes a patient body weight of 14 kg.
[c] Assumes a patient body weight of 25 kg.
[d] Assumes a patient body weight of 47 kg.

APPENDIX 1: SYSTEMATIC LITERATURE REVIEW

The CADTH Common Drug Review (CDR) undertook a systematic literature review to identify published economic literature on galsulfase for the treatment of mucopolysaccharidosis VI (Maroteaux-Lamy syndrome) (MPS VI).

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Naglazyme or Mucopolysaccharidosis.

Methodological filters were applied to limit retrieval to economic studies. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language.

The initial search was completed on September 28, 2015. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on January 20, 2016. Regular search updates were performed on databases that do not provide alert services.

The systematic literature search identified 162 citations that fulfilled the search criteria (see Appendix 3). The review criteria for retrieving articles were as follows:

- Article was in the correct condition (MPS VI).
- Article presented results of an economic evaluation.
- Article compared galsulfase with standard medical management (SMM).

Using these criteria, the review of the systematic search did not identify any articles that reported any form of economic evaluation of galsulfase for the treatment of MPS VI:

- Forty-eight were excluded as they did not report on patients with MPS VI.
- One hundred and twelve were excluded as they did not present the results of an economic evaluation.
- Two did not include galsulfase.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine): Health Economics, Health Technology Assessment Agencies. Google and other Internet search engines were used to search for additional Web-based materials, including conference abstracts. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies. See Appendix 3 for further details. A health technology assessment (HTA) review from Australia's Pharmaceutical Benefits Advisory Committee (PBAC) was identified as part of the grey literature search, assessing galsulfase for the treatment of MPS VI (see Appendix 2).

APPENDIX 2: SUMMARY OF HEALTH TECHNOLOGY ASSESSMENT FINDINGS

The grey literature search that included health technology assessment (HTA) websites retrieved an HTA review from Australia's Pharmaceutical Benefits Advisory Committee (PBAC). The PBAC reviewed galsulfase for the treatment of mucopolysaccharidosis VI (Maroteaux-Lamy syndrome) (MPS VI) for listing on the full formulary as well as Australia's Life Saving Drugs Programme (LSDP).[12] The details of the economic information that were made publicly available are listed in Table 3. No other HTA organization reviews for Naglazyme were available.

TABLE 3: SUMMARY OF HEALTH TECHNOLOGY ASSESSMENT FINDINGS

	Pharmaceutical Benefits Advisory Committee (July 2007)[a,12]
Treatment	Galsulfase (Naglazyme) (solution concentrate for IV infusion, 5 mg/5 mL) in addition to SMM
Price	Price not stated
Population	Treatment of patients with MPS VI
Comparator	Placebo in addition to SMM
Manufacturer's submitted economic analysis	Trial-based cost-consequence model was submitted 24-week time horizon The resources included were pre-treatment drug costs; galsulfase solution; galsulfase administration; SAEs requiring hospitalization; and adverse events requiring surgical and diagnostic procedures
Manufacturer's results	Over the 24-week time horizon, an average patient receiving galsulfase (plus SMM) instead of placebo (plus SMM) accrues: • additional costs of < $10 million over that period • additional 92 metres walked in 12 minutes (primary clinical outcome) • additional 53 metres walked in 6 minutes • additional 16.3 steps climbed in 3 minutes • additional 5.7 stairs climbed per minute for 3 minutes • reduction of 227 mcg/mg in urinary GAG • reduction of 0.53 hospitalizations • reduction of 0.237 surgical or diagnostic procedures
Issues noted by the review group	• Appropriate for the submission not to present a modelled economic evaluation. • Galsulfase (plus SMM) appears to have significant and clinically important advantages in effectiveness versus placebo (plus SMM) for the primary outcome, but more toxicity. • Longer-term effectiveness and toxicity of galsulfase, and impact on disease progression and mortality rates are unknown.
Recommendation	PBAC rejected the application based on unacceptably high cost-effectiveness, but recommended the government consider including galsulfase on the LSDP.
CDR assessment	CDR highlighted some areas of concern related to the results of the cost-consequence analysis submitted to PBAC regarding the clinical efficacy and safety of galsulfase (ceiling effect in walk tests; potential for reactions to galsulfase resulting in surgery). The manufacturer did not provide CDR with the analysis submitted to the PBAC, with the justification that the analysis is dated and was commissioned for a different health care system and therefore would not be appropriate. Based on the Clinical Study Reports provided by the manufacturer, CDR was unable to determine the reduction in health care resource utilization (hospitalization, procedures) to match the Australian results, although

	Pharmaceutical Benefits Advisory Committee (July 2007)[a,12]
	it is uncertain at which time point the results are presented. CDR notes that further observational efficacy data have been collected since the review by PBAC.

CDR = CADTH Common Drug Review; CSR = Clinical Study Report; GAG = glycosaminoglycan; IV = intravenous; LSDP = Life Saving Drugs Programme; MPS VI = mucopolysaccharidosis VI (Maroteaux-Lamy syndrome); PBAC = Pharmaceutical Benefits Advisory Committee; SAE = serious adverse event; SMM = standard medical management.

[a] PBAC meeting date listed. Date of publication not reported.

APPENDIX 3: PHARMACOECONOMIC LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 28, 2015
Alerts:	Biweekly search updates until January 20 2016
Study Types:	Economic literature.
Limits:	No date or language limits were used

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.po	Population group [PsycInfo only]
.kw	Keyword
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY		
Line #	**Search Strategy**	**Results**
1	N-acetylgalactosamine-4-sulfatase/ use pmez	187
2	(galsulfase* or Naglazyme* or Naglazyzme* or Aryplase* or BM 102 or BM102 or UNII-59UA429E5G or 552858-79-4 or arylsulfatase B or rhASB or N-acetylgalactosamine-4-sulfatase or ARSB).ti,ot,ab,sh,hw,rn,nm,kw. use pmez	584
3	exp Mucopolysaccharidoses/ use pmez	5668
4	Mucopolysaccharidoses/ use pmez	1958
5	Mucopolysaccharidosis VI/ use pmez	417
6	(Mucopolysaccharidosis* or Mucopolysaccharidoses* or ((Mucopolysaccharide* or glycosaminoglycan*) adj2 (storage or store or stores or enzyme*) adj2 (disorder* or disease* or Deficien* or syndrome*))).ti,ab. use pmez	3664
7	(Lipochondrodystroph* or ((Hurler* or Hunter* or Morquio* or Pfaundler* or Sanfilippo* or San Filippo* or Scheie* or Sly) adj2 (syndrome* or disease* or Deficien* or disorder*)) or Gargoylism* or alpha-L-Iduronidase Deficien* or Sulfoiduronate Sulfatase Deficien* or Iduronate Sulfatase Deficien* or I2S Deficien* or Polydystrophic Oligophrenia* or N Acetylglucosamine 6 Sulfatase Deficien* or Heparan Sulfate Sulfatase Deficien* or Sulfamidase Deficien* or NAGLU Deficien* or N-Acetyl-alpha-D-Glucosaminidase Deficien* or Eccentroosteochondrodysplasia* or Eccentro-Osteochondrodysplasia* or GALNS Deficien* or Galactosamine-6-Sulfatase Deficien* or GUSB Deficien* or beta Glucuronidase Deficien*).ti,ab. use pmez	3090
8	(Arylsulfatase B Deficien* or ((Maroteaux-Lamy or Maroteaux or Lamy) adj2 (Syndrome* or disease* or Deficien*)) or ((N-Acetylgalactosamine-4-Sulfatase adj2 Deficien*) or Polydystrophic Dwarfism* or ARSB Deficien*)).ti,ab. use pmez	283
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	7246
10	Economics/	249462
11	exp "Costs and Cost Analysis"/	472925
12	Economics, Nursing/	38119
13	Economics, Medical/	43061
14	Economics, Pharmaceutical/	8802
15	exp Economics, Hospital/	692379
16	Economics, Dental/	36770
17	exp "Fees and Charges"/	63903
18	exp Budgets/	34022
19	budget*.ti,ab.	48382
20	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti.	321063
21	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	452657
22	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab.	248854
23	(value adj2 (money or monetary)).ti,ab.	3617
24	exp models, economic/	132279
25	economic model*.ti,ab.	5078
26	markov chains/	70257
27	markov.ti,ab.	31887

MULTI-DATABASE STRATEGY		
Line #	**Search Strategy**	**Results**
28	monte carlo method/	48095
29	monte carlo.ti,ab.	64906
30	exp Decision Theory/	11828
31	(decision* adj2 (tree* or analy* or model*)).ti,ab.	34713
32	or/10-31	1747677
33	9 and 32	49
34	N-acetylgalactosamine-4-sulfatase/ use oemezd	1116
35	(galsulfase* or Naglazyme* or Naglazyzme* or Aryplase* or BM 102 or BM102 or UNII-59UA429E5G or 552858-79-4 or arylsulfatase B or rhASB or N-acetylgalactosamine-4-sulfatase or ARSB).ti,ab. use oemezd	716
36	Mucopolysaccharidoses/ use oemezd	2713
37	(Mucopolysaccharidosis* or Mucopolysaccharidoses* or ((Mucopolysaccharide* or glycosaminoglycan*) adj2 (storage or store or stores or enzyme*) adj2 (disorder* or disease* or Deficien* or syndrome*))).ti,ab. use oemezd	5067
38	(Lipochondrodystroph* or ((Hurler* or Hunter* or Morquio* or Pfaundler* or Sanfilippo* or San Filippo* or Scheie* or Sly) adj2 (syndrome* or disease* or Deficien* or disorder*)) or Gargoylism* or alpha-L-Iduronidase Deficien* or Sulfoiduronate Sulfatase Deficien* or Iduronate Sulfatase Deficien* or I2S Deficien* or Polydystrophic Oligophrenia* or N Acetylglucosamine 6 Sulfatase Deficien* or Heparan Sulfate Sulfatase Deficien* or Sulfamidase Deficien* or NAGLU Deficien* or N-Acetyl-alpha-D-Glucosaminidase Deficien* or Eccentroosteochondrodysplasia* or Eccentro-Osteochondrodysplasia* or GALNS Deficien* or Galactosamine-6-Sulfatase Deficien* or GUSB Deficien* or beta Glucuronidase Deficien*).ti,ab. use oemezd	3848
39	(Mucopolysaccharidosis* or Mucopolysaccharidoses* or ((Mucopolysaccharide* or glycosaminoglycan*) adj2 (storage or store or stores or enzyme*) adj2 (disorder* or disease* or Deficien* or syndrome*))).ti,ab. use oemezd	5067
40	34 or 35 or 36 or 37 or 38 or 39	9225
41	Economics/	249462
42	Cost/	98289
43	exp Health Economics/	671526
44	Budget/	31644
45	budget*.ti,ab.	48382
46	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti.	321063
47	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	452657
48	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab.	248854
49	(value adj2 (money or monetary)).ti,ab.	3617
50	Statistical Model/	196143
51	economic model*.ti,ab.	5078
52	Probability/	113359
53	markov.ti,ab.	31887
54	monte carlo method/	48095

MULTI-DATABASE STRATEGY		
Line #	**Search Strategy**	**Results**
55	monte carlo.ti,ab.	64906
56	Decision Theory/	2422
57	Decision Tree/	16487
58	(decision* adj2 (tree* or analy* or model*)).ti,ab.	34713
59	or/41-58	1761064
60	40 and 59	139
61	33 or 60	188
62	remove duplicates from 61	155
63	(MPS I or MPS 1 or MPS II or MPS 2 or MPS III or MPS 3 or MPS IV or MPS 4 or MPS V or MPS 5 or MPS VI or MPS 6 or MPS VII or MPS 7).ti,ab.	3599
64	32 or 59	1861841
65	63 and 64	45
66	61 or 65	193

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates of Search:	September 16, 2015
Keywords:	Naglazyme, Mucopolysaccharidosis
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine), were searched:

- Health Technology Assessment Agencies
- Health Economics.

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