Drug treatment of inborn errors of metabolism: a systematic review

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ABSTRACT

Background The treatment of inborn errors of metabolism (IEM) has seen significant advances over the last decade. Many medicines have been developed and the survival rates of some patients with IEM have improved. Dosages of drugs used for the treatment of various IEM can be obtained from a range of sources but tend to vary among these sources. Moreover, the published dosages are not usually supported by the level of existing evidence, and they are commonly based on personal experience.

Methods A literature search was conducted to identify key material published in English in relation to the dosages of medicines used for specific IEM. Textbooks, peer reviewed articles, papers and other journal items were identified. The PubMed and Embase databases were searched for material published since 1947 and 1974, respectively. The medications found and their respective dosages were graded according to their level of evidence, using the grading system of the Oxford Centre for Evidence-Based Medicine.

Results 83 medicines used in various IEM were identified. The dosages of 17 medications (21%) had grade 1 level of evidence, 61 (74%) had grade 4, two medications were in level 2 and 3 respectively, and three had grade 5.

Conclusions To the best of our knowledge, this is the first review to address this matter and the authors hope that it will serve as a quickly accessible reference for medications used in this important clinical field.

INTRODUCTION

Inborn errors of metabolism (IEM) are defined as monogenic diseases resulting in deficient activity in a single enzyme in a pathway of intermediary metabolism.[1] Although IEM are individually rare, they are collectively common (incidence likely to be more than 1/1000).[2] Over 500 human diseases due to IEM are now recognised, and this number is constantly increasing as new concepts and techniques become available for identifying biochemical phenotypes. The treatment of these disorders has seen significant advances over the past decade.[2] The progress in understanding the pathophysiology of the majority of these disorders has led to the discovery of several new therapies that have made it possible to attenuate the severity of the clinical manifestations associated with many IEM. Despite the rarity of these disorders, there is growing emphasis on the use of evidence-based medicine (EBM) in the treatment of such conditions. However, EBM faces significant practical difficulties in the field of IEM, and experts have pointed out some of these challenges.[3 4] Dosages of medications used for the treatment of various IEM can be obtained from different sources. However, these dosages vary between different sources[1–7] and are not usually supported by the level of existing evidence.

This article intends to summarise the dosages of medications used in the treatment of IEM as supported by the best level of evidence that currently exists in the literature. To the best of our knowledge, this is the first review article that addresses this issue, and the authors hope that it will provide quick and easy access to a comprehensive list of medications used in this important clinical field.

METHODS

A literature search was conducted to identify key material published in English in relation to dosages of medications for specific IEM. The medications found and their respective dosages were graded according to their level of evidence, using the grading system defined by the Oxford Centre for Evidence-based Medicine (OCEBM),[8] which, in brief, assigns level 1 to randomised controlled trials (RCT), level 2 to cohort studies, level 3 to case–control studies, level 4 to case series and level 5 to expert opinion.[8]

Search strategy

We systemically identified all known metabolic disorders or IEM as defined in well established text books in the field, namely: *The Metabolic and Molecular Bases of Inherited Disease*,[1] *Inborn Metabolic Diseases: Diagnosis and Treatment*,[5] and the *Physician's Guide to the Treatment and Follow-up of Metabolic Diseases*.[6] The references for each medication dosage mentioned in the books were reviewed. The PubMed and Embase databases were then searched for published material not covered by these textbooks. Different search terms with appropriate subheadings and keywords were used. Database searches were constructed based on two concepts: specific IEM and treatment. Using boolean operators, subject headings and text words were combined in all permutations for each individual disorder. The results from searches were combined with studies identified from the textbooks mentioned above.

Inclusion criteria

Studies considered in this review are RCT and observational studies including cohort, case–control and cross-sectional studies and case reports. Textbooks and grey literature as far back in time as possible were also included. The selection of literature for inclusion in the review was based on examination of abstracts and indexing (subject headings) where available, and on full text or the table of contents if accessible. When different dose regimens were suggested by different sources, the

authors chose the doses with the best available evidence. Non-English studies and duplicated papers were excluded.

RESULTS

Eighty-three medications used in various IEM were identified. The dosages of 17 medications (21%) had grade 1 level of evidence, 61 (74%) had grade 4, two medications were in level 2 and 3 respectively and three had grade 5. Unsurprisingly, the majority of medications that achieved grade 1 level of evidence (8/17, 47%) were enzyme replacement therapies for various lysosomal storage disorders (see table 1). These medications were novel and therefore required Food and Drug Administration (FDA) approval, which in turn required a high level of evidence. Most of the medications classified as grade 4 were approved for other indications not related to IEM before their use for specific metabolic disorders. For example, arginine was already approved for the treatment of growth hormone deficiency in children prior to the discovery of its usefulness in the management of hyperammonaemia in several urea cycle disorders.[9] Detailed information about representative examples of medications used in the treatment of IEM is given in tables 1–3. These include medications used in the treatment of lysosomal storage disorders, disorders of organic acids and amino acid metabolism or transport, and vitamins and co-factors used in the treatment of IEM. For each medication, the tables also provide information about indication in IEM, supply information, routes, dosages and level of evidence supporting its use. An additional list of medications used in the treatment of IEM is provided in the online supplementary table.

DISCUSSION

EBM is defined as conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.[10] In this systematic literature review, we used the current best evidence to select the dosages for medications that have been used for the last decade in various IEM. This will hopefully provide quick and easy access to information for clinicians in this field when determining appropriate dosages of medications that may not be routinely used.

Interestingly, most of the medications used in the field of IEM and their respective dosages only have level 4 evidence (74%). The gold standard for EBM is the RCT. However, obstacles to using RCTs to evaluate the efficacy of these medications include the rare nature of specific IEM, which makes it difficult to achieve significant statistical power when evaluating a specific treatment modality. Moreover, surrogate measures are often used when the disease is so rare or the desired outcome is so far in the future that it would take an unreasonably long follow-up period in order to obtain a sufficient number of clinical outcomes. Although the association between the surrogate measure and the true outcome may be biologically plausible, using the surrogate measure may produce misleading results if the association with the true outcome is not based on hard endpoints.[11] Additionally, since many treatments for IEM have been used for decades, it may be difficult to go back and perform RCTs to prove their efficacy. A clear example of this issue is arginine hydrochloride for the treatment of urea cycle disorders.

The above observations are also reflected in a few established guidelines for the treatment of some IEM. For example, L-carnitine supplementation for patients with glutaric aciduria type 1 (GA1) was among the recommendations considered to be good clinical practice in a recently published guideline for the diagnosis and management of GA1.[12] However, this was largely based on biological plausibility and expert opinion.[12] On the other hand, although the American College of Medical Genetics recommendation of enzyme replacement therapy in patients with Fabry disease relies on level 1b evidence, adjuvant therapy recommendations rely on evidence obtained from studies not carried out in patients with Fabry disease.[11 13]

IEM are considered orphan diseases, a situation that causes difficulties in conducting RCTs because of the small number of patients found and the paucity of funding from pharmaceutical companies relative to common diseases. The FDA relaxed their role in the approval of new drugs used for the treatment of specific IEM and considers them as orphan drugs to be prescribed under compassionate use. Some of the medications currently used in the treatment of IEM have benefited from this relaxation, including carglumic acid (Carbaglu) for the treatment of acute hyperammonaemia resulting from a deficiency of the enzyme *N*-acetylglutamate synthase, and alglucosidase α (Myozyme) which was approved in April 2006 as enzyme replacement therapy for Pompe disease.

Despite the various challenges that face the development of evidence-based practice in patients with IEM, therapeutic trials are still being conducted and may pave the way for more evidence-based therapeutic interventions for these disorders. Substrate reduction therapies and molecular chaperone therapies are examples of two therapeutic modalities with active ongoing clinical trials in some IEM (http://www.clinicaltrial.gov).

This review has several limitations and gaps and caution should be used when accessing the information in the online supplementary table. These limitations include the fact that knowledge of IEM is continuously and dynamically changing and it may not be long before the information in this review is outdated. Secondly, the existing tools frequently used for EBM such as the OCEBM grading system, were mainly designed for common disorders rather than rare diseases. This renders critical appraisal of the evidence very difficult and may be inaccurate or misleading. For example, although many studies reach level 1 evidence, all were measuring surrogate markers as the primary end point, which may not necessarily correlate with significant clinical outcomes. For example, dichloroacetate has been used for the treatment of congenital lactic acidosis in case series. When examined in an RCT, it was shown to reduce lactate, a surrogate marker, but was not associated with improved neurological or clinical outcome. Third, some medications have reached level 1 evidence when used for disorders other than IEM, but the evidence supporting their use in metabolic disorders is derived only from case reports. For example, the use of baclofen to treat spasticity in patients with glutaric aciduria type 1[12] is based on its use for treating spasticity in children with cerebral palsy.[15]

In summary, clinicians face several challenges and obstacles as they try to select the appropriate dosages of medications to treat their patients with IEM. Using the currently available evidence for these decisions may help resolve some of these difficulties until standard guidelines and recommendations are published.

Contributors MA: carried out the majority of the work, and prepared and drafted the initial manuscript; KA-T: reviewed the manuscript and the dosages and classification of evidence for every medication; HM: prepared the dosage forms and critically reviewed the article; WE: edited the manuscript; MA-J: reviewed the dosage forms and reviewed the classification of evidence for every medication. All authors approved the final manuscript as submitted.

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Table 1 Examples of medications used in the treatment of lysosomal storage disorders

	Drug	Indication(s)	How supplied*	Dose	Route	Evidence level
1	Agalsidase-α (Replagal)	Fabry disease	1 mg/ml solution for infusion	0.2 mg/kg every 2 weeks as IV infusion over 40 min[11 16]	IV	1b
2	Agalsidase-β (Fabrazyme)	Fabry disease	5 mg and 35 mg single-use vials for reconstitution to yield (5 mg/ml)	1 mg/kg every 2 weeks as IV infusion over 2–4 h[11 17]	IV	1b
3	Alglucosidase-α (Myozyme)	Pompe disease (GSD II)	50 mg single-use vials for reconstitution to yield (5 mg/ml)	20 mg/kg every 2 weeks as IV infusion over 4 h[18–20]	IV	1b
4	Cysteamine bitartrate (Cystagon)	Cystinosis	50 mg and 150 mg capsules	Begin with 10 mg/kg/day and increase weekly until the maintenance dose (60–90 mg of free base/kg/day) or (1.3–1.95 g/m^2 per day) is reached The recommended adult dose is 500 mg free base q6h; however, for both children and adults, the dose is titrated to reduce, if possible, leukocyte cystine concentration (measured 5–6 h after a dose) to below 1 nmol half-cystine/mg protein[21–23]	PO	4
5	Cysteamine hydrochloride (Cystoran)	Cystinosis	Ophthalmic drops	0.55% solution with benzalkonium chloride 0.01% as a preservative: 10–12 times/day in each eye[24 25]	Eyes	1b
6	Galsulfase (Neglazyme)	Mucopolysaccharidosis VI	5 mg/ml solution for injection	1 mg/kg/week†[26–28]	IV	1b
7	Idursulfase (Elaprase)	Hunter syndrome (mucopolysaccharidosis II)	IV solution must be diluted in 100 ml of 0.9 sodium chloride injection, each vial contains 2 mg/ml solution of idursulfase protein (6 mg) in an extractable volume of 3 ml and for single use only	0.5 mg/kg weekly over 1–3 h[29–31]	IV	1b
8	Imiglucerase (Cerezyme)	GD	200 U and 400 U powder for reconstitution	Various regimens for non-neuropathic Gaucher disease, chronic, symptomatic: Adults: Usual dosage, 60 U/kg IV over 1–2 h every 2 weeks; may range from 2.5 U/kg 3 times weekly to 60 U/kg once every 2 weeks Children(a) Safety and effectiveness have not been established in children younger than 2 years of age (b) 2 years and older: usual dosage, 60 U/kg IV over 1–2 h every 2 weeks; may range from 2.5 U/kg 3 times weekly to 60 U/kg once every 2 weeks‡[32 33] The absence of an improvement in visceral, haematological and biochemical markers within 6 months may indicate that a higher dose is required. If bone crises continue, the dose should be increased by at least 50%[32 33] For type III GD, some clinicians recommend a higher dosage: 120 U/kg/ 2 weeks[5]	IV infusion over 1–2 h	1b
9	Laronidase (Aldurazyme)	Mucopolysaccharidosis type 1	2.9 mg/5 ml solution for injection	100 U/kg/week[34]	IV	1b
10	Miglustat (Zavesca)	GD in patients unable to receive intravenous ERT, NPC	100 mg capsule	GD: 100 mg/kg/day TID[35–38] NPC: 200 mg/kg/day TID[39 40]	PO	4
11	Velaglucerase α	GD	Powder for solution for injection, 200 U/vial and 400 U/vial	60 U/kg administered every other week over 1 h§ Adjust based on disease activity	IV	1b

†Product information for Naglazyme.
‡Product information: Cerezyme injection, imiglucerase injection.
§Product information for velaglucerase α. *Available under different brand names; sometimes in various dosage forms and strengths (only a few examples are given).
ERT, enzyme replacement therapy; GD, Gaucher disease; IV, intravenous; NPC, Niemann-Pick disease type C; PO, per os (by mouth); q6h, every 6 h; TID, three times a day.

Table 2 Examples of medications used in the treatment of disorders of organic acids and amino acid metabolism or transport

	Medication	Indication(s)	How supplied	Dose	Route	Evidence level
1	Arginine hydrochloride (R-Gene)	Acute management of hyperammonaemic crises in suspected or confirmed urea cycle disorders, except arginase deficiency	10% solution for injection (100 mg/ml)	For suspected urea cycle or ASS or ASL, give: 600 mg/kg if (<20 kg) or 12 g/m^2 if (>20 kg) as a loading dose over 90 min followed by 600 mg/kg if (<20 kg) or 12 g/m^2 if (>20 kg) as maintenance infusion over 24 h. For OTC and CPS: 200 mg/kg if (<20 kg) or 4 g/m^2 if (>20 kg) as a loading dose over 90 min followed by 200 mg/kg if (<20 kg) or 4 g/m^2 if (>20 kg) as maintenance infusion over 24 h[41]	IV	4
2	L-Citrulline	CPS deficiency OTC deficiency LPI	500 mg capsules, powder	CPS and OTC deficiency: 170 mg/kg/day or 3.8 g/m^2/day[42–45] LPI: 100 mg/kg/day, however, the aim is to keep the citrulline within normal ranges In some patients 400 mg/kg/day were used[46–48]	PO	4
3	Dextromethorphan	Non-ketotic hyperglycinaemia	15 mg tablets 15 mg/5 ml syrup	5–35 mg/kg/day in 4 divided doses. Blood concentration can be monitored; the therapeutic level is not defined, but should be greater than zero (0) and lower than 100 nmol/l[49–53]	PO	4
4	Glycine	Isovaleric acidaemia -HMG-CoA lyase deficiency. May be used in 3-methylcrotonyl glycinuria	Powder	250 mg/kg/day (150–300 mg/kg/day) in 4 divided doses[5 6 54 55]	PO	4
5	Ketamine	NKH	10 mg/ml, 50 mg/ml and 100 mg/ml solution for injection (maybe be used orally after mixing the dose with 0.2–0.3 ml/kg of cola or other beverages)	1 mg/kg/day in 4 divided doses. Titrate it up to 30 mg/kg/day according to clinical and biochemical response[56–59]	Oral or IV or IM	4
6	L-Carnitine	Primary and secondary carnitine deficiency	300 mg/ml oral liquid 300 mg capsules 500 mg tablets 200 mg/ml solution for injection	Acute crises (carnitine boluses): 100 mg/kg/dose 3–4 times daily, that is (300–400 mg/kg/day) should be given. Urine output should be appropriate prior to dosing (or haemofiltration be ongoing) Chronic: 100–300 mg/kg/day in 3 divided doses[5 12 60 61]	PO or IV	4
7	L-Isoleucine	MSUD	Powder	With the help of a metabolic dietician: 20–120 mg/kg/day. Dose is adjusted as necessary to achieve normal plasma amino acids levels[62]	PO	4
8	L-Serine	3-PGDH deficiency PSAT deficiency PSPH deficiency	Powder	3-PGDH:Infantile form: 500–600 mg/kg/day in 3 divided dosesJuvenile form: 100–150 mg/kg/day in 3 divided dosesPSAT: 500 mg/kg/dayPSPH: 200–300 mg/kg/dayHowever, the doses are varied aiming to normalise CSF serine[63]	PO	4
9	L-Valine*	MSUD	600 mg capsules, powder	With the help of a metabolic dietician: 20–120 mg/kg/day. Dose is adjusted as necessary to achieve normal plasma amino acid levels[62]	PO	4
10	Mercaptopropionylglycine (Tiopronin)	Cystinuria	Tablet, 100 mg	The dosage is wide at 15–50 mg/kg/day in 2 or 3 divided doses, maximum 1000 mg/day. However, the dose depends on monitoring free urine cystine level, so modify the dose in order to maintain a level below 200 mmol/mmol of creatinine[5 6 64 65]	PO	4
11	Methionine	Several remethylation defects	Available in different dosage forms: capsules, powder and tablets	40–50 mg/kg per day, adjust the dose to maintain upper normal ranges of plasma and CSF methionine.[66] However, some investigators argue against its usage in such disorders because it may result in sustained hyperhomocystinaemia[67]	PO	4
12	*N*-carbamoylglutamate (Carbaglu)	Unknown hyperammonaemia, NAGS deficiency, CPS-1 deficiency, propionic acidaemia or methylmalonic acidaemia	200 mg tablet	100–250 mg/kg/day, then adjusted individually in order to maintain normal ammonia plasma levels and divided into 2–4 doses[68–75] Based on limited unpublished data, the maintenance dose is less than 100 mg/kg/day	PO	4

*Available under different brand names; sometimes in various dosage forms and strengths (only a few examples are given).
3-PGDH, 3-phosphoglycerate dehydrogenase; ASL, argininosuccinic acid lyase; ASS, argininosuccinic acid synthetase; CPS, carbamoyl phosphate synthetase; LPI, lysinuric protein intolerance; IM, intramuscular; MSUD, maple syrup urine disease; NAGS, *N*-acetylglutamate synthase; NKH, non-ketotic hyperglycinemia; OTC, ornithine transcarbamylase; PSAT, phosphoserine aminotransferase; PSPH, phosphoserine phosphatase.

Table 3 Examples of vitamins and co-factors used in the treatment of inborn errors of metabolism

	Vitamin/co-factor	Indication(s)	How supplied	Dose	Route	Evidence level
1	Biotin	Cofactor for carboxylases Biotinidase deficiency BRBGD Multiple carboxylase deficiency	10 mg and 50 mg tablets/ capsules 1 mg capsule IV (available as part of a multivitamin complex)	Biotinidase deficiency, co-factor for carboxylases and multiple carboxylase deficiency: 5–20 mg/day[5 6 76 77] BRBGD: 5–10 mg/kg/day[78–80]	PO	4
2	Folic acid	Long term supplementation to compensate for the so-called methylfolate trap in remethylation defect	1 mg and 5 mg tablets	Variable, 5–30 mg/day[66 67]	PO	4
3	Folinic acid	DHPR deficiency UMP synthase deficiency (hereditary orotic aciduria) Methylene synthase deficiency Methionine synthase deficiency Hereditary folate malabsorption Cerebral folate transporter Folinic acid responsive seizure Remethylation defect	5 mg, 10 mg, 15 mg and 25 mg tablets 10 mg/ml injection solution 50 mg, 100 mg, 200 mg and 350 mg powder for reconstitution (injection)	Hereditary folate malabsorption: Adult: 150–200 mg/day PO once daily; infants and children: 50 mg or 10–15 mg/kg PO once daily[81 82] Or 1.5–7.5 mg IM once daily.[82–84] However, the dose should be adjusted in the individual to achieve a CSF folate level that is normal for age[85] Other indications: 5–15 mg/day PO or IV BID[5 86]	PO or IV or IM	4
4	Hydroxocobalamin (vitamin B_{12})	Disorders of cobalamin metabolism	1000 μg/ml solution for injection Tablets	1 mg IM daily or oral dose: 10 mg once or twice daily[5 6 87–89]	IM or PO	4
5	Pyridoxine	Pyridoxine responsive CBS, PDE, pyridoxine responsive OAT, PH1	25 mg, 40 mg, 50 mg, 100 mg, 250 mg and 500 mg tablet Liquid, oral: 200 mg/5 ml	CBS: 200 mg/day or the lowest dose that produces the maximum biochemical benefit (ie, lowest plasma homocysteine and methionine concentrations), as determined by measurement of total homocysteine and amino acid levels[7 90] PDE: 100 mg IV, additional doses may be administered over the course of 30 min while observing for both a clinical and a possible electrographic response. If IV administration of pyridoxine is not possible for a first trial, pyridoxine is given orally/enterally with 30 mg/kg/day. Long term treatment: there are no clear-cut dosing recommendations, generally 15–30 mg/kg/day have been used in infants or up to 200 mg/day in neonates and 500 mg/day in adults[91] OAT deficiency: 300–600 mg/day[5 7 92] PH1: 5–10 mg/kg/day. Monitor oxalate and glycolate excretion and titrate the dose accordingly[93 94]	PO or IV (PDE) PO in others	4
6	Pyridoxal phosphate (PLP)	Pyridoxal phosphate-dependent seizures	50 mg tablet	30 mg/kg/day divided into 3 or 4 doses enterally, for 3–5 days 30–50 mg/kg/day divided into 4–6 doses[86 95]	NGT or PO	4
7	Riboflavin	GA1, MAD, mitochondrial complex 1 deficiency	25 mg, 50 mg and 100 mg tablet 400 mg capsule	GA1: There is no firm evidence that riboflavin improves the neurological outcome of GA.[12] However, responsiveness to 100–150 mg/day divided into 2–3 doses has been demonstrated in a few patients[96 97] MAD: 100–400 mg/day in 2–3 divided doses[98 99] SCAD: 10 mg/kg/ day, divided into 3 doses with a maximum of 150 mg/day[100] Mitochondrial complex 1 deficiency: 3–20 mg/kg/day divided into 3 doses[6 101]	PO	4
8	Sapropterin dihydrochloride (Kuvan)	HPA due to BH4 responsive PKU	100 mg tablet	BH4 loading test: 20 mg/kg/dose once daily for 2 consecutive days Others: 10–20 mg/kg/day once daily[102–104] Monitor phenylalanine levels and adjust the dose accordingly	Oral	1b
9	BH4	BH4 loading test, disorders of BH4 synthesis, BH4 responsive PKU. Currently replaced by Kuvan	50 mg tablet	BH4 loading test: 20 mg/kg/dose once daily for 2 consecutive days Others: 5–20 mg/kg/day, monitor phenylalanine levels and adjust the dose accordingly[102 105]	PO	4

Continued

Table 3 Continued

	Vitamin/co-factor	Indication(s)	How supplied	Dose	Route	Evidence level
10	Thiamine	Thiamine responsive MSUD, thiamine responsive pyruvate dehydrogenase deficiency and complex I deficiency	50 mg, 100 mg, 250 mg and 500 mg tablet 100 mg/ml injection	Various dosage have been used: 100 mg/day,[106] 10 mg/kg/day[2]; the dose ranges between 10 and 1000 mg/day[5 62 107 108]	PO	4
11	Ubiquinone (coenzyme Q10)	Primary CoQ10 deficiency	50 mg, 100 mg and 200 mg soft gel capsule	The dosage employed is highly variable Adult: 200–600 mg QID, paediatrics: 2–15 mg/kg/day BID[109] Other used: 30 mg/kg/day.[110] As high as 2000 mg/day has been used[111]	PO	4
12	Vitamin C	GS Hawkinsinuria, tyrosinaemia type III and transient tyrosinemia of newborn	100 mg tablet 100 mg/ml drops 1 g effervescent tablet	GS: 100 mg/kg/day[112–114] Others: 200–1000 mg/day	PO	4
13	Vitamin E	GS	100 mg capsule 50 U/ml drops	GS: 10 mg/kg/day[112–114]	PO	4

BH4, tetrahydrobiopterin; BID, twice daily; BRBGD, biotin responsive basal ganglia disease; CBS, cystathionine β synthase deficiency; CSF, cerebrospinal fluid; DHPR, dihydropteridine reductase; GA1, glutaric aciduria; GS, glutathione synthetase deficiency; HPA, hyperphenylalaninemia; IM, intramuscular; IV, intravenous; MAD, multiple acyl-CoA dehydrogenase deficiency; MSUD, maple syrup urine disease; NGT, nasogastric tube; PDE, pyridoxine dependent epilepsy; PH1, primary hyperoxaluria type 1; PKU, phenylketonuria; PO, per os (by mouth); OAT, ornithine aminotransferase deficiency; SCAD, short-chain acyl-CoA dehydrogenase deficiency; QID, four times daily.

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Notes