BIMDG
British Inherited Metabolic Disease Group

National Formulary for Inherited Metabolic Diseases

3rd Edition - 2024

(Adult & Paediatric)

W.A. Batten
(Department of Pharmacy, University Hospitals Bristol & Weston NHS Foundation Trust)

Contributing Authors/Editors:

Faiza Adrees (Department of Pharmacy, Salford Royal NHS Foundation Trust)
Ceri Gaskell (Department of Pharmacy, University Hospitals Bristol & Weston NHS Foundation Trust)
Elaine Murphy (Charles Dent Metabolic Unit, University College London NHS Foundation Trust)
James Davison (Department of Metabolic Medicine, Great Ormond Street Hospital NHS Foundation Trust)
Antonio Ochoa-Ferraro (Department of Pharmacy, University Hospitals Birmingham NHS Foundation Trust)
Roshni Vara (Inherited Metabolic Diseases, Evelina Children's Hospital)
Jules Cuthbert (Department of Pharmacy, University Hospitals Bristol NHS Foundation Trust)
Chin Gan (Department of Pharmacy, Great Ormond Street Hospital NHS Foundation Trust)
Dan Bell (Department of Pharmacy, Cambridge University Hospitals NHS Foundation Trust)
Julian Raiman (Department of Metabolic Diseases, Birmingham Women's, and Children's NHS Foundation Trust)
Tom Wyllie (Department of Pharmacy, Cardiff & the Vale University Hospital Board)
Peter Clayton (University College London)
Hugh Lemonde, (Inherited Metabolic Diseases, Evelina Children's Hospital)
Evelyn Frank, (Charles Dent Metabolic Unit, University College London NHS Foundation Trust)
Andrew Wignall (Department of Pharmacy, Nottingham University Hospitals NHS Foundation Trust)
Lorna Marks (Department of Pharmacy, Manchester University Hospital NHS Foundation Trust)
Katherine Murrish (Department of Pharmacy, Nottingham University Hospitals NHS Foundation Trust)
Stephen Bowhay (Department of Pharmacy, Royal Hospital for Children NHS Greater Glasgow, and Clyde)
Siema Akram (Inherited Metabolic Diseases, Birmingham Women's & Children's NHS Foundation Trust)
Hannah Jebb (Department of Pharmacy, University Hospitals Bristol & Weston NHS Foundation Trust)
Sam Whiting (Department of Pharmacy, University Hospitals Bristol & Weston NHS Foundation Trust)
Zoe Taylor (Department of Pharmacy, Cardiff, and Vale Health board)
Sheatha Latif (Inherited Metabolic Diseases, Birmingham Women's & Children's NHS Foundation Trust)
Trinh Huynh (Inherited Metabolic Diseases, Evelina Children's Hospital)
Simon Jenkinson (Department of Pharmacy, Royal Free London NHS Foundation Trust)
Bernd Schwahn (Inherited Metabolic Diseases, Manchester University Hospital NHS Foundation Trust)
Godfrey T Gillett (Inherited Metabolic Disease & Clinical Chemistry, Sheffield Teaching Hospital NHS Foundation Trust)
Rachel Skeath (Department of Metabolic Medicine, Great Ormond Street Hospital NHS Foundation Trust)
Patty Nguyen (Charles Dent Metabolic Unit, University College London NHS Foundation Trust)
Steven Bowhay (Royal Hospital for Children, Glasgow)
Charlotte Dawson (University Hospitals Birmingham)
Sergei Korenev (Royal Manchester Childrens)
Germaine Pierre (University Hospital Bristol)
Nishan Guha (Oxford University Hospitals)

We are grateful to Metabolic Support UK (www.metabolicsupportuk.org) who provided financial support for the completion of this project.

TABLE OF CONTENTS

PREFACE

Inherited metabolic disorders are rare conditions for which medications and medical food supplements unfamiliar to many practitioners may be indicated. Outside of specialist centres, there is likely to be limited experience of the use of these drugs / food supplements. In addition, for example for specific vitamin-responsive disorders, vitamins may be indicated at much higher doses than advised in the general population.

This formulary has therefore been developed to support prescribers across the NHS in the prescription and monitoring of these treatments for rare inherited metabolic disorders. In conjunction with this formulary, a **Shared Care Guidance Plan** has been produced to support prescribers in primary and secondary care.

The published evidence base for dosing of many unlicensed drugs commonly used in metabolic medicine is limited although there is long-standing clinical experience with their use. Variable phenotypic expression, with a wide spectrum of severity for many conditions, can result in the need for medications and supplements to be titrated over a wide dose range to achieve recommended metabolic targets or clinical response.

The drug monographs contained within this formulary give basic information on metabolic drugs which may be prescribed. It has been developed, checked for use and endorsed by the British Inherited Metabolic Disease Group (BIMDG). The monographs are abbreviated and do not provide comprehensive drug information. **ALWAYS** refer to other prescribing reference sources when prescribing for complete information on contraindications, cautions and side effects for example. Please note that although information here has been collated to reflect practice at the time of writing, we cannot be responsible for changes after this time.

The aims of this formulary are:

- To support prescribers in primary and secondary care – with a single resource for information on treatment for these conditions.
- To reduce the postal costs to tertiary care in sending out medications / supplements to patients who may live far from a specialist centre, by supporting their local secondary or primary care in the safe prescription of treatment.
- To reduce the inconvenience, loss of working time, and potential gaps in treatment caused by patients being asked to travel long distances to collect medications / supplements from a specialist centre.
- To clarify the responsibilities of tertiary, secondary and primary care in the prescribing and monitoring of these treatments.
- To provide a national information resource to pharmacists.

We are grateful to Metabolic Support UK (www.metabolicsupportuk.org) who provided financial support for the completion of this project.

Feedback on this formulary is very welcome. Please email feedback on the **BIMDG Formulary Feedback Form** found on our website.

KEY CHANGES IN THIS VERSION

Changes in this version of the formulary include but are not limited to those documented in below table. The table documents significant changes made in this version, including addition of monographs and changes to licensed indications. Monographs may still contain minor updates compared to previous versions and should be considered accordingly.

Section of Formulary	
Medicines to avoid or use with caution	Fructose excipients table added. Updates for aminoglycosides in mitochondrial disorders
Emergency guidelines and acute decompensation in inherited metabolic disorders	Stability study data added
Alirocumab	New Monograph
Atorvastatin	Monograph removed
Avalglucosidase Alfa	New Monograph
Carglumic Acid	Addition of *'Sovereign'* brand
Chenodeoxycholic Acid	Addition of unlicensed indications
Cholesterol	Addition of adult dosing in formation for Smith-Lemli-Optitz Syndrome
Cholic acid	Addition of off-label indication for adults
Cipaglucosidase Alfa	New Monograph
Empagliflozin	New Monograph
Evolocumab	New Monograph
Fosdenopterin	Update to paediatric dosing information
L-Carnitine	Addition of *'Cenotepharma'* brand, sugar-free and alcohol-free
Lomitapide	New Monograph
L-Ornithine	Ornithine hydrochloride removed (no longer available)
Migalastat	Now licensed from age 12 upwards.
Miglustat	Updates to licensed indication
Metraleptin	New Monograph
Olipudase Alfa (Xenopozyme)	New Monograph
Pegunigalsidase Alfa (Elfabrio®)	New Monograph
Sacrosidase	New Monograph
Sapropterin	Update to licensed indication
Uridine Triacetate	New Monograph
References	Additional reference sources added

Medications to avoid or use with caution in inherited metabolic disorders - Summary

Table 1 is intended as a guide only. Some medications may be safe in low doses, in adult patients, or in patients with milder phenotypes. Please discuss each case with the specialist inherited metabolic disease team to determine an individual risk/benefit evaluation if a particular medication from this table is indicated. More detailed information and references can be found in 'Appendix 1 – Medications to avoid or use with caution in inherited metabolic disorders – further information'.

Table 1 – Summary of medicines to be used with caution or avoided in IMDs

Medication or excipient	Use with caution in	Risk of
Aspartame	Phenylketonuria (PKU)	Increase in phenylalanine
Corticosteroids (high dose; intravenous)	Urea cycle disorders (UCDs) Organic acidurias (OAs) Fatty acid oxidation disorders (FAODs)	Hyperammonaemia
Lactose	Galactosaemia	Increase in galactose (& metabolites)
Lactulose	Galactosaemia	Increase in galactose (& metabolites)
Pivmecillinam	Carnitine transporter deficiency and organic acidaemias	Increased renal excretion of carnitine
Probenacid	Patients treated with sodium phenylbutyrate	Hyperammonaemia
Propofol	Long or medium chain fatty acid oxidation disorders (FAODs)	Propofol infusion syndrome; rhabdomyolysis
Sodium valproate Valproic acid	Urea cycle disorders (UCDs) Organic acidurias (OAs) Fatty acid oxidation disorders (FAODs) Non-ketotic hyperglycinaemia (NKH); Mitochondrial disorders (especially POLG-related disorders)	Hyperammonaemia; hyperglycinaemia
Aminoglycosides (*e.g.* gentamicin, tobramycin & amikacin)	Mitochondrial disorders	Aminoglycoside associated ototoxicity (including at therapeutic levels)
Fructose and sorbitol	Hereditary Fructose Intolerance (HFI) *i.e.* Aldolase B deficiency, and Fructose-1,6-Bisphosphatase Deficiency	Hepato-renal failure. Acute metabolic crisis.

Emergency Guidelines and acute decompensation in Inherited Metabolic Disorders

A number of inherited metabolic disorders are associated with **acute metabolic decompensation** and need to be treated as an emergency.

Emergency guidelines can be found on the BIMDG website and should be used in conjunction with advice from a metabolic Consultant.

For the management of acute decompensation please refer to individual patient management plans or management plans available on the British Inherited Metabolic Disease Group (BIMDG) website - http://www.bimdg.org.uk/site/guidelines.asp

Access to the **Intravenous Drug Calculation for the Emergency Management of Hyperammonaemia** is available from: https://www.bimdg.org.uk/store/guidelines/Drug_Calculator_Index_743383_12042017.pdf

Pre-made bags of infusion fluid should be used if available and additions to fluid bags should be avoided if possible (as these can be associated with significant patient safety risk due to the danger of maladministration of electrolytes). However, on occasion it may be necessary to use intravenous fluids (with additives) that are not available as pre-made bags.

Stability study of a mixed system of Sodium Benzoate, Sodium Phenylbutyrate and Arginine in 10% dextrose

F.Adrees, W. Batten, C.Marks

Arginine, sodium benzoate and sodium phenylbutyrate are used in combination by intravenous administration for the management of urea cycle disorders in concentrations of up to 50mg/ml. Data from the above study supports the compatibility of all three agents via Y-site, as is current clinical practice in the UK.

Availability of medications for Inherited Metabolic Disorders

We recommend that:

- Intravenous preparations of sodium benzoate, sodium phenylbutyrate, L-arginine and levocarnitine should be kept as stock in ALL District General Hospitals (DGHs) with neonatal units. Delay in the availability of these medications in an emergency can result can be fatal or result in severe neurological outcomes.
- Specialist hospitals for children should also keep these medications and in addition stock carglumic acid.

Below are the contact details of the hospitals in the UK where access to specialist medications for metabolic disease can be accessed in an emergency. Out of hours, please ask the operator/switchboard for the Emergency Duty Pharmacist (EDP).

Manchester University NHS Foundation Trust
Main switchboard: 0161 276 1234

Salford Royal Hospital NHS Foundation Trust
Main switchboard: 0161 789 7373

Nottingham University Hospital's NHS Trust
Main switchboard: 0115 924 9924

Cambridge University Hospitals NHS Foundation Trust,
Main switchboard: 01223 245 151

Great Ormond Street Hospital for Children NHS Foundation Trust
Main switchboard: 020 7405 9200

Evelina London Children's Hospital, Guy's & St. Thomas' NHS Foundation Trust
Main switchboard: 020 7188 7188

University College London Hospitals NHS Foundation Trust
Main switchboard: 020 3456 7890

The Royal Free London, NHS Foundation Trust
Main switchboard: 020 7794 0500

University Hospitals Bristol NHS Foundation Trust
Main switchboard: 0117 923 0000

University Hospital Wales, Cardiff & Vale University Health Board
Main switchboard: 02920 747 747

University Hospital Birmingham NHS Foundation Trust
Main switchboard: 0121 371 2000

Birmingham Women's & Children's NHS Foundation Trust
Main switchboard: 0121 333 9999

NHS Greater Glasgow & Clyde, Glasgow Royal Hospital for Children
Main switchboard: 0141 201 0000

Children's Health Ireland at Temple Street, Dublin, Ireland.
Main switchboard: +353 1 878 4200

Royal Belfast Hospital for Sick Children, Belfast Heath & Social Care Trust, Belfast, Northern Ireland
Main switchboard: 028 9024 0503

Explanation of funding terms

A list of terms below is used in this formulary. The terms aim to describe and classify the funding or commissioning route of medications used to treat the metabolic disease. These are not official NHSE terms, but are derived from the terms used. Importantly, the funding notes and terms are only applicable to the NHS in England. They are not relevant to the NHS in the devolved nations of Scotland, Wales and Northern Ireland.

Commissioned by NHS England via national LSD centres

High cost medications not reimbursed through national prices (tariff) and directly commissioned by NHS England to an individual trust. Specifically, they are high cost medications used to treat Lysosomal Storage Disorders (LSDs). The trust must be commissioned by NHS England to provide care for those with LSDs as set out in the relevant NHSE policies. Some high cost medications require a 'Prior Approval Performa' or 'Blueteq' form to be completed prior to prescribing. Consult the latest version of 'Medicines not reimburse through national prices and directly commissioned by NHS England' also known as 'NHS England High Cost Drug List' or your local Hospital Pharmacy for further information.
The latest versions of the list can be accessed from: https://www.england.nhs.uk/publication/nhs-england-drugs-list/

Individual Funding Request (IFR)

Individual funding requests (or IFRs) are made to NHS England by clinicians when they believe that a patient's clinical circumstances are exceptional and because of this, they would benefit from a treatment that isn't usually commissioned or funded, for that patient, by the NHS. Contact your local Hospital Pharmacy for further information.

NHSE commissioned/PbR excluded

High cost medications not reimbursed through national prices and directly commissioned by NHS England to an individual trust. Some high cost medications for metabolic diseases are suitable to be prescribed between the specialist metabolic centre and secondary care network model. Some high cost medications require a 'Prior Approval Performa' or 'Blueteq' form to be completed prior to prescribing. Consult the latest version of 'Medicines not reimburse through national prices and directly commissioned by NHS England' also known as 'NHS England High Cost Drug List' or your local Hospital Pharmacy for further information.
The latest versions of the list can be accessed from: https://www.england.nhs.uk/publication/nhs-england-drugs-list/

PbR/in tariff

A medication that is not directly funded by NHS England. These medications are not high cost and are considered to be 'in tariff'. Financially, there are no restrictions on who can prescribe these medications.

Note on Funding in Scotland (NHS Scotland)

Funding streams within NHS Scotland health boards differ significantly to NHS England. Decisions on new therapies are taken by the Scottish Medicines Consortium and communicated to health board Drugs and Therapeutics Committee's for local implementation. Local formulary paperwork and advice should be taken for Individual Patient Treatment Request (IPTR), Peer Approval Clinical System Level 1 and 2 (PACS).

Central funding as part of the Ultra Orphan and Metabolic Risk Share is available and should be consulted when requests are received.

References

NHS England, 2019. *NHS Commissioning >> Key Documents.* Accessed 31/10/2019, available from: https://www.england.nhs.uk/commissioning/spec-services/key-docs/

This patient has a rare inherited disorder of metabolism and has been seen in a specialist inherited metabolic disease unit and advised to commence / continue a medication or medical food supplement as below. This medication is approved by the British Inherited Metabolic Disease Group and listed in the BIMDG formulary.

SHARED CARE GUIDANCE

Section 1: Summary

DATE OF THIS PLAN	
Patient name	
NHS Number / Hospital number	
Patient date of birth	
Name of condition	
Medication / Medical Food Supplement name	
Indication	
Speciality / Department	Inherited Metabolic Diseases
Trust(s)	

Section 2: Treatment Schedule

Usual dose and frequency of administration	
Route and formulation	
Duration of treatment	Lifelong, or until no longer appropriate

Section 3: Monitoring

Please give details of any tests that are required before or during treatment, including frequency, responsibilities (please state whether they will be undertaken in primary or secondary care), cause for adjustment and when it is required to refer back to the specialist.

Baseline tests – where appropriate
Subsequent tests – where appropriate

Section 4: Side effects

Please list the most common side effects and management. Please provide guidance on when the GP should refer back to the specialist.

Side effects and management	
Referral back to specialist	Any of the above. Evidence of reduced efficacy at recommended dose.

Section 5: Clinically significant drug interactions

Section 6: Contra-indications, Cautions and Special Recommendations

Section 7: Advice for the patient

1. Contact your GP or metabolic centre if you have any concerns when taking this medication.
2. Your patient support group can be found at -

Section 8: Responsibilities

Select those that apply

	Specialist IMD centre	Local Hospital	GP
Initiating treatment and prescribing for the first three months	X		
Undertaking the clinical assessment and monitoring for the first three months.	X		
Communicate details of the above to GP within the first month of treatment.	X		
Refer patients to GP and provide information of further action where appropriate *e.g.* blood tests due.	X		
To provide advice to primary care when appropriate.	X	X	
Review concurrent medications for potential interaction prior to initiation of any medication.	X	X	X
Stopping treatment where appropriate or providing advice on when to stop.	X		
Responsible for taking over prescribing after the first three months			
Responsible for the clinical assessment and monitoring after the first three months			
Refer for advice to specialist where appropriate.		X	X
Reporting adverse events to the MHRA.	X		

Section 9: Specialist Centre Contact Details

	Name	Organisation	Telephone	Email
Consultant				
Pharmacist				
Dietitian				
Clinical Nurse Specialist				

AGALSIDASE ALFA
(Replagal®)

Action: Enzyme replacement Therapy - Recombinant analogue of α-galactosidase A [1, 2]

Indication: Fabry disease (also known as Anderson-Fabry disease/ α-galactosidase A deficiency) [1, 2]

Preparation & Supplier details: 1mg/mL concentrate for infusion (3.5 mL) [Replagal©]; Shire Pharmaceuticals Ltd. (Takeda) [1]

Funding notes: Commissioned by NHS England via national LSD centres [3]

Suggested local formulary status: Red – hospital only

Additional information: Not licensed in children less than 7 years [4]
Store in a refrigerator at 2 – 8 ° C [4]
Human Fibroblast cell line origin [4]

Paediatric Drug Information

Dose: Child 7 - 18 years: 200micrograms/kg alternate weeks via IV infusion [1, 2, 4]

Administration: Consult local protocol or Summary of Product Characteristics (SPC)

Adult Drug Information

Dose: 200micrograms/kg every 2 weeks via IV infusion [1, 2, 4]

Administration: Consult local protocol or Summary of Product Characteristics (SPC)

AGALSIDASE BETA
(Fabrazyme®)

Action: Enzyme replacement Therapy - Recombinant analogue of α-galactosidase A [1, 2, 5]

Indication: Fabry disease (also known as Anderson-Fabry disease/ α-galactosidase A deficiency) [1, 2, 5]

Preparation & supplier details: 5 mg & 35 mg vials for infusion [Fabrazyme©]; Genzyme Therapeutics Ltd. [1]

Funding notes: Commissioned by NHS England via national LSD centres [3]

Suggested local formulary status: Red – hospital only

Additional information: Not licensed in children less than 8 years [5]
Store in the refrigerator [5]
Alternative dosing regimen where dose is reduced after 6 months to 300 micrograms/kg on alternate weeks (see SPC and clinical trial for more information) [5]

Paediatric Drug Information

Dose: **Child 8-18 years:** 1mg/kg every 2 weeks via IV infusion [1, 2, 5]

Administration: Consult local protocol or Summary of Product Characteristics (SPC)

Adult Drug Information

Dose: 1mg/kg every 2 weeks via IV infusion [1, 2, 5]. Lower doses of 0.3 mg/kg every 2 weeks following 6 months of higher dose have been used [5]. This lower dose maintained clearance of GL-3 in certain cell types in some patients; however the long term clinical relevance of these findings has not been established [5].

Administration: Consult local protocol or Summary of Product Characteristics (SPC)

ALGLUCOSIDASE ALFA

(Myozyme®)

Action: Enzyme Replacement Therapy (ERT) - Recombinant analogue of human α-glucosidase [1, 2, 6]

Indication: Pompe disease [1, 2, 6]

Preparation & supplier details: 50 mg vial for infusion [Myozyme©]; Genzyme Therapeutics Ltd.[1]

Funding notes: Commissioned by NHS England via national LSD centres [3]

Suggested local formulary status: Red – hospital only

Additional information: Store in the refrigerator [6]
Monitor IgG concentration [1]
Infusion related reactions are very common- consider premedication with antihistamine, antipyretics and/or corticosteroid [1]. Consult SPC for full information.

Paediatric Drug Information

Dose: **Neonate – 18 years:** 20 mg/kg every 2 weeks by IV infusion [1, 2, 6]
Infantile onset Pompe disease: 20 mg/kg weekly for 12 weeks then every 2 weeks thereafter (unlicensed) [7]

Administration: Consult local protocol or Summary of Product Characteristics (SPC)

Adult Drug Information

Dose: 20 mg/kg every 2 weeks by IV infusion [1, 2, 6]

Administration: Consult local protocol or Summary of Product Characteristics (SPC)

ALIROCUMAB

Action: Alirocumab binds to a pro-protein involved in the regulation of LDL receptors on liver cells (PCSK9).
LDL-C receptor numbers are increased, which results in increased uptake of LDL-C from the blood [197,198].

Indication: Primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia [197,198,199].

Preparation & Supplier details: 75mg pre-filled pen, 150mg, 300mg pre-filled pen [Praluent®]; Sanofi [197]

Funding notes: Commissioned by ICBs for primary hypercholesterolaemia or mixed dyslipidaemia.

Suggested local formulary status: Red – hospital only

Additional information:

Refer to NICE TA for commissioning criteria. Consider use when LDL-C concentrations are persistently above a specified threshold despite maximal tolerated lipid-lowering therapy [199]
Not licensed in children [197, 198]
Store in a refrigerator at 2 – 8 ° C [197]
To be administered into the thigh, abdomen or upper arm [197]

Paediatric Drug Information

No information available

Adult Drug Information

Indication: Primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia

Dose: 75mg or 150mg every 2 weeks by subcutaneous injection or 300mg every month by subcutaneous injection[197,198]

ALLOPURINOL

Action: Xanthine oxidase inhibitor [2]

Indication: Hyperuricaemia disorders *e.g.* Phosphoribosyl pyrophosphate (PRPP) synthetase superactivity [2, 9]
Lesch–Nyhan syndrome [1, 2, 9], Adenine phosphoribosyltransferase (APRT) deficiency [2, 9] and xanthinuria [9]

Preparation & supplier details: 100 mg & 300 mg (28 tablets)
100 mg per 5 mL sugar free suspension 150 mL (U); Rosemont Pharmaceuticals

Funding notes: PbR/in tariff

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescriptions

Additional information: Preferably taken after food [1]. Tablets can be crushed and dispersed in water[8]
Dose above 300 mg given in divided doses [1, 8]
Side effects include: Rash - withdraw if occurs. If mild: re-introduce cautiously but stop immediately if recurs [1, 8]
Dose reduction required in renal failure [8]
Ensure adequate fluid intake [1]
Monitor xanthine and oxypurinol levels, particularly in renal impairment [9]
Drug interactions: azathioprine, ACE inhibitors, mercaptopurine & thiazide diuretics [1,8] - seek advice. List not exhaustive.

Paediatric Drug Information

Indication: Hyperuricaemia disorders (as above)

Dose: **Child 1 month to 15 years:**
Initially, 10-20 mg/kg, orally, ONCE daily [1, 2, 8]. Maximum daily dose is 400 mg [1].
Child 15 -18 years:
Initially, 100 mg, orally ONCE daily, increased according to response. Maximum daily dose is 900 mg/day and maximum 300 mg/dose [1, 2, 8].

Adult Drug Information

Indication: Hyperuricaemia disorders (as above)

Dose: 2 – 10 mg/kg, orally, ONCE DAILY [2]
Initially 100 mg, orally ONCE daily [10]. Usual maintenance doses: 100 – 200 mg, orally, ONCE daily in mild conditions, 300 – 600 mg in moderate conditions and 700 – 900 mg ONCE daily in severe conditions for prophylaxis of gout and uric acid and oxalate renal stones; prophylaxis of hyperuricemia associated with cancer chemotherapy [10].

ALPHA TOCOPHEROL ACETATE
(Vitamin E)

Action: Replenishes vitamin E stores and free radical scavenger [2]

Indication:
Vitamin E deficiency [1]
Glutathione synthase deficiency [2]
Abetalipoproteinemia [2, 10]
Friedreich's ataxia [11]
Hypobetalipoproteinaemia [12]
Chylomicron retention disease [13]

Preparation & supplier details:
75-unit (50.25 mg), 200-unit (134 mg) and 400-unit (268 mg) capsules in packs of 100
500 mg/5 mL liquid

Funding notes: PbR/in tariff

Suggested local formulary status: Green – secondary or primary care initiation

Additional information:
Consider dilution of liquid in neonates due to high osmolality, particularly in preterm and low birth weight neonates [1].
GI disturbances (diarrhoea and abdominal pain) can occur with higher doses [8]
Monitoring of plasma vitamin E levels recommended
The role of antioxidants in Friedreich's ataxia is yet unclear [11].
Consider water-soluble preparation of vitamin E if struggling to obtain sufficient levels with alpha tocopherol acetate. Water-soluble preparation of vitamin E is: D-alpha tocopherol (as Tocofersolan) [Vedrop] 50 mg/mL oral solution.

Paediatric Drug Information

Indication: **Vitamin E deficiency**

Dose:
Neonate: 10 mg/kg, orally, ONCE a day [1]
Child: 2 – 10 mg/kg, orally, ONCE a day increasing to a maximum of 20 mg/kg if needed [1, 8]
In cholestasis, doses up to 200 mg/kg may be required to achieve adequate vitamin E levels [14]

Indication: **Glutathione synthase deficiency**

Dose: 10 mg/kg, orally ONCE a day [2]

Indication: **Abetalipoproteinaemia**

Dose: 50 - 100 mg/kg, orally, daily [1, 2, 8, 12]

Indication: **Friedreich's ataxia [11]**

Dose: 2 - 20mg/kg/day, orally [11] capping at 1.4 grams/day [11]

Indication: **Chylomicron retention disease**

Dose: 50 units/kg/day (33.5 mg/kg/day), orally [13]. Increasing to 100 units/kg/day (67 mg/kg/day) , orally, if required [13]. Maximum of 3200 units/day (2.1 grams/day) [13]

Adult Drug Information

Indication:	**Vitamin E deficiency**
Dose:	2 – 10 mg/kg, orally, ONCE a day increasing to a maximum of 20 mg/kg if needed [1, 10]
Indication:	**Abetalipoproteinemia**
Dose:	67 - 200 mg/kg (100 – 300 units/kg), orally, daily in divided doses [12]
Indication:	**Friedreich's ataxia [11]**
Dose:	1400 mg (2100 units), orally ONCE a day [11]

ASCORBIC ACID
(Vitamin C)

Action: Co-factor and antioxidant [2]

Indication: Glutathione synthase deficiency [1, 2]

Preparation & supplier details: 50 mg, 100 mg, 200 mg and 500 mg tablets (28 tablets)

Funding notes: in tariff/PbR

Suggested local formulary status: Green – primary or secondary care can initiate

Additional information: Give in divided doses [8]
Not licensed for metabolic disease [8]

Paediatric Drug Information

Indication: **Glutathione synthase deficiency**

Dose: 100 mg/kg/day, orally [2]. Consider capping at 1 gram/day [1]

Adult Drug Information

Dose: Consider capping at 1 gram/day [1, 2]

ASFOTASE ALFA

Action: Enzyme replacement therapy: human recombinant tissue-nonspecific alkaline phosphatase-Fc-deca-aspartate fusion protein promoting mineralisation of the skeleton in patients with hypophosphastasia [15].

Indication: Long term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia to treat the bone manifestations of the disease [15].

Preparation & supplier details: 40mg/ml solution for injection (18 mg, 28 mg, 40 mg vials)
80mg/0.8ml (100mg/ml) solution for injection vial [15]
[Strensiq©]; available from Alexion Pharma UK Ltd.

Funding notes: Commissioned by NHS England via nationally HPP specialist centres; Highly Specialised Technology (HST6) and Managed Access Agreement only (prior approval required) [16]

Suggested local formulary status: Red – Hospital only

Additional information: Store in a refrigerator (2°C – 8°C) [15]
Neonatal presentation, treatment is considered urgent and should be initiated as soon as possible [16].
Recommended maximum volume of medicinal product per injection should not exceed 1 ml. If more than 1 ml is required, multiple injections may be administered at the same time [15].
Injection site reactions are very common (observed in 74% of patients in clinical studies) but most were mild and self-limiting. Most commonly these include bruising and erythema, with additional systemic adverse effects including headache, pain in extremity and pyrexia [15].

Paediatric Drug Information

Dose: 1mg/kg SIX times per week or 2mg/kg THREE times per week by subcutaneous injection, refer to dosing chart in Summary of Product Characteristics for suggested dosing [15]. In exceptional cases, doses of up to 6mg/kg three times a week have been used following urgent review and approval by the National Authorisation Panel[214]

Adult Drug Information

Indication: As per paediatric dosing information above

Dose: As per paediatric dosing information above

AVALGLUCOSIDASE ALFA

(Nexviadyme®)

Action: Recombinant human acid α-glucosidase (rhGAA) that provides an exogenous source of acid α-glucosidase (GAA) [195].

Indication: Long term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency) [195].

Preparation & supplier details: Vial, 100mg/ml powder for concentrate for solution for infusion [195].

Funding notes: NHSE Commissioned [196]

Suggested local formulary status: Red – Hospital only

Additional information: Store in a refrigerator (2°C – 8°C) [195]. To be diluted in 5% Dextrose prior to infusion [195]. The infusion should be administered incrementally as determined by patient response and comfort. It is recommended that the infusion begins at an initial rate of 1mg/kg/hour and is gradually increased every 30 minutes if there are no signs of infusion-associated reactions (IARs) by 2mg/kg/hour to a maximum of 7mg/kg/hour in 4 steps. For patients with Infantile-Onset Pompe Disease (IOPD), a 5 step to 10mg/kg/hour for patients on an increased dose can be considered [195].

Paediatric Drug Information

Dose: 20mg/kg once every two weeks. Dose modification for IOPD patients who experience lack of improvement or insufficient response in cardiac, respiratory, and/or motor function while receiving 20 mg/kg, dose increases to 40 mg/kg every other week should be considered in the absence of safety concerns (e.g., severe hypersensitivity, anaphylactic reactions, or risk of fluid overload) [195].

Adult Drug Information

Indication: As per paediatric dosing information above

Dose: 20mg/kg once every two weeks [195]

BETAINE

Action: Remethylation of homocysteine to methionine [2]

Indication: Cystathionine beta-synthase deficiency (classical homocystinuria) [1, 2, 9]
Remethylation disorders (Methionine Synthase deficiency, disorders/intracellular defects of Cobalamin (B_{12}) metabolism [1, 2, 9], and 5,10-methylenetetrahydrofolate reductase (MTHFR) [2, 9]

Preparation & supplier details: 500 mg tablets in packs of 28 tablets (U).
UCLH brand from Clinigen & Mawdsleys, IPS Specials brand from ParaPharm Development Ltd.
500 mg/mL oral solution (100 mL bottle) (U); Veriton Pharma (Special Products)
500 mg/mL oral solution (100 mL bottle) (U); Veriton Pharma (Special Products)
Betaine 1 gram per 1-gram powder pack of 180 gram [Cystadane©]; Recordarti Rare Diseases

Funding notes: NHSE commissioned/PbR excluded (all forms)

Suggested local formulary status: Red – hospital only

Additional information: **Cystadane powder** comes with spoons (100 mg – green, 150 mg – blue, 1 g – pink). Dose measured with level scoops of these. It can be mixed with water/squash/fruit juice/milk/low protein milk, or a spoonful of food [8, 17]. Take straight away [8].
Cystadane powder is the only licensed preparation and therefore should be considered first line.
The **liquid** is strawberry flavour. Discard 28 days after reconstitution. Dilute dose with 10 times its volume with water before administration (give immediately) [8].
Monitor plasma-methionine concentration before and during treatment [1]

Paediatric Drug Information

Dose: **Neonate – 9 years:** 50 mg/kg, orally TWICE a day (max. 150mg/kg/day), adjusting as per response [1, 2, 9]
Child 10 – 17 years: 3 grams BD (max. 20 grams/day), adjusting according to response [1]

Indication: **Combined Cobalamin C deficiencies**

Dose: As above but doses up 250 mg/kg/day [18]

Adult Drug Information

Dose: 3 g twice daily, adjusted according to response; max. 20 g/day [10]

BIOTIN
(Vitamin B_7)

Action: Functions as an essential co-factor for carboxylation, transcarboxylation & decarboxylation reactions of gluconeogenesis, lipogenesis, fatty acid synthesis & catabolism of leucine and other amino acids [2, 8]

Indication: Defects of biotin metabolism including:
Biotinidase deficiency, multiple carboxylase deficiency, thiamine transporter 2 deficiency (biotin-responsive basal ganglia disease) [2].

Preparation & supplier details: 5 mg tablets (60 tablets); Clinigen or Durbin (U) (Bayer brand (licensed outside UK))
5 mg/mL solution for injection (6 ampoules) (U) Clinigen
5 mg tablets (30 tablets) (AAH Pharmaceuticals)

Funding notes: in tariff/PbR
For the very high doses sometimes used in biotin-responsive basal ganglia disease an IFR may be required

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescriptions

Additional information: Water soluble B vitamin also known as vitamin H [8]
Crush & disperse tablets in water [8]
Give as a slow intravenous injection/bolus over 3 – 5 minutes [8]
Biotin deficiency can occur with valproate therapy [9]

Paediatric Drug Information

Indication: Isolated carboxylase defects [1] including holocarboxylase synthetase deficiency [9]

Dose: **Neonate:** 5 mg IV or orally, ONCE daily, usual maintenance 10 – 50 mg, ONCE daily [1].
Child: 10 mg IV or orally, ONCE daily [1, 9], usual maintenance 10 – 50 mg, ONCE daily [9, 19], up to a max. 100 mg ONCE daily adjusted according to response [1].

Indication: Defects of biotin metabolism, Biotinidase deficiency [1]

Dose: **Neonate:** 10 mg IV or orally, ONCE daily, usual maintenance 5 - 20 mg, ONCE daily [1].
Child: 10 mg IV or orally, ONCE daily, usual maintenance 5 - 20 mg, ONCE daily, adjusted according to response [1]. Multiple carboxylase deficiency may require higher doses [2]. Doses as high as 5-10 mg/kg/day, orally, have been used in biotin-thiamine responsive basal ganglia disease [19]

Adult Drug Information

Indication: Limited information – Consult paediatric information above

Dose: Limited information – Consult paediatric information above

BUROSUMAB

Action: Human monoclonal antibody that inhibits the activity of fibroblast growth factor 23, thereby increasing renal tubular reabsorption of phosphate and increasing serum concentration of vitamin D [1, 20]

Indication: X-linked hypophosphatemia for children & young adults with growing bones [1, 20, 21]

Preparation & supplier details: 10 mg/mL, 20 mg/mL and 30 mg/mL solution for injection [Crysvita]; Kyowa Kirin Ltd.

Funding notes: NHSE commissioned as per NICE Highly Specialised Technology guidance (HST8) only via patient access scheme (PAS) for children and young adults [1, 3, 21]
Early Access Programme (EAP) only for adults (see below).

Suggested local formulary status: Red – hospital prescription only

Additional information: Subcutaneous injection areas include: arm, abdomen, buttock or thigh [1, 20]
Round dose to nearest 10 mg [1]
Contraindicated with concurrent use of oral phosphate or vitamin D analogues—discontinue 1 week before initiation of burosumab [1, 20]
Maximum volume per injection: 1.5 mL – if volume > 1.5 mL then split over 2 different injection sites [1, 20]
Store in a refrigerator (2 - 8 °C) [1, 20]
Specific monitoring required: please refer to SPC for further information of monitoring [20]
Not licensed for use in adults [21]
Very common Adverse Drug Reactions (ADRs) include: injection site reaction, headache, pain in extremities decreased vitamin D levels, rash, toothache, tooth abscesses, myalgia and dizziness [21]. The SmPC recommends a starting dose of 0.8mg/kg every 2 weeks in children and young people. However, some patients can normalise serum phosphate and ALP concentrations on a starting dose of 0.4mg/kg and therefore this is recommended as the starting dose by the BNFc, NICE and the British Paediatric and Adolescent Bone Group [219]

Paediatric Drug Information

Dose:

Child 1 – 17 years
Initially, 0.4 mg/kg, by subcutaneous injection, every TWO weeks [1, 20, 21]. Subsequent doses adjusted according to response increasing in steps of 0.4 mg/kg at intervals of least 4 weeks [1]
Maximum dose 2 mg/kg (90 mg) [1, 21, 214]
Usual maintenance dose: 0.8 mg/kg, by subcutaneous injection, every TWO weeks (max dose 90 mg) [1, 20, 21]
Round dose to nearest 10 mg [1, 21]

Adult Drug Information

Indication:

Available via an early access programme only for adults ≥ 18 years with X-linked hypophosphatemia who fulfil one or more of the following criteria:
1) Those who have non-healing or slow healing fractures or pseudo fractures.
2) Those with moderate or severe pain, stiffness, and /or fatigue which in the view of the treating physician is attributable to XLH and impacts quality of life.
3) Those who have undergone or require orthopaedic surgery, dental surgery with bone involvement, or spinal surgery for a predefined period before and after surgery, (for 3 months pre-surgery and post-surgery until 6 months after surgical wound healing; to be defined and confirmed by the treating clinician).

Dose: 1 mg/kg rounded to the nearest 10 mg up to a maximum dose of 90 mg by subcutaneous injection once every 4 weeks [1, 20].

CARGLUMIC ACID
(N-Carbamoyl Glutamate)

Action: Structural analogue of N-acetylglutamate which directly activates carbomoyl phosphate synthase-I, the first enzyme in the urea cycle, thus allowing incorporation of ammonia into the urea cycle for detoxification [22].

Indication: Licensed in hyperammonaemia due to:
N-acetylglutamate synthase primary deficiency (NAGs deficiency) [22]
the organic acidaemias, namely isovaleric acidaemia (IVA), methymalonic acidaemia (MMA) and propionic acidaemia (PA) [22].
Occasionally used in hyperammonemia of unknown cause to provide empirical cover.

Preparation & supplier details: 200 mg dispersible tablets (packs of 5, 15 and 60 tablets) [Carbaglu©]; Recordati Rare Diseases (allow 5 working days for delivery)
200 mg dispersible tablets (packs of 12 and 60)[Ucedane©]; Lucane Pharma
200 mg dispersible tablets (packs of 5, 15 and 60 tablets); Sovereign Medical
100 mg/mL Powder for reconstitution for oral suspension 50 mL bottle (U); Veriton Pharma (Special Products Ltd).

Funding notes: NHS England; PbR excluded [3]

Suggested local formulary status: Red – hospital only

Additional information: Give immediately before feeds [8, 22]
Can cause raised transaminases and increased sweating. Systemic surveillance of liver, renal, cardiac functions and haematological parameters is recommended [8, 9]
In the long term, it may not be necessary to increase the dose according to body weight as long as adequate metabolic control is achieved [22]
Dispersible tablets:
Store in a refrigerator - (2°C – 8°C) [8, 22]
After opening, do not refrigerate and do not store above 30 °C and use within 3 months of opening [8, 22]
Disperse tablet in a minimum of 5 – 10 mL of water [8, 22]
Can be used via nasogastric tubes [22]
Tablets can be halved [22]and quartered, round dose to nearest quarter or half.
For Carbaglu© and Sovereign Medical brands only [191]:
Store in a refrigerator - (2°C – 8°C) [8, 22]
After opening, do not refrigerate and do not store above 30 °C and use within 3 months of opening [8, 22]
For Ucedane© brand only: store at room temperature. [192]

Paediatric Drug Information

Dose: **Neonate – child:** 50 – 125 mg/kg, orally, TWICE a day before feeds; maintenance for NAGS 5 – 50 mg/kg, orally TWICE a day; total daily dose may be given in 3 – 4 divided doses, adjusting according to plasma ammonia [1, 2, 8, 9, 22]

Indication: **Carglumic acid responsiveness test:** Recommended before initiating any long term treatment in Organic acidaemia, see SPC, section 4.2 for dosing information [22].

Adult Drug Information

Dose: As per paediatric dosing [10]. In the long term, it may not be necessary to increase the dose according to body weight as long as adequate metabolic control is achieved [22].

CHENODEOXYCHOLIC ACID

Action: Inhibits cholesterol 7 α-hydroxylase (rate limiting enzyme in bile-acid biosynthesis) [2] reducing the production of unsaturated bile acids that can inhibit bile secretion and chenodeoxycholic acid also fuels bile acid secretion and facilitates the absorption of fats and fat-soluble vitamins [23].
In CTX it reduces the build-up of cholestanol that contributes to neuropathology, xanthomata and atherosclerosis [23].

Preparation & supplier details: 250 mg capsules (100 capsules) (U); Leadiant Biosciences *via* Mawdsleys.

Funding notes: NHSE commissioned/PbR excluded, specialist centres only (NHS England Ref.: 170127P) [24]

Suggested local formulary status: Red – hospital only

Additional information: **Children, adolescents & adults unable to swallow capsules and or need to take a dose below 250 mg: Open 250 mg capsule and** add the contents of capsule to 25 mL of sodium bicarbonate solution 8.4% (1 mmol/mL) to produce a suspension containing chenodeoxycholic acid 10 mg/mL and use immediately after preparation, discarding any remaining suspension [1, 24, 25].
For infants: Open 250 mg capsule and add contents of capsule to 50 mL of sodium bicarbonate solution 8.4% (1 mmol/mL) to produce a suspension containing chenodeoxycholic acid 5 mg/mL [25]

Paediatric Drug Information

Indication: **Cerebrotendinous xanthomatosis (CTX) also known as 27-hydroxylase deficiency** [2]

Dose: **1 month – 18 years:** 5 mg/kg/day, orally, 3 divided doses, to a maximum of 15 mg/kg/day, maximum 1000 mg/day [1] **(NHSE Commissioned)**

Indication: **(Off-label/unlicensed use): 3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency (also known as 3β-dehydrogenase hydroxysteroid deficiency or 3β-HSD deficiency or 3β-dehydrogenase deficiency) in combination with cholic acid if first line cholic acid monotherapy fails.**

Dose: 7.5 mg/kg/day, orally [23]

Indication: **(Off-label/unlicensed use): Δ^4-3-Oxosteroid 5 β-reductase deficiency (5 β-reductase deficiency) in combination with cholic acid if first line cholic acid monotherapy fails.**

Dose: 7.5 mg/kg/day, orally [23]

Indication: **(Off-label/unlicensed use): 2- (or α-) methylacyl-CoA racemase deficiency (AMACR) in combination with cholic acid if first line cholic acid monotherapy fails** [24]

Dose: No dose documented

Indication: **(Off-label/unlicensed use): CYP7A1 deficiency in combination with cholic acid if first line cholic acid monotherapy fails** [24]

Dose: No dose documented

Indication: **(Off-label/unlicensed use): Defective synthesis of bile acid** [1] **(Not NHSE commissioned)**

Dose: **Neonate & Child:** Initially 15 mg/kg/day, orally, in THREE divided doses, reduced to 7.5 mg/kg/day, orally in 3 divided doses [1]

Indication: **(Off-label/unlicensed use): Smith-Lemli-Optiz syndrome** [1] **(Not NHSE commissioned)**

Dose: **Neonate & Child:** 7 mg/kg, orally ONCE a day or in divided doses [1]

Adult Drug Information

Indication:	**Cerebrotendinous xanthomatosis (CTX) also known as 27-hydroxylase deficiency**
Dose:	750mg/day, increased if necessary to 1000mg/day, orally [2] **(NHSE Commissioned)**
Indication:	(Off-label/unlicensed use): 3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency (also known as 3β-dehydrogenase hydroxysteroid deficiency or 3β-HSD deficiency or 3β-dehydrogenase deficiency) in combination with cholic acid if first line cholic acid monotherapy fails [24]
Dose:	No dose documented (NHSE Commissioned)
Indication:	(Off-label/unlicensed use): Δ^4-3-Oxosteroid 5 β-reductase deficiency (5 β-reductase deficiency) in combination with cholic acid if first line cholic acid monotherapy fails [24]
Dose:	No dose documented (NHSE Commissioned)
Indication:	(Off-label/unlicensed use): 2- (or α-) methylacyl-CoA racemase deficiency (AMACR) in combination with cholic acid if first line cholic acid monotherapy fails [24]
Dose:	No dose documented (NHSE Commissioned)
Indication:	(Off-label/unlicensed use): CYP7A1 deficiency in combination with cholic acid if first line cholic acid monotherapy fails [24]
Dose:	No dose documented (NHSE Commissioned)

CHOLESTEROL

Action: Replenishment of cholesterol [2] and inhibition of HMG-CoA reductase thereby reducing an accumulation of cholesterol precursors [23]

Indication: Smith-Lemli-Optiz Syndrome (SLO) [2, 9]
Chondrodysplasia punctata Conradi-Hünermann [9]
CHILD syndrome [9]

Preparation & supplier details: 150 mg/mL oral suspension (Blackcurrant flavoured) (100 mL bottles) (U)**;** St. Mary's Pharmaceutical Unit (SMPU), Cardiff & Vale Uni. Health Board
Powders of varying strengths (U); Prepared extemporaneously by Pharmacy

Funding notes: in tariff/PbR

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescriptions

Additional information: Oral suspension has a 3-month expiry from manufacture and requires refrigerated storage [26]

Cholesterol powder can be mixed with a vegetable oil before administration [1]
Simvastatin may be useful in mildly affected SLO [9]
In an emergency where enteral administration is not possible, frozen plasma has been used as a source of LDL [9]

Paediatric Drug Information

Indication: **Smith-Lemli-Opitz Syndrome [2, 9]**

Dose: **Neonate:**
25 - 40 mg/kg/day, orally, THREE to FOUR divided doses [1, 2, 23]

1 month – 18 years:
25 – 40 mg/kg/day, orally, THREE to FOUR divided doses [1, 2, 23]; adjusted according to response to 60 mg/kg/day in FOUR divided doses [4] and even as high as 300 mg/kg/day [2, 23].

Indication: **Chondrodysplasia punctate, Conradi-Hünermann and CHILD Syndrome ****nb.* **experimental use* [9]**

Dose: 50 – 150 mg/kg/day [9]

Adult Drug Information

Indication: **Smith-Lemli-Opitz Syndrome**

Dose: 50 - 100mg/kg/day, orally, THREE to FOUR divided doses [9], and even as high as 300 mg/kg/day [2, 23] (higher doses in infants [9]).

CHOLIC ACID

Action: Replenishment of primary bile acids [1]

Indication: Inborn errors of primary bile acid synthesis, namely Δ^4-3-Oxosteroid 5 β-reductase deficiency and 3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency [1, 2, 28]
Some single enzyme peroxisomal defects [2]

Preparation & supplier details: 50 mg & 250 mg capsules (30 capsules); [1, 28] Cell Therapies Research & Services (CTRS)

Funding notes: NHSE commissioned/PbR excluded (NHS England Ref.: 170127P)

Suggested local formulary status: Red – hospital only

Additional information: Administration of the total daily dose in divided doses is advised to mimic the continuous production of cholic acid in the body, and to reduce capsule burden per administration [3]. Take with food at the same time of day morning and evening to optimise bioavailability and tolerability [28]
Capsules can be swallowed whole or capsules may be opened and contents added to formula, juice, fruit compote or yoghurt [1, 28]
Monitor serum and urine bile acid concentrations every 3 months for the first year, then every 6 months for three years, then annually [1]
Monitor liver function tests at the same or greater frequency e.g. hepatic impairment [28]
Side effects: diarrhoea, pruritus (may indicated overdose) [28]
See SmPC for monitoring requirements.

Paediatric Drug Information

Indication: **3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency (also known as 3β-dehydrogenase deficiency or 3β-HSD deficiency)**

Dose: **Monotherapy: 1 month – 18 years:** 5 – 15 mg/kg/day, orally, in divided doses [1, 28]
Minimum daily dose is 50 mg and maximum daily dose is 500 mg [1, 28]. Adjust dose in 50 mg steps [1, 28]
In combination with chenodeoxycholic acid if monotherapy fails: 7mg/kg/day (off-label/unlicensed use). Minimum daily dose is 50mg and maximum dose is 500mg. Adjust dose in 50mg steps.

Indication: **Δ^4-3-Oxosteroid 5 β-reductase deficiency (5 β-reductase deficiency) [24]**

Dose: **Monotherapy: 1 month – 18 years:** 5 – 15 mg/kg/day, orally, in divided doses [1, 28] Minimum daily dose is 50 mg and maximum daily dose is 500 mg [1, 28]. Adjust dose in 50 mg steps [1, 28]
In combination with chenodeoxycholic acid if monotherapy fails: 8mg/kg/day (off-label/unlicensed use). Minimum daily dose is 50 mg and maximum daily dose is 500 mg. Adjust dose in 50 mg steps.

Indication: **(Off-label/unlicensed use). Cerebrotendinous xanthomatosis (CTX) also known as sterol 27-hydroxylase deficiency [24]**

Dose: **Monotherapy if chenodeoxycholic acid is not tolerated or effective: 1 month – 18 years:** 5 – 15 mg/kg/day, orally, in divided doses [1]
Minimum daily dose is 50 mg and maximum daily dose is 500 mg [1]. Adjust dose in 50 mg steps [1]
Combination therapy if monotherapy with chenodeoxycholic acid and monotherapy with cholic acid fails (off-label/unlicensed use): No dose documented, see information for other bile acid synthesis disorders.

Indication: **(Off-label/unlicensed use): 2- (or α-) methylacyl-CoA racemase deficiency (AMACR deficiency) in combination with cholic acid if first line cholic acid monotherapy fails** [24]

Dose: **Monotherapy. 1 month – 18 years:** 5 – 15 mg/kg/day, orally, in divided doses [1] Minimum daily dose is 50 mg and maximum daily dose is 500 mg [1]. Adjust dose in 50 mg steps [1]
In combination with chenodeoxycholic acid if monotherapy fails: Dose not documented.

Indication: **(Off-label/unlicensed use): CYP7A1 deficiency (cholesterol 7 α-hydroxylase deficiency) in combination with cholic acid if first line cholic acid monotherapy fails** [24]

Dose: **Monotherapy. 1 month – 18 years:** 5 – 15 mg/kg/day, orally, in divided doses [1] Minimum daily dose is 50 mg and maximum daily dose is 500 mg [1]. Adjust dose in 50 mg steps [1]
In combination with chenodeoxycholic acid if monotherapy fails: Dose not documented.

Adult Drug Information

Indication: **3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase deficiency and Δ4-3-Oxosteroid-5β-reductase deficiency** [2, 28]

Dose: 5 – 15 mg/kg/day, orally, in divided doses [1, 28]. Minimum daily dose is 50 mg and maximum daily dose is 500 mg [1, 28]

Indication: **(Off-label/unlicensed use): Cerebrotendinous xanthomatosis (CTX) also known as 27-hydroxylase deficiency only if treatment with chenodeoxycholic acid is no longer tolerated or effective**

Dose: 5 – 15 mg/kg/day, orally, in divided doses [1, 28]. Minimum daily dose is 50 mg and maximum daily dose is 500 mg [1, 28] **(NHSE Commissioned)** [24].

CIPAGLUCOSIDASE ALFA
(Pombiliti®)

Action:	Recombinant lysosomal acid α-glucosidase (rhGAA) providing exogenous acid α-glucosidase (GAA) enzyme source [193,194].
Indication:	In conjunction with Miglustat (Opfolda) is indicated in the long-term treatment of adults symptomatic patients with confirmed diagnosis of Late-Onset Pompe Disease (LOPD, GAA deficiency) [194].
Preparation & supplier details:	105mg/vial of lyophilized powder for concentrate for solution for infusion [194].
Funding notes:	NHSE Commissioned[193]
Suggested local formulary status:	Red – Hospital only
Additional information:	Store in a refrigerator (2°C – 8°C) [194].
Paediatric Drug Information	Not licensed
Adult Drug Information	
Dose:	20mg/kg once every two weeks [194]

CITRATE

Action: Citrate (bicarbonate) alkali source to increase blood pH
Potassium supplementation

Indication: Metabolic and/or renal acidosis [8]
Primary hyperoxaluria type I [8]
Hypokalaemia

Preparation & supplier details: Potassium citrate Mixture BP 1.5 gram/5 mL (150 mL bottle); AAH Pharmaceuticals
Tricitrate oral solution (citric acid monohydrate/potassium monohydrate/ sodium citrate dehydrate) (334 mg/550 mg/500 mg/ 5 mL); Guys & St. Thomas NHS FT
Effercitrate (potassium citrate & citric acid) 1.5g/0.25 g tablets (x); AAH Pharmaceuticals

Funding notes: in tariff/PbR

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescriptions

Additional information: 1 mmol of citrate is approximately equivalent to 3 mmol of bicarbonate [8]
Potassium citrate Mixture BP 1.5 gram/5mL, 1 mL provides 2.8 mmol of potassium and 0.9 mmol of citrate (= 2.8 mmol of bicarbonate) [8]
Tricitrate oral solution, 1 mL provides 1 mmol of sodium, 1 mmol of potassium and 0.7 mmol of citrate (= 2 mmol of bicarbonate) [8]
Effercitrate 1.5g/0.25g tablets, each tablet provides 14 mmol of potassium, 4.5 mmol of citrate (= 14 mmol of bicarbonate)
Effercitrate tablets are preferred to Potassium citrate Mixture BP in ketogenic diets as the carbohydrate content is less (7.3 mg of carbohydrate per tablet)
Monitor serum potassium and serum bicarbonate [1, 8]

Paediatric Drug Information

Dose: 0.5 – 1 mmol of citrate/kg/day, orally, in divided doses, adjusting according to response (see additional information for electrolytes equivalences) [8]

CO-ENZYME Q_{10}

(Ubidecarenone/Ubiquinone)

Action: Coenzyme for enzymes within the mitochondrial oxidative phosphorylation pathway.

Indication: Inborn errors of CoQ_{10} synthesis & mitochondrial disorders/cytopathies [1, 2, 8]

Preparation & supplier details: 30, 100 and 300 mg capsules (60 capsules) (U) Lambert's Healthcare or Pharmanord
30 mg/5 mL 473 mL liquid (U); Clinigen
50 mg/5 mL 500 mL (*nb.* contains Vitamin E) (U); Mawdsley Brooks

Funding notes: in tariff/PbR

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescriptions

Additional information: Use capsules for all patient unless an exception has been made.
Pierce capsule and give capsule contents with small amount food/liquid if unable to swallow capsules.
Capsule contents can be administered via enteral feeding tubes (clinical experience). Liquid (30 mg/5 mL) is very oily in nature and is difficult to use, and anecdotal experience can worsen vomiting.
50 mg/5 mL liquid contains Vitamin E and is formulated as a syrup
Reduce dose in moderate and severe hepatic impairment [1]
Take with food in 1 – 2 divided doses to optimise absorption [8]
May reduce insulin requirement in diabetes mellitus [1]
Can cause alertness/wakefulness, divide total daily dose giving larger proportion of dose in the morning
Anecdotal evidence suggests gastro-intestinal absorption is capped at 2400 mg (2.4grams a day) [29]

Paediatric Drug Information

Dose: Initially, 5 mg, orally ONCE to TWICE a day adjusted according to response, maximum 200 mg/day for neonate and 300 mg/day for older children [1, 2]
However, smallest capsule size is 30 mg, so realistically normally start at this higher dose of 30mg.
10 - 30mg/kg/day, orally, in 1 - 2 divided doses [9, 29], capping at adult doses of
1- 4 grams/day [9]
Higher doses reserved for disorders of co-enzyme Q_{10} biosynthesis [9]

Adult Drug Information

Dose: 1- 4 grams/day, orally in 1 – 2 divided doses [9]

COLESTYRAMINE

Action: Bile acid sequestrant [2]

Indication: Sitosterolemia [9]

Preparation & supplier details: 4-gram sachets in packs of 50 (sugar-free also available (Questran light). Multiple licensed generics and brands also available.

Funding notes: in tariff/PbR

Suggested local formulary status: Green – primary or secondary care to initiate

Additional information:
Possible deficiency of vitamins A, D, and folic acid with prolonged treatment [1, 2]
supplementation of these may be required [1, 8]
Poor tolerability/compliance is common [1]
Gastrointestinal side effects are common *e.g.* constipation, nausea & vomiting [1]
Increase bleeding tendency can occur with vitamin K deficiency [1], may require supplementation [1].
Binds/chelates drugs in the gastrointestinal tract – take other medications 1 hour before or 4 – 6 hours after cholestyramine [1]
Children with familial hypercholesterolemia may be monitored and treated in paediatric inherited metabolic disease clinics. NICE guidelines for the management of paediatric FH are available here

Paediatric Drug Information

Indication: **Sitosterolemia**

Dose:
Child 6 – 11 years: Initially 4 grams, orally, ONCE a day then increased up to 4 g, THREE times a day adjusting according to response [1]
Child 12 – 17 years: Initially 4 grams orally, ONCE a day, then increased in steps of 4 g every week; increased to 12 – 24 g /day orally in 1 – 4 divided doses adjusting according to response, maximum of 36 grams a day [1]
***NOTE: Published reports of treatment for sitosterolemia are with colestyramine 8-15 g/day. Treatment with higher doses, such as those licensed for other hyperlipidaemias have not been reported** [30, 31]

Adult Drug Information

Indication: **Sitosterolemia**

Dose:
Initially 4 grams, orally, ONCE a day, then increased in steps of 4 g every week; increased to 12 – 24g /day in 1 – 4 divided doses adjusting according to response, maximum of 36 grams/day [10]
***NOTE: Published reports of treatment for sitosterolemia are with colestyramine 8-15 g/day. Treatment with higher doses, such as those licensed for other hyperlipidaemias have not been reported** [30, 31]

COPPER HISTIDINE

Action: Increase intracellular copper [2]

Indication: Menke's Disease and Occipital Horn Syndrome [2, 9, 32]

Preparation & supplier details: 500 micrograms/mL subcutaneous injection (10 amps) (U)
Available from London, Northwick Park Hospital Pharmacy; 0208 869: 2295/2211/5827

Funding notes: in tariff/PbR

Suggested local formulary status: Red – hospital only

Additional information: Store in a refrigerator (2 – 8°C) & protect from light
Preparation should be bright, clear blue colour. If solution black/blue or black in colour- do not use [32]
Weekly for first 4 weeks: FBC, U&Es, LFTs, plasma [copper], clotting weekly then monthly [33]
At 8 weeks of age & 8 weekly thereafter: U&Es, LFTs, plasma [copper], clotting, kidney USS [33]

At 4 months of age and 4 monthly thereafter: U&Es, FBC, LFTs, plasma [copper], USS kidney, Echocardiogram and ECG, tubular phosphate excretion & fractional sodium excretion [33]
Supplied on set 2 monthly basis (56 day expiry) [34]
24-hour copper excretion not routinely recommended in young children [35]
Efficacy is optimised if commenced within first weeks of life [2]
Consider only starting treatment for Menke's in asymptomatic neonates [36]

Paediatric Drug Information

Indication: **Menke's Disease**

Dose: 250 micrograms, by subcutaneous injection TWICE daily for the first year of life then
250 microgram, by subcutaneous injection ONCE daily after the first year of life [2, 36]
Adjust dose as per [copper] plasma.

CREATINE MONOHYDRATE

Action: Replenishes creatine to provide creatine phosphate (a high energy phosphate that is released in the anaerobic respiration [2, 37]

Indication: Guanidinoacetate methyltransferase (GAMT) deficiency [2, 8, 9, 37, 38]
Arginine:Glycine amidinotransferase (AGAT) deficiency [2, 9, 37]
Gyrate Atropy (Ornithine aminotransferase (OAT) deficiency [2, 9, 37]
Transporter defect (see Saudubray)

Preparation & supplier details: Powder 100 grams; from Veriton Pharma (Special Products) (U)
5-gram powder (30 sachets); Vitaflo (U)

Funding notes: in tariff/PbR
Nb. Vitaflo provide Free of Charge as compassionate use

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescription

Additional information: Powder can be dissolved in a glass of fruit juice and this reconstituted solution can be stored at 2 – 8° C in a refrigerator for no more than 24 hours [37]
Powder can also be sprinkled onto food [37]
Each 5-gram sachet can be dissolved in 20 mL of water, shaken and stirred well (3 mins) [8]
Whole sachets can be mixed with protein substitute or added to modular feeds [8]

Paediatric Drug Information

Dose: **Guanidinoacetate methytransferase (GAMT) deficiency**
300 – 800 mg/kg/day orally in 3 to 6 divided doses [2, 8, 9, 37]
Dose upto 1200 mg/kg have been used in the literature [8]

Other information: Give in combination with L-ornithine [8, 9]
May be combined with an arginine restricted diet [2, 9]
May be given with sodium benzoate if GAA levels fail to fall [38]

Dose: **Arginine: Glycine amidinotransferase (AGAT) deficiency**
100 – 800 mg/kg/day orally in 3 to 6 divided doses [2, 9]

Dose: **Gyrate atrophy/Ornithine aminotransferase (OAT) deficiency**
Up to 2 grams/kg/day [9]

CYANOCOBALAMIN
(Vitamin B_{12})

Action: Co-factor of methylmalonyl mutase and methionine synthase

Indication: Vitamin B_{12} deficiency of dietary origin [2]
Transcobalamin deficiency [2]

Preparation & supplier details: 50 microgram tablets; 100 microgram tablets, 50 microgram tablets; Advanz Pharma
1000 microgram tablets (50 tablets) (U); Clinigen
1 mg/mL injection (5 ampoules),); Cytamen Injection, RPH Pharmaceuticals AB

Funding notes: in tariff/PbR

Suggested local formulary status: Green – primary or secondary care can initiate.

Additional information: Hydroxocobalamin has replaced cyanocobalamin as the vitamin B_{12} of choice. It is retained in the body longer than cyanocobalamin [10]

Paediatric Drug Information

Indication: **Transcobalamin deficiency**

Dose: 500 micrograms – 1 mg daily PO or IM initially then twice weekly [18]

Indication: **Vitamin B_{12} deficiency of dietary origin**

Dose: 50 – 105 micrograms daily in 1 – 3 divided doses [1]

Adult Drug Information

Dose: 50 – 150 micrograms PO OD between meals [10]
1 mg IM repeated 10 times at intervals of 2 – 3 days, maintenance 1 mg every month [10]

FOSDENOPTERIN

(Cyclic Pyranopterin Monophosphate)

Action: Substrate replacement therapy to provide an exogenous source of cPMP, which is converted to molybdopterin [209].

Indication: Molybdenum co-factor deficiency type A [209-211].

Preparation & supplier details: Nulibry 9.5mg powder for solution for injection [209].

Funding notes: not commissioned/IFR only

Suggested local formulary status: Red – hospital only.

Additional information: for intravenous use only at an infusion rate of 1.5ml/min after reconstitution with 5mL sterile water for injection. Dose volumes below 2mL may require syringe administration by slow intravenous push [1].

Paediatric Drug Information

Dose:

Preterm neonate (gestational age less than 37 weeks) [209]
Initial dose: 0.4mg/kg once daily
Dose at month 1: 0.7mg/kg once daily
Dose at month 3: 0.9mg/kg once daily

Term neonate (gestational age 37 weeks and above) [209]
Initial dose: 0.55mg/kg once daily
Dose at month 1: 0.75mg/kg once daily
Dose at month 3: 0.9mg/kg once daily

Paediatric (from 1 year to less than 18 years of age) and adult [209]
0.9mg/kg (based on actual body weight) once daily

DEXTROMETHORPHAN

Action: Competitive N-methyl-d-aspartate NMDA channel antagonist preventing binding of glycine [2]

Indication: Non-ketotic hyperglycinaemia (NKH) [2, 8, 9]

Preparation & supplier details: [Delsym] 30 mg/5 mL liquid in bottles of 89 mL; Unlicensed Medicines (U)
[Robitussin/Benylin] 7.5 mg/5 mL liquid in bottles of 100 or 250 mL; AAH Pharmaceuticals
[Perrigo] 30 mg/5 mL liquid in bottles of 89 mL; Durbin PLC (U)
[Cough Gels] 15 mg capsules in packs of 20 capsules; Clinigen (U)

Funding notes: in tariff/PbR

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescriptions

Additional information: Both Delsym and Perrigo brand are extended release formulations and can be given BD [8]
Delysm brand contains the excipient sodium metabisulfite [42]. Sodium metabisulfite has been associated with bronchospasm in atopic individuals and can also cause gastric irritation [43].
Delsym is relatively alcohol free (0.26 %) but contains 1.7 grams of sugar per 5 mL, this commonly affects ketosis in patients on a ketogenic diet [8].
Perrigo brand & Cough Gel brand contains the excipient propylene glycol [42, 44]. Propylene glycol is avoided in neonates and those with renal impairment [43].
Robitussin/Benylin contains 2.5 % v/v ethanol [45].
Robitussin/Benylin & Cough Gel capsules are not long acting; therefore, total daily dose is given in 3 divided doses [8].
Cough Gel capsules, contain glycerin, propylene glycol, & sorbitol [42] but considered more 'ketogenic friendly' as lower carbohydrate content.
Dextromethorphan may cause respiratory depression and so may be an increased risk of pneumonia with high doses [2, 8].
Dependence and a withdrawal syndrome have been reported on cessation.

Paediatric Drug Information

Dose: 2.5 mg/kg, orally, TWICE a day, increasing to 5 mg/kg TWICE a day (Delsym & Perrigo brand only) [2, 8, 9]. Doses as high as 35 mg/kg/day in divided doses have been used [2, 8].
Robitussin/Benylin & cough gel capsule brands - Use in 3 divided doses.

DIAZOXIDE

Action: Inhibits insulin secretion [2]

Indication: Hyperinsulinism [2]
Hyperinsulinism Hyperammoniaemia Syndrome (HIHA) [9]

Preparation & supplier details: 50 mg/mL (30 mL); Clinigen (U)
50 mg tablets (100 tablets)

Funding notes: in tariff/PbR

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescription

Additional information: During long therapy monitor for: leucopenia, thrombocytopenia, growth assessment, bone assessment, psychological assessment and blood pressure [1, 8, 19]
Give lower doses (2 – 5 mg/kg/day) if risk of pulmonary hypertension [2]
Gastrointestinal adverse effects common at therapeutic doses in adults, including nausea/vomiting, anorexia and constipation [46]
Caution as causes fluid retention – given in combination with a diuretic (*i.e.* chlorothiazide that has a synergistic effect) [8]

Paediatric Drug Information

Dose: **Neonates:** 5 mg/kg, orally TWICE daily, adjusted to response, maintenance may be lower, but up to 7 mg/kg, orally THREE times a day may be needed [1, 2, 9]

1 month plus: 1.7 mg/kg, orally THREE times a day, adjusted according to response. Maximum dose: 15 mg/kg/day [1]

Adult Drug Information

Dose: Initially 5 mg/kg, daily, orally, in 2 – 3 divided doses, adjusted according to response; maintenance 3 – 8 mg/kg, daily, orally, in 2 – 3 divided doses [10]

ELIGLUSTAT

Action: Substrate Reduction Therapy (SRT) as a Glucosylceramide synthase inhibitor [10]

Indication: Gaucher Disease Type I [10]

Preparation & supplier details: 84 mg capsules (56 capsules) [Cerdelga©]; Sanofi-Genzyme Ltd.

Funding notes: Commissioned by NHS England via nationally commissioned LSD centres; Highly Specialised Technology Guidance 5 (HST5) [3, 47]

Suggested local formulary status: Red – hospital only

Additional information: Contraindicated in those with cardiac disease, QT interval prolongation, and concurrent use of Class IA and Class III antiarrhythmics; certain degrees of hepatic impairment and those taking certain medications [10, 48]. Consult SPC for detailed information [10, 48]
Dose dependent on CYP2D6 metaboliser status, therefore CYP2D6 metaboliser status should ALWAYS be determined before the initiation of treatment [10]
Contraindicated if CYP2D6 ultra-rapid metaboliser (URM) or indeterminate metaboliser [10, 48]
If a dose is missed, then take the prescribed dose at the next scheduled time. The next dose should not be doubled [48]
Dose adjustment is required in hepatic & renal impairment (see SPC for recommendations) [48]

Eliglustat has multiple drug interactions, particularly drugs that inhibit or induce the CYP2D6 and CYP3A4 systems; or the P-glycoprotein (P-gp) system and care should be taken when prescribing concomitant medications [48]. Consult SPC and your pharmacist for detailed information for drug interactions.

Adult Drug Information

Dose: **CYP2D6 Poor metaboliser**
84 mg, orally, ONCE a day [10, 48]

Dose: **CYP2D6 intermediate or extensive metaboliser**
84 mg, orally, TWICE a day [10, 48]

ELOSULFASE ALFA

Action: Enzyme replacement therapy – recombinant analogue of N-acetylgalactosamine-6-sulfatase [1, 2, 3, 49]

Indication: Mucopolysaccharidosis (MPS) type IV_A (Morquio A Syndrome) [1, 2, 49]

Preparation & supplier details: 5 mg/ 5 mL vial for intravenous infusion [Vimizim©]; BioMarin Ltd. [1]

Funding notes: Commissioned by NHS England via nationally commissioned LSD centres; Highly Specialised Technology (HST) and Managed Access Agreement only [3]

Suggested local formulary status: Red – hospital only

Additional information: Each vial contains 8 mg of sodium and 100 mg of sorbitol (E420) [49]
Store at 2 – 8 ° C in a refrigerator [49]
Consider pre-medication with an antihistamine +/- paracetamol 30 mins prior to the start of the infusion [50]

Paediatric Drug Information

Dose: 2 mg/kg via intravenous infusion once a week [1, 2, 49]. Round up to the next whole vial or use alternate dosing for an overall 2 mg/kg average [50].

Administration: Consult local protocol or Summary of Product Characteristics (SPC) [49]

Adult Drug Information

Dose: 2 mg/kg via intravenous infusion once a week [1, 2, 49]. Round up to the next whole vial [50]

Administration: Consult local protocol or Summary of Product Characteristics (SPC) [49]

EMPAGLIFLOZIN

Action: A sodium-glucose co-transporter-2 (SGLT2) inhibitor which reduces plasma levels of 1,5-anhydroglucitol (1,5-AG) and its toxic derivatives in neutrophils [220].

Indication: Glycogen storage disease type 1b (GSD 1b)] and glucose-6- phosphatase catalytic subunit 3 deficiency (G6PC3 deficiency) [220,221,223]

Preparation & Supplier details: 10mg and 25mg tablets (packs of 28 tablets) [Jardiance ©]; Boehringer Ingelheim Ltd

Funding notes: PbR/in tariff**.** Suggested local formulary status: Amber.

Additional information: Off-label/unlicensed use for GSD1b and G6PC3 deficiency**/**Tablets can be crushed and dispersed in water**.** Risk of diabetic ketoacidosis (DKA) [226]. Inform patients of signs and symptoms of DKA. Test for raised ketones in with any signs and symptoms of DKA even if plasma glucose levels are near-normal, use in caution in patients with risk factors for DKA. The MHRA and EMA advise interrupting empagliflozin treatment in patients with diabetes who are hospitalised for major surgery or acute serious illness, however, for GSD1b or G6PC3 deficiency this risk of DKA needs to be balanced against the patients' neutrophil function [226].

Risk of Fournier's gangrene. Patients should be advised to seek urgent medical attention if they experience severe pain, tenderness, erythema, or swelling in the genital or perineal area, accompanied by fever or malaise [226].

Paediatric Drug Information

Indication: Glycogen storage disease type 1b (GSD 1b)

Dose: 0.2 to 0.7mg/kg/day orally in a single or 2 divided doses (max 25mg/day). Titrate as per tolerance and clinical response [220,221].

Indication: Glucose-6-phosphatase catalytic subunit 3 deficiency (G6PC3 deficiency)

Dose: 0.1 to 0.7mg/kg/day orally in a single or 2 divided doses (max 25mg/day). Titrate as per tolerance and clinical response [220,222].

Adult Drug Information

Indication: Glycogen storage disease type 1b (GSD 1b) and Glucose-6-phosphatase catalytic subunit 3 deficiency (G6PC3 deficiency)

Dose: Initially 5mg to 10mg/day titrated up to 10 to 25mg/day in single or 2 divided doses. Titrate as per tolerance and clinical response [223,224,225].

EVOLOCUMAB

Action: Evolocumab binds to a pro-protein involved in the regulation of LDL receptors on liver cells (PCSK9). LDLC receptor numbers are increased, which results in increased uptake of LDL-C from the blood [200].

Indication: Primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed Dyslipidaemia[200-203]. Homozygous familial hypercholesterolaemia (HoFH) [201]

Preparation & Supplier details: 140mg pre-filled pen [Repatha®]; Amgen UK [200,231].

Funding notes: Commissioned by ICBs for primary hypercholesterolaemia or mixed dyslipidaemia. Commissioned by NHS England for HoFH via specialist lipid clinics[3]

Suggested local formulary status: Red – hospital only

Additional information: Refer to NICE TA for commissioning criteria. Consider use when LDL-C concentrations are Persistently above a specified threshold despite maximal tolerated lipid-lowering therapy (statins plus ezetimibe)[201]. Review treatment after 12 weeks, stop if targets in HDL or LDL-C (30% reduction or more) have not been achieved. Patients currently receiving apheresis can be offered Evolocumab [202].Not licensed in children less than 10 years [201]. Store in a refrigerator at 2– 8 ° C [200]. The needle cover of the pre-filled pen is made from dry natural rubber (a derivative of latex) which may cause severe allergic reactions [231]. To be administered into the thigh, abdomen or upper arm [1]

Paediatric Drug Information

Indication: Primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia

Dose: Child > 10 years: 140mg by subcutaneous injection every 2 weeks [200,231].

Indication: Homozygous familial hypercholesterolaemia (HoFH)

Dose: Child > 10 years: 420mg by subcutaneous injection monthly for the first 12 weeks which can then be increased to 420mg every 2 weeks [200,203]

Adult Drug Information

Indication: Primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia

Dose: 140mg by subcutaneous injection every 2 weeks [231].

Indication: Homozygous familial hypercholesterolaemia (HoFH)

Dose: 420mg by subcutaneous injection monthly for the first 12 weeks which can then be Increased to 420mg every 2 weeks [200,201]

EZETIMIBE

Action: Inhibits cholesterol absorption [1, 2]

Indication: Sitosterolaemia [1, 2]
Adjunct treatment for familial hypercholesterolaemia

Preparation & supplier details: 10 mg tablets (28 tablets)

Funding notes: in tariff/PbR

Suggested local formulary status: Green – primary or secondary care to initiate

Additional information: Avoid in moderate and severe hepatic impairment (Child-Pugh score 7 – 15) [1, 51]
Can cause myotoxicity [1]
Children with familial hypercholesterolemia may be monitored and treated in paediatric inherited metabolic disease clinics. NICE guidelines for the management of paediatric FH are available at: https://www.nice.org.uk/guidance/cg71

Paediatric Drug Information

Indication: Adjunct to dietary measures for homozygous Sitosterolaemia [2]

Dose: **Child 5 – 9 years:** 10 mg, orally ONCE a day (*Nb.* Based on limited data from two studies of monotherapy (Clauss 2009 & Yeste 2009) [51]
Child 10 – 17 years: 10 mg, orally, ONCE a day [1, 2]

Adult Drug Information

Indication: Adjunct to dietary measures for homozygous Sitosterolaemia [10]

Dose: 10 mg, orally, ONCE a day [10]

FOLIC ACID
(Vitamin B_9)

Action:	Source of folate
Indication:	Homocystinuria (cystathionine beta-synthase deficiency) [9] Methylenetetrahydrofolate reductase (MTHFR) deficiency thermolabile variants [9] Hereditary folate malabsorption [2] Remethylation defects (intracellular cobalamin defects and methionine synthase deficiency) [9]
Preparation & supplier details:	5 mg tablets (28 tablets) 400 microgram (90 tablets) 2.5 mg/5 mL sugar-free liquid; (150 mL) Rosemont Pharmaceuticals Ltd. 1mg/ml Oral Solution Colonis Pharma Limited
Funding notes:	in tariff/PbR
Suggested local formulary status:	Green – primary or secondary care to initiate
Additional information:	In conditions where CSF folate levels are low, consider using folinic acid (calcium folinate)

Paediatric Drug Information

Indication:	**Mild & classical homocystinuria (cystathionine beta-synthase deficiency) [9]; methionine synthase deficiency; Methylenetetrahydrofolate reductase (MTHFR) deficiency [9]**
Dose:	5 - 10 mg, orally, ONCE a day [9]
Indication:	**Hereditary folate malabsorption**
Dose:	up to 60 mg, orally, ONCE a day, consider calcium folinate if high doses fail to raise cerebrospinal fluid (CSF) folate [2].
Indication:	**Other metabolic disorders**
Dose:	**Child 1 month – 1 years:** 2.5 – 5 mg, orally, ONCE a day **Child 12- 17 years:** 5 – 10 mg, orally, ONCE a day [1]

Adult Drug Information

Indication:	Limited information – Consult paediatric information above
Dose:	Limited information – Consult paediatric information above

FOLINIC ACID (Calcium Folinate)

(Vitamin B_9)

Action: CNS accessible source of folate [2]

Indication:
Severe 5,10-methylene-tetrahydrofolate reductase (MTHFR) deficiency [2, 9, 10, 52]
Non-ketotic Hyperglycinaemia (NKH) [9]
Disorders of cobalamin metabolism [2, 9]
DHPR deficiency (Biopterin recycling defect) [1, 2, 8, 9]
UMP synthase (hereditary orotic aciduria) [2]
Methionine synthase deficiency [2]
Disorders of folinate deficiency *e.g.* hereditary folate malabsorption [2, 9] and Cerebral folate transporter deficiency [2, 9], dihydrofolate reductase deficiency [9]
Formiminotransferase deficiency [9]

Preparation & supplier details:
15 mg tablets (10 and 30 tablet packs)
30 mg/10 mL injection (5 x 10 mL); Alliance Healthcare Ltd.
10 mg/mL (1 mL) Injection; Hospira UK Ltd.

Funding notes: in tariff/PbR

Suggested local formulary status: Green – primary or secondary care can initiate

Additional information:
Round to nearest 15 mg tablet
Tablets can be crushed and dispersed in water
Injection can be given orally [8]

Paediatric Drug Information

Indication: **Homocystinuria and deficiencies & defects in cystathionine beta-synthase deficiency; Non-Ketotic Hyperglycinaemia (NKH) [9]; Methionine synthase deficiency** [2]

Dose: 15 mg, orally, ONCE a day [1, 9]

Indication: **Severe 5,10-methylene-tetrahydrofolate reductase (MTHFR) deficiency [2, 9]**

Dose: 15 mg, orally ONCE a day – increasing to 60 mg, orally, ONCE a day to obtain adequate clinical response and CSF folate concentrations.
Consider calcium mefolinate (mefolinic acid) if high doses of calcium folinate fail to raise cerebrospinal fluid (CSF) folate [9, 53]

Indication: **Disorders of cobalamin metabolism** [2, 9]

Dose: 15 mg, orally ONCE a day [2, 9, 23] up to 45 mg, orally, ONCE a day as determined by clinical response and CSF folate levels [9]

Indication: **DHPR deficiency (Biopterin recycling defect)** [1, 2, 8, 9]

Dose: 15 mg, orally ONCE a day. higher doses determined by clinical response and CSF folate levels [1, 8, 9]

Indication: **Hereditary folate malabsorption [2, 9]**

Dose: 45 - 60 mg, orally, ONCE a day [2, 9] increasing to 20 mg/kg, orally FOUR times a day [2, 9] to obtain adequate CSF response or consider 5 mg IV, ONCE a day [2, 9]. Doses as high as 400 mg a day have been used [2]. Alternatively, 5 mg IM TWICE weekly [54]

Indication:	**Cerebral folate transporter deficiency and dihydrofolate reductase deficiency** [2, 9]
Dose:	15 mg, orally, ONCE a day [2] or 3 – 5 mg/kg/day [54] (10 – 20 mg/kg/day) (book differs to online)

Adult Drug Information

Indication:	Limited information – Consult paediatric information above
Dose:	Limited information – Consult paediatric information above

GALACTOSE
(D-Galactose)

Action: Restores missing galactose compound to correct abnormal galactosylation [2]

Indication: Phosphoglucomutase 1 deficiency (PGM1-CDG) [2, 55]
SLC39A8-Congenital Disorder of Glycosylation (CDG) (SLC39A8) [56, 57]
SLC35A2-Congenital Disorder of Glycosylation (CDG) (SLC35A2) [58]

Preparation & supplier details: Powder; Special Labs (U)
'Progalin Galactosepulver', 1-gram sachets (250 & 500 sachet packs); (U)
Vitaflo (U)
Powder (250 g); Fagron (U)
Powder (1 kg); Sigma-Aldrich (U)

Funding notes: "in tariff"/PbR

Suggested local formulary status: Amber - hospital to initiate, GP to continue repeat prescriptions

Additional information: Powder from Special Labs has a 90-day expiry from manufacture
Progalin Galactosepulver sachets are an import from Germany – 2-week lead time
Use with diazoxide if needed in cases of severe hypoglycaemia

Paediatric Drug Information

Indication: **Phosphoglucomutase 1 deficiency (PGM1-CDG)**

Dose: 0.5 – 1 g/kg, orally ONCE a day, maximum of 50 g/day [55] in 3 – 6 divided doses.

Indication: **SLC35A2-Congenital Disorder of Glycosylation (SLC39A8-CDG)**

Dose: 1 – 2 g/kg/day, given in 5 divided doses [57]. Up to a maximum of 3.75 g/kg/day over 22 hours gastrointestinal pump feeding [57]. Uridine (150 mg/kg/day) may be given alongside to ensure sufficient uridine available for UDP-galactose formation [57].

Indication: **SLC35A2-Congenital Disorder of Glycosylation (SLC35A2-CDG)**

Dose: 1 g/kg/day orally in divided doses [58].

Adult Drug Information

Indication: Limited information – Consult paediatric information above

Dose: Limited information – Consult paediatric information above

GALSULFASE
(Naglazyme®)

Action: Enzyme Replacement Therapy (ERT) - recombinant analogue of human N-acetylgalactosamine 4-sulfatase [2, 59]

Indication: Mucopolysaccharidosis VI (MPS VI), also known as Maroteaux-Lamy syndrome [2, 59]

Preparation & supplier details: 1 mg/mL concentrate for solution for infusion (5 mL vial) [Naglazyme©]; BioMarin Ltd.[59]

Funding notes: Commissioned by NHS England via national LSD centres [3]

Suggested local formulary status: Red – hospital only

Additional information:
Store in the refrigerator [49]
Pre-treat with antihistamine and anti-pyretic to minimise infusion-related reactions [49]
Children less than 5 years of age were not included in the phase III study.
Data is available for patients less than 1 year of age from the phase IV study.
Consult Summary of Product Characteristics (SPC) for detailed information [49]

Paediatric Drug Information

Dose: **Child 5 years – 17 years:** 1 mg/kg every week via an intravenous infusion over 4 hours [1, 2, 49]
Less than 5 years of age if required (unlicensed)

Administration: Consult local protocol or Summary of Product Characteristics (SPC)

Adult Drug Information

Indication: 1 mg/kg every week via an intravenous infusion over 4 hours [2, 10, 49]

Administration: Consult local protocol or Summary of Product Characteristics (SPC)

GLYCEROL PHENYLBUTYRATE

Action: Ammonia scavenger – a nitrogen-binding agent that provides an alternative vehicle for waste nitrogen/ammonia excretion. [1, 60]

Indication: Hyperammonaemia due to Urea Cycle Disorders (UCDs) – see SPC for list of licensed UCDs [60]

Preparation & supplier details: Oral liquid 1.1g/ml (25 mL) [Ravicti©]; Immedica

Funding notes: NHSE commissioned/PbR excluded [3]

Suggested local formulary status: Red – hospital only

Additional information:
Limited shelf life - discard contents of bottle 14 days after opening [1, 60]
Contraindicated for the treatment of acute hyperammonaemia [1, 60]
Do not mix with water [60]
Dose may be added to a small amount of apple sauce, ketchup, or squash puree and should be used within 2 hours when stored at room temperature (25° C) [60]
Ravicti may be mixed with the following feeds (Cyclinex-1, Cyclinex-2, UCD-1, UCD-2, Polycose, Pro Phree and Citrulline) and used within 2 hours when stored at 25° C, or up to 24 hours, refrigerated [60]
Do not rinse oral syringe with water between daily doses and use a new syringe each day - the presence of water can cause degradation of glycerol phenylbutyrate [60]
Round dose up to the nearest 0.1 mL in children less than 2 years and 0.5 mL in children 2 years and older [60]
Can be used via enteral feeding tubes – refer to SPC for detailed information.
6 mmol of Nitrogen is removed by 1 mmol of glycerol phenylbutyrate [61]

Paediatric Drug Information

Indication: Urea Cycle Disorders (UCDs) recommended starting dosage in phenylbutyrate-naïve patients

Dose:

Neonate (body surface area (BSA) up to 1.3 m^2:
Initially 8.5mL/m^2/day (9.4g/m^2) daily in divided doses, usual maintenance 4.5 mL/m^2/day - 11.2 mL/m^2/day (5.3 - 12.4g/m^2/day) in 3 – 6 divided doses, rounded to the nearest 0.1 mL and given with each feed; orally/enterally [1, 60]

Child 2 months – 17 years with BSA < 1.3 m^2:
Initially 8.5 mL/m^2/day (9.4 g/m^2/day) in 3 – 6 divided doses with meals/feeds titrated as needed to a maximum 11.2 mL/m^2/day (12.4 g/m^2/day); orally/enterally [1, 60]

Child 2 months – 17 years with BSA ≥ 1.3 m^2:
Initially 7 mL/m^2/day (8 g/m^2/day) in 3 – 6 divided doses with meals/feeds titrated as needed to a maximum 11.2 mL/m^2/day (12.4 g/m^2/day); orally/enterally [1, 60]

For dose conversion between glycerol phenylbutyrate (Ravicti) and other oral ammonia scavengers; or dose conversion between intravenous ammonia scavengers and glycerol phenylbutyrate (Ravicti), please refer to SPC for detailed information.

Adult Drug Information

Indication: Urea Cycle Disorders (UCDs) recommended starting dosage in phenylbutyrate-naïve patients

Dose:

BSA < 1.3 m^2: Initially 8.5 mL/m^2/day (9.4 g/m^2/day) in 3 – 6 divided doses with meals/feeds titrated as needed to a maximum 11.2 mL/m^2/day (12.4 g/m^2/day); orally/enterally [10, 60]

BSA ≥ 1.3 m^2: Initially 7 mL/m^2/day (8 g/m^2/day) in 3 – 6 divided doses with meals/feeds titrated as needed to a maximum 11.2 mL/m^2/day (12.4 g/m^2/day); orally/enterally [10, 60]

For dose conversion between glycerol phenylbutyrate (Ravicti) and other oral ammonia scavengers; or dose conversion between intravenous ammonia scavengers and glycerol phenylbutyrate (Ravicti), please refer to SPC for detailed information.

GLYCINE

Action: Forms isovalerylglycine with high renal clearance [2, 9]
Replenishes serine [2, 9]

Indication: Isovaleric acidaemia [2, 9]
Serine deficiency disorders (3-phosphoglycerate dehydrogenase deficiency; phosphoserine aminotransferase deficiency; 3-Phosphoserine phosphatase deficiency) [2, 9]

Preparation & supplier details: 1 g powder sachets (25 sachets); The Specials Laboratory (PCCA Ltd.)
500 mg powder sachets (30 sachets); Vitaflo

Funding notes: in tariff/PbR

Suggested local formulary status: Red – hospital only

Additional information: Dissolve each 500 mg sachet in 20 mL of water, stir and allow up to 3 minutes for full dissolution [8]
Can be given as concentrated as a 100 mg/mL aqueous solution [2]
Sachets can be mixed with protein substitute/added to modular fees to facilitate administration. If part doses of sachets are needed, then add the corresponding volume of diluted solution before mixing [8].

Paediatric Drug Information

Indication: **Isovaleric acidaemia**

Dose: **Child (all ages):** 150mg – 300 mg/kg/day, orally, in 3 divided doses. Doses up to 600 mg/kg/day have been used during decompensation [2, 8, 9].

Indication: **Serine Deficiency Disorders (as an adjunct to serine supplementation)**

Dose: **Child (all ages):** 200mg– 300mg/kg/day, orally, in divided doses. Titrate as per plasma amino acids and clinical response [2, 9].

Adult Drug Information

Indication: Limited information – Consult paediatric information above

Dose: Limited information – Consult paediatric information above

HAEM ARGINATE (Haematin/Haemin/Human Hemin)

Action: Inhibits 5-aminolevullinic acid synthase [2]

Indication: Acute porphyrias [1, 2, 9]
Tyrosinaemia type I – has been used to support management of an acute neurological crisis [62]

Preparation & supplier details: 25 mg/mL concentrate solution for infusion (10 mL) [Normosang®]; Recordati Rare Diseases Uk Ltd

Haem arginate cannot be obtained directly from the manufacturer and supplies should be obtained directly from the designated porphyria centres in office hours:
King's College Hospital, London (020 3299 5776) or
University Hospital of Wales, Cardiff (02920 746 588) [63]

In order to contact the service and centres during or out of normal working hours users are asked to follow the following procedure:

1.) Telephone University Hospital of Wales Switchboard **02920 747 747** and ask for the **National Acute Porphyria Service.**
2.) The switchboard operator will advise the user which centre is providing the emergency cover that week according to an agreed rota.
3.) The switchboard will provide the user with a telephone contact number or long-range pager number as arranged by each centre.
4.) During office hours, for patients already being managed by a designed porphyria centre, contact that centre for advice and supply.

Funding notes: NHSE commissioned/PbR excluded [3]

Suggested local formulary status: Red – hospital only

Additional information: Refer to BIMDG Adult Emergency Management Plan
Nb. excipients: ethanol 1 gram/10 mL and 4 g/10 mL propylene glycol. Increased risk of extravasation and toxicity in children [43]

Paediatric Drug Information

Indication: Acute porphyrias

Dose: **Child (all ages):** Initially 3 mg/kg (Max. 250 mg) via intravenous infusion ONCE daily for 4 days [2]. If inadequate response, repeat 4-day course with close biochemical monitoring [2]. Maximum of 250 mg/day [2].

Adult Drug Information

Indication: Acute porphyrias

Dose: Initially 3 mg/kg (Max. 250 mg) via intravenous infusion ONCE daily for 4 days [2, 10, 64], rounding to the nearest 1 mL [65]. If inadequate response, repeat 4-day course with close biochemical monitoring. Maximum of 250 mg/day.

Administration: Haem arginate is irritant to veins [64, 65]
Via an intravenous infusion over 30 – 60 mins through a filter into a large antebrachial vein or central vein [1, 64, 65]
Dilute requisite dose in 100 mL sodium chloride 0.9 % in a glass bottle [1, 63-65]. However, as sterile glass bottles are difficult to obtain, a pragmatic approach to avoid delaying emergency treatment, would be to use plastic containers and the infusion should be administered immediately [65].
Administer 1 hour after dilution in glass bottle [1], use immediately if diluted in plastic [65].

Maximum concentration: 2.5 mg/mL [10].
Administer in alternate arms each day [10, 64]
Following infusion, immediately rinse vein with 100 - 250 mL sodium chloride 0.9 % (initially 3 – 4 boluses of 10 mL, then infuse the remainder of the under gravity [10, 63, 64].
Always check cannula before, during and after infusion [65]
Repetitive peripheral use may lead to the loss of superficial venous system and the consequent need for a central line. Central lines, may in time become obstructed with haem deposits. Haem arginate may be administered over 60 minutes in 100 mL of human albumin (20 %) to reduce these problems (unlicensed use – anecdotal evidence) if 20 % human albumin is clinically suitable [65, 66]

HYDROXOCOBALAMIN
(Vitamin B_{12})

Action: Co-factor for methylmalonyl mutase and methionine synthase [2]

Indication:
Disorders of cobalamin metabolism [2, 9]
Congenital transcobalamin II deficiency [1]
5,10-methylene-tetrahydrofolate reductase (MTHFR) deficiency [1, 2, 9]
Acquired vitamin B_{12} deficiency/Macrocytic anaemia [1]
B_{12} responsive Methylmalonic Aciduria (MMA) [1, 2, 9]

Preparation & supplier details: 1 mg/mL solution for injection (5 x 1 mL)
'Megamilbedoce' 10mg/2 mL solution for injection (10 x 2 mL) and Hydroxocobalamin acetate sterop 10 mg/2 mL solution for injection and oral solution (5 x 2 mL); Durbin PLC, Clinigen (U)

Funding notes: in tariff/PbR

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescriptions
Green – secondary or primary care initiation for acquired vitamin B_{12} deficiencies

Additional information:
Injection can be given orally but it will not be absorbed in malabsorption states, post-gastrectomy or in pernicious anaemia [8].
Effect will not be prolonged when given orally or parenterally [8]
Can discolour urine red [1]
If administering injection preparation orally, use a filter needle to draw up solution from glass ampoules.
Use 10 mg/ 2mL for IM doses more than 1mg
Hydroxocobalamin acetate sterop 10 mg/2 mL does not contain benzyl alcohol [67]

Paediatric Drug Information

Indication: **Disorders of cobalamin metabolism**

Dose: **Child (all ages):** 1 - 2 mg IM ONCE a day initially decreasing to ONCE or TWICE WEEKLY according to response [2, 9]. Dose escalation of 300 micrograms/kg (maximum 20 mg IM OD) have been used [5, 68, 69]

Indication: **Transcobalamin deficiencies**

Dose: **Child (all ages):** 1 mg IM THREE times a WEEK for 1 year, then 1 mg ONCE a week thereafter adjusted according to clinical response [1]

Indication: **5,10-methylene-tetrahydrofolate reductase (MTHFR) deficiency**

Dose: **Child 1month – 17 years:** 1 mg IM MONTHLY [9]

Indication: **Acquired vitamin B_{12} deficiency (macrocytic anaemia) without neurological involvement**

Dose: **Child (all ages):** Initially 0.25 – 1 mg IM on ALTERNATE DAYS for 1 – 2 weeks, then 0.25 mg IM WEEKLY until FBC normal, then 1 mg IM every 2- 3 months [1].

Indication: **Acquired vitamin B_{12} deficiency (macrocytic anaemia)** with neurological involvement

Dose: **Child (all ages):** Initially 1 mg IM on ALTERNATE DAYS until no further improvement, then 1 mg IM every 2 months [1].

Indication: **Methylmalonic Aciduria (B_{12} responsive)**

Dose: **Child (all ages):** 1 mg IM ONCE a day for ONE week then 1 mg ONCE or TWICE a week [1]. Once response is established, can switch to oral route: 5 – 10 mg, orally, ONCE or TWICE a week (some children do not respond to the oral route) [1]. Tailor dosing to response: dose ranges include 1 – 14 mg/week IV/IM and 5 – 21 mg/week, orally [70]. Daily dosing can be used if needed [70].

Indication: **Leber's Optic Atrophy**

Dose: **Child (all ages):** 1 mg IM, ONCE a day for TWO weeks then 1 mg TWICE a week until no further improvement then 1 mg IM every 1 – 3 months [1].

Adult Drug Information

Indication: **Acquired vitamin B_{12} deficiency (macrocytic anaemia) without neurological involvement**

Dose: Initially 1 mg IM THREE times a week for TWO weeks, then 1 mg IM every 2- 3 months [10].

Indication: **Acquired vitamin B_{12} deficiency (macrocytic anaemia) with neurological involvement**

Dose: Initially 1 mg IM on ALTERNATE DAYS until no further improvement, then 1 mg IM every 2 months [10].

Other indications - Limited information – Consult paediatric information above

5-HYDROXYTRYPTOPHAN
(Oxitriptan)

Action: Neurotransmitter replacement [2]

Indication: Disorders of neurotransmitter synthesis and tetrahydrobiopterin (BH4) defects/deficiencies such as: Guanosine triphosphate cyclohydrolase I (GTPCH) deficiency; 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency, dihydropterin reductase (DHPR) deficiency [2, 8, 9]

Preparation & supplier details: 50 mg capsules (packs of 50); Special Products (Veriton Pharma) (U)
100 mg tablets (packs of 60); Lamberts Healthcare (U)

Funding notes: in tariff/PbR

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescriptions

Additional information: Monitor response clinically and CSF 5-HIAA levels to adjust dose [2, 8]
Poor phenylalanine control impairs neurotransmitter levels in the CSF [8].
To be used alongside levodopa aiming for a dose of 2 mg/kg/day less then levodopa to enable an appropriate HVA:5-HIAA CSF ratio [8].
Co-careldopa and 5-hydroxytryptophan should be introduced sequentially and increased slowly in increments not more than 1 mg/kg over days or weeks [2, 9] because they can both cause gastrointestinal side effects [2, 8].
Can cause gastrointestinal side effects which can limit treatment and be intolerable – in these cases monotherapy with co-careldopa may be sufficient [9].

Paediatric Drug Information

Dose: **Child (all ages):**
1 – 2 mg/kg, orally, in 4 – 6 divided doses [2, 8], increasing gradually in increments nor more than 1 mg/kg over 2-3 days [8] or over weeks [8] to a maximum dose of 8 – 10 mg/kg/day, orally, in 4 – 6 divided doses [2, 8, 9].

Aim for a dose of 2 mg/kg/day less then levodopa to enable an appropriate HVA:5-HIAA CSF ratio [8].

Adult Drug Information

Indication: Limited information – Consult paediatric information above

Dose: Limited information – Consult paediatric information above

IDURSULFASE
(Elaprase®)

Action: Enzyme Replacement Therapy (ERT) – recombinant human analogue of iduronate-2-sulfatase [2, 71]

Indication: Mucopolysaccharidosis II (MPS II), also known as Hunter Syndrome [2, 71]

Preparation & supplier details: 2 mg/mL concentrate solution for infusion (6 mg/3 mL) vial; Shire Pharmaceuticals Ltd. (Takeda) [71]

Funding notes: Commissioned by NHS England via national LSD centres [3]

Suggested local formulary status: Red – hospital only

Additional information: Store in a refrigerator [71]
Pre-treat with antihistamine and anti-pyretic to minimise infusion-related reactions (IRRs) [71] . To be given as an intravenous infusion over approx. 3 hours initially, gradually reducing duration of infusion if no IRRs – consult local protocol or Summary of Product Characteristics (SPC) [71]

Paediatric Drug Information

Dose: **Child 5 – 17 years:** 0.5 mg/kg by intravenous infusion ONCE weekly [1, 2, 71]
Unlicensed at younger ages

Administration: Consult local protocol or Summary of Product Characteristics (SPC)

Adult Drug Information

Dose: 0.5 mg/kg intravenous infusion ONCE weekly [2, 10, 71]

Administration: Consult local protocol or Summary of Product Characteristics (SPC)[71]

IMIGLUCERASE
(Cerezyme®)

Action: Enzyme Replacement Therapy (ERT) – recombinant analogue human β-glucocerebrosidase [2, 72]

Indication: Type I and III Gaucher Disease [2, 72]

Preparation & supplier details: 200 unit and 400-unit vials for infusion [Cerezyme®]; Sanofi-Genzyme [72]

Funding notes: Commissioned by NHS England via national LSD centres [3]

Suggested local formulary status: Red – hospital only

Additional information: Monitor for immunoglobulin G (IgG) antibodies to imiglucerase [1]
Store in a refrigerator [72]
To be given as an intravenous infusion – consult local protocol or Summary of Product Characteristics (SPC) [72]
Doses as low as 15 units/kg by intravenous infusion every 2 weeks has been shown to improve haematological parameters and organomegaly, but not bone parameters [72]

Paediatric Drug Information

Indication: **Gaucher Disease type I:**

Dose: **Neonate & Child (all ages):**
60 units/kg intravenous infusion every 2 weeks adjusted according to response. 30 units/kg intravenous infusion every 2 weeks may be adequate [1, 2, 72]

Indication: **Gaucher Disease type III:**

Dose: **Neonate & Child (all ages):**
60 – 120 units/kg intravenous infusion every 2 weeks adjusted according to response [1]

Administration: Consult local protocol or Summary of Product Characteristics (SPC)

Adult Drug Information

Indication: **Gaucher Disease I & III**

Dose: Initially 60 units/kg intravenous infusion every 2 weeks [10]. Maintenance doses to be adjusted according to response with doses as low as 15 units/kg intravenous infusion every 2 weeks being used but noting that at this dose, improvement is seen in haematological parameters and organomegaly but not bone parameters [10, 72]

LARONIDASE
(Aldurazyme®)

Action: Enzyme Replacement Therapy (ERT) – recombinant analogue human α-L-iduronidase [2, 73]

Indication: Mucopolysaccharidosis I (MPS I) [2, 73]

Preparation & supplier details: 100 units/mL concentrate for solution for infusion (5 mL) vial [Aldurazyme®]; Sanofi Genzyme

Funding notes: Commissioned by NHS England via national LSD centres [3]

Suggested local formulary status: Red – hospital only

Additional information: Store in a refrigerator [73]
Pre-treat approximately 60 mins before infusion with antihistamine and/or anti-pyretic to minimise infusion-related reactions [73]
To be given as an intravenous infusion over approx. 3 - 4 hours initially – consult local protocol or Summary of Product Characteristics (SPC) [73]
Monitor for immunoglobulin G (IgG) antibodies to laronidase [1]

Paediatric Drug Information

Dose: **Child (all ages):**

100 units/kg by intravenous infusion ONCE weekly [1, 2, 73]

Administration: Consult local protocol or Summary of Product Characteristics (SPC)

Adult Drug Information

Dose: 100 units/kg by intravenous infusion ONCE weekly [2, 10, 73]

Administration: Consult local protocol or Summary of Product Characteristics (SPC)

L-ARGININE (Arginine)

Action: Replenishes arginine and is a substrate/precursor for nitric oxide (NO) [2, 9]
Chaperone molecule in Pyruvate Dehydrogenase Deficiency (PDH) [74, 75]

Indication: Urea cycle disorders of which include: Ornithine Transcarbmylase (OTC) deficiency, Carbamylphosphate synthase I (CPSI) Deficiency, Citrullinaemia type I, Arginosuccinic aciduria (ASA), Citrullinaemia type II (Citrin deficiency), N-Acetyl glutamate synthase (NAGs) deficiency [2, 9]
Mitochondrial Encephalomyopathy, Lactic Acidosis, Stroke-like episodes (MELAS) [2, 9]
Pyruvate Dehydrogenase Deficiency (PDhH) [74, 75]
Patients on restricted diets who develop arginine deficiency

Preparation & supplier details: 500 mg capsules (500 capsules); Martindale Pharmaceuticals (U)
500 mg & 2-gram sachets (30 sachets); Vitaflo (U)
1-gram tablets (90 tablets); Lamberts (U)
100 mg/mL oral solution (200 mL); Veriton Pharma (Special Products) (U)
5 gram/10 mL (50 %) intravenous injection (10 amps); Veriton Pharma (Special Products) (U)

Funding notes: in tariff/PbR

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescriptions

Additional information: Injection may be given orally [8].
Vials are single use only.
Take with meals/feeds [1]
Monitor plasma pH and chloride [1] when given IV
As a precursor of nitric oxide can cause hypotension, flushing and vomiting – monitor BP [1]
Arginine can stimulate the release of insulin and glucagon – monitor blood sugar levels
Should not be given with nitrates.
Contraindicated in arginase deficiency [2]
Blood levels should be maintained between 50 – 200 micromol/L [8]
In obese patients it may be more appropriate to dose on body surface area than body weight [76]

Paediatric Drug Information

Indication: **Acute treatment of hyperammonaemia in OTC deficiency and CPSI deficiency**

Dose: **Child (all ages):** Generally, if unwell but tolerating orally, increase arginine dose to 150 mg/kg/day, orally, divided into 2 hourly doses [77]. If requires IV treatment, give 250 mg/kg/day as a continuous IV infusion and follow Individualised Patient Plan or BIMDG Emergency Guideline [77].

Indication: **Maintenance treatment of hyperammonaemia in OTC deficiency and CPSI deficiency**

Dose: **Neonate & child up to 20 kg**
100 – 250 mg/kg/day, orally, in 3 - 4 divided doses with meals/feeds [1, 2, 8, 9, 77]

Dose: **Child 20 kg and above**
2.5 – 6 g/m^2/day, orally, in 3 - 4 divided doses with meals/feeds, maximum of 6 grams a day [1, 8, 77]

Indication: **Acute treatment of hyperammonaemia in citrullinemia and ASA**

Dose: **Child (all ages):** Generally, if unwell and tolerating orally, increase arginine dose to 400 mg/kg/day, orally, divided into 2 hourly doses [78]. If requires IV treatment, give loading dose of 300 mg/kg as an IV infusion over 90 mins followed by 300 mg/kg/day as a continuous IV infusion, increasing to a maximum of 400 mg/kg/day [78].
Follow Individualised Patient Plan or BIMDG Emergency Guideline [78].

Indication: **Maintenance treatment of hyperammonaemia in citrullinaemia and ASA**

Dose: **Neonate & child up to 20 kg**
100 – 300 mg/kg/day, orally, in 3 - 4 divided doses with meals/feeds. Maximum of 6 grams a day [1, 2, 8]. Doses up to 800 mg/kg/day have been used in ASA but it is now discouraged [8, 79].

Dose: **Child 20 kg and above**
1.5 – 6 g/m^2/day, orally in 3 - 4 divided doses with meals/feeds, maximum of 6 grams a day [1, 8]

Indication: **Acute treatment of hyperammonaemia in NAGS deficiency**

Dose: **Child (all ages):** 150 mg/kg/day as a continuous IV infusion (no loading dose required) [80]
Follow Individualised Patient Plan or BIMDG Emergency Guideline [80]

Indication: **Acute treatment of hyperammonaemia due to unknown cause**

Dose: **Child (all ages):** Give loading dose of 150 mg/kg as an IV infusion over 90 mins followed by 300 mg/kg/day as a continuous IV infusion, increasing to a maximum of 500 mg/kg/day [81].
Follow BIMDG Emergency Guideline [81].

Indication: **Acute stroke associated with MELAS**

Dose: **Child (all ages):** 500 mg/kg (max. 30 gram) IV over 30 minutes within 3 hour of symptom onset 500 mg/kg/day as a continuous IV infusion for 3 – 5 days, then transfer to maintenance dose [82]
Maximum of 30 grams/day

Indication: **Maintenance dose following stroke associated with MELAS**

Dose: **Child (all ages):** 150 – 300 mg/kg/day, orally in 3 divided doses [82, 83]. Maximum of 24 grams/day [83].

Indication: **Chaperone therapy in PDH1A**

Dose: Experimental use and limited information, 2.8 grams a day of arginine (5 grams of arginine aspartate), orally in divided doses. Consult article for further information [83, 84].

Adult Drug Information

Indication: **Acute treatment of hyperammonaemia in OTC deficiency and CPSI deficiency**

Dose: 100 mg/kg/day as a continuous IV infusion.
Follow Individualised Patient Plan or BIMDG Emergency Guideline [76].

Indication: **Maintenance treatment of hyperammonaemia in OTC deficiency and CPSI deficiency**

Dose: Limited information - As per paediatric dosing information above, cap at 6 grams a day [1]

Indication:	**Acute treatment of hyperammonaemia in citrullinaemia and ASA**
Dose:	500 mg/kg/day as a continuous IV infusion. Follow Individualised Patient Plan or BIMDG Emergency Guideline [76].
Indication:	**Maintenance treatment of hyperammonaemia in citrullinaemia and ASA**
Dose:	Limited information - As per paediatric dosing information above, cap at 6 grams a day [1]
Indication:	**Acute treatment of hyperammonaemia in NAGs**
Dose:	100 mg/kg/day as a continuous IV infusion. Follow Individualised Patient Plan or BIMDG Emergency Guideline [76].
Indication:	**Acute stroke associated with MELAS**
Dose:	10 g/m^2 (30 gram max) as an IV over 30 mins within 3 hour of symptom onset followed by 10 g/m^2 as a continuous IV infusion for 3 – 5 days, then transfer to maintenance dose [82] . Maximum of 30 grams/day.
Indication:	**Maintenance dose following stroke associated with MELAS**
Dose:	150 – 300 mg/kg/day, orally in 3 divided doses [82, 83]. Maximum of 24 grams/day [83].

L-CARNITINE (Levocarnitine)

Action: An amino acid derivative [8] responsible for the removal of toxic acyl-CoA intermediates from within the mitochondria [2] and co-factor in fatty acid metabolism [2, 8]

Indication: **Primary carnitine deficiencies**, such as: Carnitine transporter deficiency, Carnitine palmitoyltrasferase (CPT I) deficiency, Carnitine acylcarnitine translocase (CACT) deficiency, Carnitine palmitoyltransferase II (CPT II) deficiency [2, 9]
Secondary carnitine deficiencies, such as: Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, Multiple acyl-CoA dehydrogenase (MAD) deficiency (Glutaric Aciduria II), Lysinuric protein intolerance (LPI) [2]; and Valproate induced carnitine deficiency [9, 85]
Organic acidaemias, such as: Isovaleric Aciduria (IVA), Propionic Aciduria (PA), Methylmalonic Aciduria (MMA) [1, 9, 85]

Preparation & supplier details: 100 mg/mL (10 %) oral solution, (10 mL); Mawdsley Brooks Ltd, Alliance Healthcare(U)
300 mg/mL (30 %) oral solution, (20 & 40 mL); Mawdsley Brooks Ltd, Alliance Healthcare
300mg/ml (30%) oral solution (20ml & 50ml), Cenotepharma (sugar- free and alcohol-free)
1-gram chewable tablets (packs of 10 tabs); AAH Pharmaceuticals
500 mg capsules (60 capsules); Lamberts **(**U), Alliance Healthcare
1 gram/5 mL Injection (5 x 5 mL) [Carnitor®]; DRUGSRUS Ltd.

Funding notes: NHSE commissioned/PbR excluded [3]

Suggested local formulary status: Red – hospital only

Additional information: Gastrointestinal side effects (nausea, vomiting, diarrhoea) are common and dose-related particularly, when given orally [1, 8]
Slow and persistent titration of oral doses, with less concentrated preparations, in frequent divided doses can aid toleration and compliance of carnitine therapy.
Fishy body odour can occur [1, 8] dose reduction, temporary cessation of therapy (if clinically appropriate) in hot weather can aid toleration and compliance of carnitine therapy.
Anecdotal evidence that riboflavin supplementation reduces fishy body odour associated with carnitine therapy [86]
Can be diluted in fruit juice or water if needed [8]
500 mg capsules [Lamberts brand] do not contain any carbohydrate and are therefore suitable for use in the ketogenic diet.
Do not give if cardiomyopathy or cardiac arrhythmias unless on the advice of metabolic consultant.

Paediatric Drug Information

Indication: **Primary Carnitine Deficiencies**

Dose: **Neonate & Child (all ages):**
100 [1, 2, 8, 9] – 400 [87] mg/kg/day, orally, in 2 – 4 divided doses [1, 2, 8]
100 mg/kg/day slow IV bolus over 2-3 minutes in 2 – 4 divided doses or can be given via continuous intravenous infusion as 100 mg/kg over 30 minutes, followed by 4 mg/kg/hour [1, 2, 8, 9]

***NOTE: BNFC suggests capping dose at maximum 3 g daily – in practice higher doses may be required – discuss with inherited metabolic team and review patient carnitine concentrations regularly.**

Indication: **Secondary Carnitine Deficiencies**

Dose: **Neonate & Child (all ages):**
100 – 200 mg/kg/day, orally, in 2 – 4 divided doses, maximum of 3 grams a day [1, 2, 8]
50 mg/kg/day, orally, in 2 – 4 divided doses may sufficient for chronic valproate induced carnitine deficiency, maximum of 3 grams a day [85]

Indication: **Organic Acidurias**

Dose: **Neonate & Child (all ages):**
100 – 200 mg/kg/day orally in 2 – 4 divided doses, maximum of 3 grams a day [1, 2, 8, 87]
100 mg/kg/day slow IV bolus over 2-3 minutes in 2 – 4 divided doses or can be given via continuous intravenous infusion as 100 mg/kg over 30 minutes, followed by 4 mg/kg/hour [1, 2, 8]

Nb. Patients with chronic renal failure given lower doses on advice of metabolic consultant

Indication: **Acute treatment of hyperammonaemia due to unknown cause**

Dose: **Child (all ages):** Give loading dose of 100 mg/kg as an IV infusion over 90 mins followed by 100 mg/kg/day as a continuous IV infusion, increasing to a maximum of 300 mg/kg/day [81]
Maximum of 3 grams a day
Follow BIMDG Emergency Guideline [81].

Indication: **Management of acute decompensation of MMA** [88]

Dose: 200 mg/kg/day, orally, in 2- 4 divided doses [88]
100 mg/kg IV over 30 mins as a loading dose followed by 4 mg/kg/hr as a continuous maintenance infusion, Maximum of 3 grams a day [88]

Indication: **Management of acute decompensation of IVA [89]**

Dose: 100 mg/kg/day, orally, in 2-4 divided doses, maximum of 3 grams a day [89]
100 – 200 mg/kg/day IV in 2-4 divided doses, maximum of 3 grams a day (slow IV bolus or over 24 hours via continuous intravenous infusion) [89]

Indication: **Management of acute decompensation of PA [90]**

Dose: 100 - 200 mg/kg/day, orally, in 2-4 divided doses, maximum of 3 grams a day [90]
4 – 8 mg/kg/hr as a continuous intravenous infusion, maximum of 3 grams a day [90]

Adult Drug Information

Indication: **Primary Carnitine Deficiencies**

Dose: 100 [2, 10] – 400 [87] mg/kg/day, orally, in 2 – 4 divided doses [2, 10]
100 mg/kg/day slow IV bolus in 2 – 4 divided doses [2, 10]
***NOTE: BNF suggests capping dose at maximum 3 g daily – in practice higher doses may be required – discuss with inherited metabolic team and review patient carnitine concentrations regularly.**

Indication: **Secondary Carnitine Deficiencies**

Dose: 100 – 200 mg/kg/day, orally, in 2 – 4 divided doses, maximum of 3 grams a day [2, 10]

Indication: **Management of acute decompensation of MMA & PA [91, 92]**

Dose: 100 mg/kg/day, orally, in 2-4 divided doses [91, 92]
100 mg/kg/day as a continuous intravenous infusion, maximum of 3 grams a day [91, 92]

L-CITRULLINE

Action: Replenishes the amino acids citrulline and arginine [2]

Indication: An alternative to l-arginine in Ornithine Transcarbamylase (OTC) deficiency, Carbamoylphosphate synthase I (CPSI) Deficiency [2, 8, 9]
Lysinuric protein intolerance (LPI) [2, 8, 9]

Preparation & supplier details: 200 mg and 1-gram sachets (30 sachets); Vitaflo (U), 100g Powder Nutricia via Alliance Healthcare Direct

Funding notes: in tariff/PbR

Suggested local formulary status: Red – hospital only

Additional information: Each sachet contains maltodextrin [8]
Mix each sachet with 20 mL of water, stirring well, allowing up to 3 minutes for full dissolution [8]
Sachets can be mixed with protein substitute/added to modular fees to facilitate administration. If part doses of sachets are needed, then add the corresponding volume of diluted solution before mixing [8]
Monitor citrulline levels to ensure in normal range [8]

Paediatric Drug Information

Indication: **OTC deficiency & CPSI deficiency**

Dose: **Neonate:**
150 mg/kg/day, orally, in 3 – 4 divided doses, adjusted according to response [1]
Child (all ages):
100 – 200 mg/kg/day, orally, in 3 - 4 divided doses [1, 2, 8, 9] OR
3.8 g/m^2/day, orally, in 3 - 4 divided doses [2]

Indication: **LPI**

Dose: **Child (all ages):**
50 – 100 mg/kg/day, orally in 3 – 5 divided doses [2, 8], doses up to 400 mg/kg/day have been used [8]

Adult Drug Information

Dose: Limited information – Consult paediatric information above

L-DOPA (Levodopa)

(Co-careldopa (Carbidopa/Levodopa))

Action: Replacement of the neurotransmitter [2]

Indication: Disorders of L-dopa synthesis *e.g.* tetrahydrobiopterin (BH_4) deficiencies, tyrosine hydroxylase (TH) deficiency,

(3)

Preparation & supplier details:
Co-careldopa (Carbidopa/Levodopa) 0.25 mg/1 mg/mL oral suspension (U)
Co-careldopa (Carbidopa/Levodopa) 1.25 mg/5 mg/mL oral suspension (U)
Oral suspensions as extemporaneous product or from The Specials Laboratory (PCCA Ltd.)
Co-careldopa (Carbidopa/Levodopa) 12.5mg/50 mg, 10 mg/100 mg, 25 mg/100 mg, 25mg/250 mg tablets, 25 mg/100 MR tablets and 50/200 mg tablets
Co-beneldopa (Benserazide/Levodopa) 12.5mg/50 mg, 25 mg/100 mg dispersible tablets, 25 mg/100 mg MR capsule, 12.5 mg/50 mg, 25 mg/100 mg, 50 mg/200 mg capsules

Funding notes: in tariff/PbR

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescriptions

Additional information:
Always given in combination with a DOPA decarboxylase inhibitor in a 1:4 DOPA decarboxylase inhibitor: levodopa ratio [2] namely, carbidopa or benserazide as co-careldopa and co-beneldopa respectively [10].
At high doses, consider a 1:10, carbidopa:levodopa preparation [8]
Use of co-careldopa is preferred in children.
Do not crush co-careldopa tablets for use of part doses of tablets in children. Co-careldopa is very slightly soluble in water [93] and will result in inaccurate dosing and increased risk of side effects if using part doses of tablets for the small doses required in children. Use liquid for doses less than a tablet size. Consider rounding dose to tablet size if appropriate.
Monitor CSF HVA levels and adjust dose accordingly alongside clinical response [2, 8]
Take after meals/food [8]
Side effects include: excessive daytime sleepiness, nausea, vomiting, postural hypotension. [1]
May cause sleep disturbances, keep last dose to early evening. See 5-hydroxytrptohan (Oxitriptan) for information when used in conjunction

Paediatric Drug Information

Indication: Disorders of L-dopa synthesis *e.g.* tetrahydrobiopterin (BH4) & dihydrobiopterin defects/deficiencies

Dose:
Neonate & Child (doses expressed as levodopa):
1 – 2 mg/kg/day, orally, in 4 divided doses, increasing every 4 – 5 days according to response; maintenance dose 10 - 12 mg/kg/day, orally, in 4 – 6 divided doses [1, 2, 8]. At higher doses consider a 1:10, carbidopa: levodopa preparation [1, 2]

Indication: L-dopa responsive dystonia

Dose:
Child (3 months – 17 years):
1 mg/kg/day, orally, in 3 divided doses, increased according to response every 2 – 3 days increased if necessary up to 3 – 5 mg/kg/day, orally, in 3 divided doses [1, 8, 94]. Occasionally, doses as high as 10 – 20 mg/kg/day, orally, in divided doses are required but genetic diagnostic confirmation is required before dose escalation [94]

Adult Drug Information

Indication: Limited information – Consult paediatric information above

Dose: Limited information – Consult paediatric information above

LIPOIC ACID (Thioctic acid)

(α-lipoic acid)

Action: Anti-oxidant [29] and co-factor in pyruvate dehydrogenase deficiency

Indication: Mitochondrial disorders [29, 95, 96]
Pyruvate Dehydrogenase (PDH) deficiency [79, 97, 98]

Preparation & supplier details: 300 mg tablets (pack of 90); Lamberts **(U)**
200 mg capsules (pack of 50); Solgar **(U),** 100mg capsules (pack of 90) by Nature's Bounty via Clinigen (U)

Funding notes: in tariff/PbR

Suggested local formulary status: Red – hospital only

Additional information: Lamberts' brand contains 9 mg of glycerine, check with ketogenic dietitian
Solgar brand contains nil carbohydrate and is suitable for the ketogenic diet.
Nature's Bounty brand contains rice powder, gelatine and cellulose.

Paediatric Drug Information

Dose: Limited information, 50 – 300 mg, orally, once a day [29, 95]

Adult Drug Information

Dose: Limited information – as per paediatric dosing but doses as high as 600 mg a day, orally, have been used [99, 100]

L-ISOLEUCINE

Action: Branched chain amino acid supplementation

Indication: Maple Syrup Urine Disease [2, 9]

Preparation & supplier details: 50 mg and 1000 mg sachets in packs of 30; Vitaflo (U)
100-gram powder; Nutricia (U)

Funding notes: in tariff/PbR

Suggested local formulary status: 50 mg sachets – Amber – hospital to initiate, GP to continue repeat prescriptions as per specialist dietetic advice [8]
1000 mg sachets – Red – hospital only [8]

Additional information: Intake must be frequently titrated against blood levels [8]
Mix sachet with usual MSUD amino acid supplement [8]
1000 mg sachets to be used on a named patient basis only for approved uses such as: high doses meaning 50 mg sachets would provide excessive carbohydrate, acutely unwell fluid restricted patients [8]
1000 mg sachets available from hospital pharmacy only [8]
Powder soluble in water with the addition of flavouring permitted [101]
Powder can be added to liquid or powdered formula (add before reconstitution) [101]
Aim for isoleucine values of 50 – 150 micromole/L [9]

Paediatric Drug Information

Dose: **Neonate and Child (all ages)**

20 – 120 mg/kg/day, orally, in divided doses [8] maximum of 300 – 400 mg/day [2]

Adult Drug Information

Dose: 300 – 400 mg/day [2]

L-LEUCINE

Action: Branched chain amino acid supplementation

Indication: Maple Syrup Urine Disease – **only used in very exceptional circumstances on direct advice by specialist IMD team only** [2]

Preparation & supplier details: 100 mg sachets in packs of 30; Vitaflo (U)
100-gram powder; Nutricia (U)

Funding notes: in tariff/PbR

Suggested local formulary status: Red – hospital only

Additional information: Dissolve each sachet in 20 mL of water, stir and allow up to 3 minutes for full dissolution.
Sachets can be mixed with protein substitute/added to modular fees to facilitate administration [102]
Powder soluble in water with the addition of flavouring permitted [103]
Powder can be added to liquid or powdered formula (add before reconstitution) [103]

Paediatric Drug Information

Dose:

Neonates (severe form):
80 – 110 mg/kg/day, orally in divided doses, (300 – 400 mg/kg/day), adjusted according to levels [2]

Child (classical form):
500 – 700 mg/kg/day orally in divided doses, adjusted according to levels [2]

Adult Drug Information

Dose: 500 – 700 mg/kg/day orally in divided doses, adjusted according to levels [2]

L-LYSINE

Action: Increase plasma lysine levels [2]

Indication: Lysinuric protein intolerance [2, 8]

Preparation & supplier details: 4-gram sachets in packs of 30; Vitaflo (U)
100-gram powder; Nutricia (U)
500mg tablets/capsules, Lamberts Healthcare Ltd.

Funding notes: in tariff/PbR

Suggested local formulary status: Red – hospital only

Additional information: Each sachet contains maltodextrin [8]
Dissolve each sachet in 20 mL of water, stir and allow up to 3 minutes for full dissolution [8]
Sachets can be mixed with protein substitute/added to modular fees to facilitate administration. If part doses of sachets are needed, then add the corresponding volume of diluted solution before mixing [8]
Can cause osmotic diarrhoea so start at a low dose and increase gradually according to tolerability [8]
Powder soluble in water with the addition of flavouring permitted
Powder can be added to liquid or powdered formula (add before reconstitution) [104]

Paediatric Drug Information

Dose: Start at 5 mg/kg/day, orally, in divided doses [8], gradually increasing to 10 – 20 mg/kg/day, orally, in divided doses as per plasma levels [8]. Dose up to 30 mg/kg/day in 3 divided doses have been used [1]

Adult Drug Information

Dose: Limited information – Consult paediatric information above. Adjust according to plasma levels.

L-METHIONINE

Action: Increase plasma methionine levels

Indication: Methionine synthase deficiency (CblG disease) [2, 8]

Preparation & supplier details: 500 mg tablets in packs of 100; Clinigen (U)
500mg capsules in packs of 60; Lamberts Healthcare Ltd (U)
100 mg sachets in packs of 30; Vitaflo (U)

Funding notes: in tariff/PbR

Suggested local formulary status: Red – hospital only

Additional information: Each sachet contains maltodextrin [8]
Dissolve each sachet in 20 mL of water, stir and allow up to 3 minutes for full dissolution [8]. Sachets can be mixed with protein substitute/added to modular fees to facilitate administration. If part doses of sachets are needed, then add the corresponding volume of diluted solution before mixing [8]

Paediatric Drug Information

Dose: 40 – 50 mg/kg/day, orally, in 2 – 4 divided doses [2, 8]. Doses up to 100 mg mg/kg/day, orally in divided doses have been used [8].

Adjust dose to maintain upper normal ranges of plasma and CSF methionine [8]

Adult Drug Information

Dose: Limited information – Consult paediatric information above. Adjust according to plasma levels.

LOMITAPIDE
(Lojuxta®)

Action: Selective inhibitor of microsomal transfer protein (MTP) reduces lipoprotein secretion and circulating concentrations of lipoprotein-borne lipids such as cholesterol and triglycerides. [204,205]

Indication: Homozygous Familial Hypercholesterolaemia [204,205]
Familial Chylomicronaemia Syndrome (compassionate) [208]

Preparation & supplier details: 5mg, 10mg, 20mg hard capsules, Amryt Pharmaceutical

Funding notes: Commissioned by NHSE for adults with homozygous familial hypercholesterolaemia [206,207]

Suggested local formulary status: Red – hospital only

Additional information:
To be taken at least two hours after evening meal.[204,205]
Adjustments required with some statins. With atorvastatin: separate the dose of the medicines by 12 hours or reduce the dose of lomitapide by half. With simvastatin: maximum dose of 40mg simvastatin.[204,205]
Start at 5mg OD and titrate up as tolerated, depending on Liver Function test results [204]
Metabolised by CYP3A4 – check with you pharmacist for drug interactions [204]
Do not drink grapefruit juice (food-drug interaction) [204]
Consult SPC for dose adjustment in renal impairment [204,205]
Consult SPC for dose adjustment if abnormal LFTs occur [204,205]
Lomitapide reduces the absorption of vitamin E and fatty acids – supplementation is indicated [204,205]
Monitor LFTs at baseline, monthly and before each dose increase in the first year of treatment, then at least 3 monthly and before each dose increase in the subsequent years of treatment [204,205]
Screen for hepatic steatosis & fibrosis before treatment and annually whilst on treatment [204,205]
To be used in conjunction with a low fat diet (<20% energy from fat) to reduce the occurrence and severity of gastrointestinal reactions with lomitapide.[204,206]

Paediatric Drug Information

No information available

Adult Drug Information

Dose: 5 mg, orally ONCE daily for 2 weeks; then increase if necessary to 10 mg, orally, ONCE daily for at least 4 weeks; then increase to 20 mg, orally, ONCE daily for at least 4 weeks; then increase in steps of 20 mg, orally, ONCE daily adjusted at intervals of at least 4 weeks to a maximum of 60 mg per day [204,205]

L-ORNITHINE

Action: Competitive inhibitor of Arginine: Glycine amidinotransferase (AGAT) thereby reducing guanidinoacetate production [2]

Indication: Guanidinoacetate methyltransferase (GAMT) deficiency [2]

Preparation & supplier details: L-ornithine aspartate [Hepa Merz], orange flavoured 3-gram sachets (packs of 100);
Clinigen (U)
500mg capsules, Lamberts healthcare.

Funding notes: in tariff/PbR

Suggested local formulary status: Red – hospital only

Additional information: Dissolve each sachet in of water, stir and allow up to 3 minutes for full dissolution [8]
Sachets can be mixed/added to modular feeds to facilitate administration [8]
Use in conjunction with creatine supplementation (dietary restriction of arginine and sodium benzoate also have been used as adjuncts) [8, 9]

Paediatric Drug Information

Dose: 100 – 800 mg/kg/day, orally, in divided doses [2, 8, 9]

Adult Drug Information

Dose: Limited information – Consult paediatric information above. Adjust according to plasma levels.

L-PHENYLALANINE

Action: Amino acid precursor for tyrosine and monoamine neurotransmitters [2]

Indication: Phenylalanine load test for the investigation of dopamine responsive dystonia and disorders of tetrahydrobiopterin [105]
Phenylalanine supplementation in Tyrosinaemia type 1 [106]

Preparation & supplier details: 500 mg capsules, packs of 60; Lamberts Healthcare Ltd. **(U)**

Funding notes: in tariff/PbR

Suggested local formulary status: Red

Additional information: **For phenylalanine load test:** Prepare in orange juice. Do not use milk, add protein or products containing aspartame [105]. Ensure phenylalanine is completely consumed by rinsing out the glass if necessary with further orange juice. Physiological response is not affected by L-dopa.

Paediatric Drug Information

Indication: Phenylalanine supplementation, *e.g.* Tyrosinaemia type 1 [106]

Dose: Titrated to target plasma phenylalanine concentration.

Indication: Phenylalanine load test [105]

Dose: 100 mg/kg as a single dose, orally, prepared in orange juice as above [105]

Adult Drug Information

Dose: Limited information – Consult paediatric information above. Adjust according to plasma levels.

L-SERINE

Action: Replenishment of the amino acid serine [2, 9]

Indication: Serine deficiency disorders (3-phosphoglycerate dehydrogenase deficiency; phosphoserine aminotransferase deficiency; 3-Phosphoserine phosphatase deficiency) [2, 9, 107]

Preparation & supplier details: 100-gram powder; Nutricia **(U)**

Funding notes: in tariff/PbR

Suggested local formulary status: Red – hospital only

Additional information: Glycine can be added alongside L-serine if seizures persist [2, 9, 107]
L-serine was given to a pregnant mother where the foetus was known to be affected with 3-phosphoglycerate dehydrogenase deficiency at a dose of 5 grams, orally TDS (190 mg/kg/day) [2, 108]

Paediatric Drug Information

Dose: 200 – 700 mg/kg/day, orally, in 6 divided doses [2, 9, 107]. Milder phenotypes respond to dose in the range of 100 – 150 mg/kg/day, orally, in divided doses without glycine [2]. Adjust according to plasma levels.

Adult Drug Information

Dose: Limited information – Consult paediatric information above. Adjust according to plasma levels.

Further references

Pineda, M., Vilaseca, M.A., Artuch, R., Santos, S., 2000. 3-phosphoglycerate dehydrogenase deficiency in a patient with West syndrome. *Developmental Medicine & Child Neurology* 42, pgs. 629 – 633

L-VALINE

Action: Branched chain amino acid supplement [8]

Indication: Maple Syrup Urine Disease (MSUD) [2, 8]

Preparation & supplier details: 50 mg & 1000 mg sachets in packs of 30 **(U)**; Vitaflo
100-gram powder **(U)**; Nutricia

Funding notes: in tariff/PbR

Suggested local formulary status: 50 mg sachets – Amber – hospital to initiate, GP to continue repeat prescriptions as per specialist dietetic advice [8]
1000 mg sachets – Red – hospital only [8]

Additional information: Intake must be frequently titrated against blood levels [8]
Mix sachet with usual MSUD amino acid supplement [8]
1000 mg sachets to be used on a named patient basis only for approved uses such as: high doses meaning 50 mg sachets would provide excessive carbohydrate, acutely unwell fluid restricted patients [8]
1000 mg sachets available from hospital pharmacy only [8]
Powder soluble in water with the addition of flavouring permitted [109]
Powder can be added to liquid or powdered formula (add before reconstitution) [109]

Paediatric Drug Information

Dose: 20 – 120 mg/kg/day, orally, in divided doses, adjusted according to levels [2]. Minimum valine requirements are usually 200 – 250 mg/day [2, 8]
Cap at 250 mg/day Maximum requirements can be occasionally increased to 300 – 400 mg, orally, per a day in divided doses, in the recovery phase to help stimulate protein synthesis [2]

Adult Drug Information

Dose: Limited information – Consult paediatric information above. Adjust according to plasma levels.

MANNOSE (D-mannose)

Action: Improves glycosylation [2]

Indication: Mannosephosphate isomerase deficiency (MPI-CDG) also known as CDG-Ib or PMI deficiency

Preparation & supplier details: Powder, 50 gram **(U)**; The Specials Laboratory (PCCA Ltd.)
Powder, 250 gram **(U)**; Nutricia via AAH Pharmaceuticals

Funding notes: in tariff/PbR

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescriptions

Additional information: D-mannose, a naturally-occurring hexose, a stereoisomer to glucose.

Paediatric Drug Information

Dose: 1 gram/kg/day, orally, in 4 – 6 divided doses [2]

Adult Drug Information

Dose: Limited information – Consult paediatric information above. Adjust according to plasma levels.

MEFOLINIC ACID (Calcium Mefolinate)

Action: Increases the availability of 5- methyltetrahydrofolate [2, 40, 53]

Indication: Severe 5,10-methylene-tetrahydrofolate reductase (MTHFR) deficiency [2, 53]

Preparation & supplier details: 15 mg tablets [Prefolic] 30 tablets **(U)**; Zambron Pharmaceuticals via Clinigen Healthcare Ltd. and Mawdsley's.

Funding notes: in tariff/PbR

Suggested local formulary status: Red – hospital only

Additional information: Take care when prescribing and dispensing to ensure CALCIUM MEFOLINATE (MEFOLINIC ACID) is supplied and not calcium folinate (folinic acid) – dispensing/prescribing errors have occurred.

Paediatric Drug Information

Dose: 15 – 60 mg, orally, ONCE a day [53]

Adult Drug Information

Dose: 15 – 60 mg, orally, ONCE a day [53]

MERCAPTAMINE (Cysteamine)

Action: Depletes lysosomal cystine

Indication: (Nephropathic) Cystinosis [110]

Preparation & supplier details: Cystagon 50 mg & 150 mg hard capsules; Recordati Rare Diseases UK Ltd.
Procysbi 25 mg & 75 mg GR capsules; Chiesi Ltd.
Cystadrops 3.8 mg/mL eye drop solution: Recordarti Rare Diseases UK Ltd.
Mercaptamine 0.55 % eye drops (U); Guys & St. Thomas' NHS Foundation Trust

Funding notes: Cystagon 50 mg & 150 mg hard capsules - NHSE commissioned/PbR excluded [3]
Procysbi 25 mg & 75 mg GR capsules – not commissioned/IFR only in England and Scotland [3]
Procysbi commissioned in Wales[215]
Cystadrops 0.38 % eye drops - not commissioned/IFR only [3]
Mercaptamine 0.55 % eye drops PF - NHSE commissioned/PbR excluded [3]

Suggested local formulary status: Red – hospital only

Additional information: Cysteamine has an unpleasant taste and smell and can affect body odour and breath [8]
Capsules can be opened and contents sprinkled onto soft food or into drink, but due to strong, unpleasant taste, choose strong flavours [8]
Cysteamine capsules = bitartrate salt, mercaptamine 0.55% eye drops = hydrochloride salts [8]

Take with food [110]. White cell cystine levels should be monitored regularly to assess efficacy [1, 8]. Mercaptamine has been confused with mercaptopurine. Care must be taken to ensure the correct drug is prescribed and dispensed. The unlicensed 0.55% eye drops are not viscous and may need to be used more frequently e.g. every waking hour or 6 to 8 times a day[216]

Paediatric Drug Information

Indication: **(Nephropathic) Cystinosis (Cystagon only)**

Dose: **Neonate – Child (< 50 kg):**
Initially one-sixth to one quarter of the expected maintenance dose, gradually increased over 4 – 6 weeks to avoid intolerance [1, 8, 110]
Maintenance dose: 1.3 g/m^2/day, orally, in 4 divided doses (maximum of 2 grams/day) [1, 8, 110]

Child (> 50 kg):
Initially one-sixth to one quarter of the expected maintenance dose, gradually increased over 4 – 6 weeks to avoid intolerance [1, 8, 110]
Maintenance dose: 2 grams, orally, in 4 divided doses [1, 8, 110]

For dosing information on Procysbi refer to the SPC.

Indication: **Corneal cystine deposits in patients with cystinosis**

Dose: 1 drop into EACH eye FOUR times a day[1]. Dose may be reduced according to response [1]

Adult Drug Information

Indication: **(Nephropathic) Cystinosis (Cystagon only)**

Dose: **> 50 kg:**
Initially one-sixth to one quarter of the expected maintenance dose, gradually increased over 4 – 6 weeks to avoid intolerance [10, 110]

Maintenance dose: 2 grams, orally, in 4 divided doses [10, 110]

For dosing information on Procysbi refer to the SPC.

Indication: **Corneal cystine deposits in patients with cystinosis**

Dose: 1 drop into EACH eye FOUR times a day [1]
1 drop FOUR time a day (3.8mg/ml eye drops only).

For dosing information on Procysbi refer to the SPCs.

MERCAPTOPROPIONYLGLYCINE (Tiopronin)

Action: Chelating agent [2]

Indication: Cystinuria and associated cystine nephrolithiasis [2, 111]

Preparation & supplier details: 100 mg tablets (100 tablets); [Thiola©] **(U);** import from Japan via Clinigen**,** 100mg delayed release tablets (Ascot Laboratories)

Funding notes: Not commissioned - IFR only [3]

Suggested local formulary status: Red – hospital only

Additional information:
LFTs, FBCs, Zinc, Copper & urinary protein excretion monitoring is required [2]
Urinary cystine should be measured 1 month after starting treatment and every 3 months thereafter [112]
Captopril may be used as an alternative (less effective but less toxic) [2]
Dose should be adjusted to reduce urinary cystine levels to below the solubility limit (< 250 mg/L) [111]
To be taken 1 hour before or 2 hours after a meal/food [111, 112]
To be used alongside treatments that alkalinise the urine and increased water intake as directed by doctor [2, 3, 111]

Paediatric Drug Information

Dose:
Child 9 – 17 years:
15 mg/kg/day, orally, in 3 divided doses up to a maximum of 1 gram/day, orally, in 3 divided doses [2, 111, 112]

Adult Drug Information

Dose:
800 mg/day, orally, in 3 divided doses up to a maximum of 1 gram/day, orally, in 3 divided doses [2, 111, 112]

METRELEPTIN

Action: Recombinant human leptin analogue used in states of leptin deficiency [185].

Indication: Adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy:

- with confirmed congenital generalised lipodystophy (*Berardinelli-Seip syndrome*) or acquired generalised lipodystophy (*Lawrence syndrome*) in adults and children 2 years of age and above
- with confirmed familial partial lipodystophy or acquired partial lipodystophy (*Barraquer-Simons syndrome*), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control. [185]

Congenital leptin deficiency (off-label) [186]

Preparation & supplier details: 3mg vial, 5.8mg vial, 11.3mg vial [Myalepta®]; Amryt Pharmaceuticals [185]

Funding notes: NHSE commissioned/PbR excluded (all forms) for both above indications [186,187], separate Blueteq forms for each indication

Suggested local formulary status: Red – hospital only

Additional information: All vials are reconstituted to a 5mg/mL concentration; doses are commonly expressed in millilitres. [186]
Vials are for single use only. [185]
Store in a refrigerator (2°C – 8°C). [185]

Paediatric Drug Information

Indication: Lipodystrophy (≥2 years of age with generalised lipodystrophy, or ≥12 years of age with partial lipodystrophy) [185]

Dose:

Baseline weight	Starting daily dose (injection volume)	Dose adjustments (injection volume)	Maximum daily dose (injection volume)
Males and females ≤ 40 kg	0.06 mg/kg (0.012 mL/kg)	0.02 mg/kg (0.004 mL/kg)	0.13 mg/kg (0.026 mL/kg)
Males > 40 kg	2.5 mg (0.5 mL)	1.25 mg (0.25 mL) to 2.5 mg (0.5 mL)	10 mg (2 mL)
Females > 40 kg	5 mg (1 mL)	1.25 mg (0.25 mL) to 2.5 mg (0.5 mL)	10 mg (2 mL)

Indication: Congenital leptin deficiency (off-label) [186]

Dose: Limited information - The starting dose in children is calculated to achieve 10% of the predicted normal peak serum leptin concentration (0.028 milligrams per kilogram of lean body mass daily in a reported case). Injected ONCE or TWICE daily.

Adult Drug Information

Indication: Lipodystrophy (generalised or partial) [185]

Dose: Consult paediatric information above

Indication: Congenital leptin deficiency (off-label) [186]

Dose:	Limited information - in adults the dose is titrated to achieve normal leptin concentrations (2.8 – 5.3 mg daily in reported cases). Injected ONCE or TWICE daily.

METRONIDAZOLE

Action: Antibiotic with high activity against anaerobic bacteria gut thereby reducing intestinal propionate production [2, 10]

Indication: Propionic acidaemia and methylmalonic acidaemia [2, 9]

Preparation & supplier details: 200 mg & 400 mg tablets (21 tablets)
200 mg/5 mL oral suspension, 100 mL; Rosemont Pharmaceuticals Ltd.

Funding notes: PbR/in tariff

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescriptions

Additional information: Use tablets dispersed in water for patients on concomitant gastric acid suppressant drugs *e.g.* PPIs and H_2-antagonsists. This is because suspensions are formulated as the benzoate salt and requires low (acidic) pH for absorption [8]. For this reason, metronidazole suspension is unsuitable in those patients with diarrhoea (reduced GI transit time) and for jejunal enteral feeding tubes [8]
Metronidazole interacts with alcohol and should not be used together and for 48 hours following the last dose of metronidazole [8, 10]. For this reason, care should be taken dispensing metronidazole suspension to ensure the preparation does not contain alcohol [10].
Reduce dose in hepatic impairment [8, 10]
For PA and MMA, give DAILY or CYCLICALLY *i.e.* daily for 10 days each month [2, 8]
Metronidazole reduces urinary excretion of propionate metabolites by 40 % [2]
Long term cyclical/intermittent metronidazole therapy may be as effective as continuous treatment and prevent side effects of the drug such as leukopenia, peripheral neuropathy, and pseudomembranous colitis [2,217]

Paediatric Drug Information

Dose: 7.5 – 20 mg/kg/day, orally, 1 – 3 divided doses a day CONTINUOUSLY or for 10 consecutive days each month [2, 8, 9]
Doses usually given in 2 – 3 divided doses [8]
Maximum dose 400 mg TDS or 1200 mg/day [8]

Adult Drug Information

Dose: Limited information – Consult paediatric information above

MIGALASTAT
(Galafold©)

Action: A pharmacological chaperone that binds to that active sites of certain mutant forms of alpha galactosidase A, thereby stabilising in the endoplasmic reticulum and facilitating normal trafficking to lysosomes [10]

Indication: Fabry's disease, (also known as Anderson-Fabry disease and α-galactosidase A deficiency) [10, 113]

Preparation & supplier details: 123 mg hard capsules, (14; capsules) [Galafold©]; Amicus Therapeutics Europe Ltd.

Funding notes: Commissioned by NHS England via national LSD centres [3]

Suggested local formulary status: Red – hospital only

Additional information: Take at the same time on ALTERNATE days [1, 10, 113]
Take on an empty stomach and do not take with food – do not consume food for at least 2 hours before and 2 hours after taking migalastat to give a minimum 4 hours fast [113]
Clear liquids, including carbonated drinks, can be consumed during this period [113]
Absorption is reduced by 40 % when taken with food [113].
If a dose is missed (entirely for the day, *i.e.* not within 12 hours that dose is normally taken) the missed dose should not be taken, but instead, the dose should be taken on the normal day at the normal time (not to be taken on 2 consecutive days) [10]

Paediatric Drug Information

Dose: **Child 12years and older:**
123 mg, orally, on ALTERNATE days [1,113]

Adult Drug Information

Dose: 123 mg, orally, on ALTERNATE days [10, 113]

MIGLUSTAT

Action: Inhibitor of glucosylceramide synthase, the first enzyme of glycosphingolipid (GSL) synthesis [1, 2, 10]

Indication: Gaucher Disease Type I (mild – moderate) where enzyme replacement therapy is unsuitable [1, 2, 10]. Late onset Pompe disease (in combination with Cipaglusoidase Alfa). Niemann Pick C Disease (progressive neurological manifestations) [1, 2, 10, 114]

Preparation & supplier details: 100 mg hard capsules, (84 capsules) [Zavesca©]; Janssen-Cilag Ltd. & Accord Healthcare Ltd. & AAH Pharmaceuticals Ltd. &Flynn Pharma Lts. & Sovereign Medical Ltd. & Piramal Ltd. [10]
65mg hard capsules (Opfolda®). Amicus Therapeutics

Funding notes: Commissioned by NHS England via national LSD centres for Gaucher disease type I, Neimann-Pick type C and late onset Pompe disease. [3] Not routinely commissioned in Tangier disease.

Suggested local formulary status: Red – hospital only

Additional information: Temporary dose reduction may be required due to diarrhoea [10, 114]
A reduced disaccharide diet can reduce severity of diarrhoea [114]
Avoid if eGFR less than 30ml/minute/1.73^2. Consult product literature for dose adjustments.
Effective contraception should be used during treatment and men should not father children for 3 months following treatment [10, 114]
Growth retardation has been reported as a side effect [1, 114]
Monitor cognitive & neurological function; platelet count and growth [1]
Miglustat is soluble in water. Capsules can be opened and their contents dispersed in water to make an oral solution [115] contact Janssen-Cilag for advice on this.
Specific to Opfalda® brand: food must not be consumed 2hr before and 2hrs after administration. If dose is missed give as soon as possible, cipaglucosidase infusion to be started 1hr after administration of Opfalda® [10]

Paediatric Drug Information

Indication: **Niemann Pick C Disease (progressive neurological manifestations) [1, 114]**

Dose:

Child 4 – 11 years [1, 114]

BSA (< 0.48 m^2)	100 mg, orally, ONCE a day
BSA (0.48 – 0.73 m^2)	100 mg, orally, TWICE a day
BSA (0.74 – 0.88 m^2)	100 mg, orally, THREE times a day
BSA (0.89 – 1.25 m^2)	200 mg, orally, TWICE a day
BSA (1.26 m^2 & above)	200 mg, orally, THREE times a day

Child 12 – 17 years [1, 114]
200 mg, orally, THREE times a day

Adult Drug Information

Indication: **Gaucher disease type I (mild – moderate)**

Dose: 100 mg, orally, THREE times a day reducing to ONCE or TWICE a day if not tolerated [2, 10, 114]

Indication: **Niemann Pick C Disease (progressive neurological manifestations)**

Dose: 200 mg, orally, THREE times a day [10, 114]

Indication: Late Onset Pompe Disease with Cipaglucosidase alfa [(2)].

Dose: **Patients weighing 50kg or more [(2)]**

260mg, orally, 1 hour before the start of the Cipaglucosidase alfa infusion, on an empty stomach (2 hours fasting before and after).

Patients weighing 30kg or more and less than 50kg [2]

195mg, orally, 1 hour before the start of the Cipaglucosidase alfa infusion, on an empty stomach (2 hours fasting before and after).

Indication: Tangier Disease [3].

Dose: 200mg, orally, THREE times a day

NICOTINAMIDE
(Vitamin B_3)

Action: Amide derivative of vitamin B_3 (niacin/nictonic acid) to replenish nicotinamide deficiency due to tryptophan deficiency [2]

Indication: Hartnup disease [2, 9]

Preparation & supplier details: 100 mg tablets, in packs of 100; Nutrition Warehouse Ltd. (U)
500 mg tablets, in packs of 100**;** Clinigen (U)

Funding notes: PbR/in tariff

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescriptions

Additional information: Not licensed for indication

Paediatric Drug Information

Dose: Limited information 50 – 300 mg/day, orally, in divided doses [2, 9, 116]
Not licensed in children less than 12 years of age [116]

Adult Drug Information

Indication: 50 – 300 mg/day, orally in divided doses [2, 9, 116]

NITISINONE (NTBC)

Action: Competitive Inhibition of 4-hydroxyphenylpyruvate dioxygenase [2, 9, 117]

Indication: Tyrosinaemia type I [1, 2, 8, 9, 117]
Alkaptonuria (adults only) **(avoid in pregnancy)** [2, 9]

Preparation & supplier details: Orfadin 2 mg, 5 mg, 10 mg, 20 mg hard capsules (60 capsules) and 4 mg/mL oral suspension (90 mL) [Orfadin©]; Swedish Orphan Biovitrum Ltd
Nitisinone Dipharma 2mg, 5 mg, 10 mg & 20mg hard capsules; Logixx Pharma Solutions Ltd.

Funding notes: NHSE commissioned/PbR excluded [3]

Suggested local formulary status: Red – hospital only

Additional information: Ophthalmology examination and review (slit-lamp examination) indicated prior to starting treatment and annually thereafter [8, 117]
Full Blood Count (FBCs) prior to starting treatment and 6 monthly thereafter [1, 8, 117]
Regular Liver Function Tests (LFTs) [1, 8, 117]
To be used alongside a tyrosine and phenylalanine restricted diet to maintain a plasma tyrosine of 200 – 400 micromole/L [2]
Additional therapeutic drug monitoring (TDM) includes urine succinylacetone, alpha-fetoprotein and occasionally urine 5-aminolevulinate (ALA) and erythrocyte porphobilinogen (PBG)-synthase activity [117]; If available blood spot or plasma NTBC and succinlyacetone levels.
Refer to SPC for further information
Take capsules 1 hour before food/feed and suspension with food/feed [1, 8, 117, 118]
Capsules can be opened and the contents suspended in a small amount of water or formula diet and taken immediately [1, 117, 118]
Store suspension in fridge (2 – 8 °C) [118]
Shake bottle of oral suspension vigorously (20 seconds for first use, and at least 5 seconds for subsequent uses) to allow adequate re-dispersion of oral suspension [118]
Orfadin capsules do not contain gelatine

Paediatric Drug Information

Indication: **Tyrosinaemia Type I**

Dose: Initially 1 mg/kg/day, orally, in 2 divided doses adjusted according to response to a maximum of 2 mg/kg/day [1, 2, 8, 9, 117]. Dose can be given as a ONCE daily dose instead of 2 divided doses once initial clinical status has resolved [2, 117]

Adult Drug Information

Indication: **Tyrosinaemia Type I**

Dose: Initially 1 mg/kg/day, orally, in 2 divided doses adjusted according to response to a maximum of 2 mg/kg/day [2, 9, 10, 117]. Dose can be given as a ONCE daily dose instead of 2 divided doses [2, 117]. **Avoid in pregnancy** [2, 10, 117]

Indication: **Alkaptonuria**

Dose: 2 mg, orally, once daily is used [119]

OCTREOTIDE

Action: Somatostatin analogue [2]

Indication: Congenital & persistent hyperinsulinism [2] unresponsive to diazoxide and glucose [1]

Preparation & supplier details: Solution for injection (vials):
50 micrograms/mL (1 mL), 100 micrograms/mL (1 mL), 200 micrograms/mL (5 mL), 500 micrograms/mL (1 mL)
Solution for injection (pre-filled syringes):
500 micrograms/mL

Funding notes: NHSE commissioned/PbR excluded [3]

Suggested local formulary status: Red – hospital only

Additional information: Octreotide infusions should be withdrawn slowly, halving the rate every 6 - 12 hours [8]
For subcutaneous or intravenous infusion, dilute with sodium chloride 0.9 % to not less than 1:1 and not more than 1:9 by volume (all vials sizes and strengths) [1, 8]
Syringe must be replaced every 8 hours (8-hour expiry from dilution) [8, 120]

Paediatric Drug Information

Dose:

Neonate:
2 – 5 micrograms/kg, by subcutaneous injection, every 6 – 8 hours adjusted according to response, increasing if necessary to 7 microgram/kg every 4 hours (7 microgram/kg dose, rarely required) [1, 2]

Child > 1 month:
1 – 2 microgram/kg, by subcutaneous injection, every 4 – 6 hours adjusted according to response, increasing if necessary to 7 microgram/kg every 4 hours (7 microgram/kg dose, rarely required) [1, 2]

Total daily dose can be given as a continuous infusion (subcutaneous or intravenous) [2, 8]

Adult Drug Information

Dose: No dose for above indications, dose as per paediatric dosing. Adult dosing for other indications, refer to BNF

OLIPUDASE ALFA
(Xenpozyme®)

Action: Recombinant human acid sphingomyelinase

Indication: Treatment of non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) in paediatric and adult patients with type A/B or type B.

Preparation & supplier details: 20mg vials for infusion, Sanofi Ltd.

Funding notes: Pending decision

Suggested local formulary status: Red – hospital only

Paediatric Drug Information

Dose: The recommended maintenance dose of Xenpozyme is 3 mg/kg* every 2 weeks FOLLOWING dose escalation phase (see below):

Dose escalation phase
The recommended starting dose of Xenpozyme is 0.03 mg/kg* for paediatric patients, and the dose should be subsequently increased according to the dose escalation regimen presented in Table 2:

Table 2: Dose escalation regimen in paediatric patients

Paediatric patients (0 to <18 years old)	
First dose (Day 1/Week 0)	0.03 mg/kg*
Second dose (Week 2)	0.1 mg/kg*
Third dose (Week 4)	0.3 mg/kg*
Fourth dose (Week 6)	0.3 mg/kg*
Fifth dose (Week 8)	0.6 mg/kg*
Sixth dose (Week 10)	0.6 mg/kg*
Seventh dose (Week 12)	1 mg/kg*
Eighth dose (Week 14)	2 mg/kg*
Ninth dose (Week 16)	3 mg/kg* (recommended maintenance dose)

**Actual body weight will be used for patients with a BMI ≤ 30. For patients with a BMI > 30, an optimal body weight will be used as described below.*

Adult Drug Information

Dose: The recommended maintenance dose of Xenpozyme is 3 mg/kg* every 2 weeks FOLLOWING dose escalation phase (see below):

Dose escalation phase:
The recommended starting dose of Xenpozyme is 0.1 mg/kg* for adults (also see missed doses subsection for additional guidance) and subsequently, the dose should be increased according to the dose escalation regimen presented in Table 1:

Table 1: Dose escalation regimen in adults

Adult patients (≥18 years old)	
First dose (Day 1/Week 0)	0.1 mg/kg*
Second dose (Week 2)	0.3 mg/kg*

Third dose (Week 4)	0.3 mg/kg*
Fourth dose (Week 6)	0.6 mg/kg*
Fifth dose (Week 8)	0.6 mg/kg*
Sixth dose (Week 10)	1 mg/kg*
Seventh dose (Week 12)	2 mg/kg*
Eighth dose (Week 14)	3 mg/kg* (recommended maintenance dose)

**Actual body weight will be used for patients with a BMI ≤ 30. For patients with a BMI > 30, an optimal body weight will be used as described below.*

Maintenance phase

*Actual body weight will be used for patients with a BMI ≤30. For patients with a BMI > 30, an optimal body weight will be used as described below.

PANTOTHENIC ACID
(Vitamin B_5)

Action: Co-factor for the synthesis of co-enzyme A and metabolism of proteins, carbohydrates and fats [121]

Indication: Barth syndrome, previously known as 3-methylglutaconic aciduria type II [2, 18]

Preparation & supplier details: 550 mg capsules (50); Solgar, **(**U)
500 mg capsules as calcium pantothenate (60); Lamberts Healthcare Ltd., (U)

Funding notes: in tariff/PbR

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescriptions

Additional information: No longer recommended in 6th Edition of Saudubray
The value of pantothenic acid has not been proven [122]

Paediatric Drug Information

Dose: 15 – 150 mg/kg/day, orally, in 3 divided doses[18]

Adult Drug Information

Dose: Limited information – Consult paediatric information above

PEGUNIGALSIDASE ALFA

(Elfabrio®)

Action: Enzyme Replacement Therapy -Pegylated recombinant form of human α-galactosidase [211].

Indication: Fabry disease (also known as Anderson-Fabry disease / α-galactosidase A deficiency) [211].

Preparation & supplier details: 2mg/ml (10mL) concentrate for solution for infusion [211]. Chiesi Limited.

Funding notes: Commissioned by NHS England via specialist centres; Technology appraisal guidance (TA915) [212].

Suggested local formulary status: Red – Hospital only.

Additional information: Licensed for adult patients with confirmed diagnosis of Fabry Disease.
Store in a refrigerator at 2 - 8 ° C [211].
The company provides it according to the commercial arrangement [212].

Adult Drug Information

Dose: 1mg/kg every 2 weeks via intravenous infusion [211].

Administration: Initial infusion time should be at least 3 hours [211].
Infusion rate can be increased gradually by reducing infusion by 30 minutes every third infusion if tolerated [213].
Total volume depends on patient's body weight [211].
Consult local protocol or Summary of Product Characteristic (SPC).

PENICILLAMINE (D-penicillamine)

Action: Chelating agent to aid elimination of copper ions in the urine [1, 2]

Indication: Wilson Disease [1, 2, 8, 9]
Cystinuria [1, 2, 8]

Preparation & supplier details: 125 mg & 250 mg (56 tablets)

Funding notes: in tariff/PbR

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescriptions

Additional information: Patients who are hypersensitive to penicillin may react rarely to penicillamine [1, 123]
Dose adjustment is required in renal impairment [1]
Monitor FBCs weekly for 1st 2 months of treatment or after any dose increase. Withdraw if platelet count falls below 120,000/mm^3, or white blood cells below 2500/mm^3, or if 3 successive falls within reference range. Restart at reduced dose once back in reference range.
Many patients with hepatic involvement with WD may have low platelet counts as a result of hypersplenia. Discuss management with specialist WD team and agree individual guidelines for these patients. Similarly, leukopenia may be a feature of hepatic involvement. Always relate WBC to norms for the patient's ethnic origin [124].
Permanent withdrawal may be indicated if leucopenia or thrombocytopenia reoccurs; any decision to withdraw should be in discussion with specialist WD team [1, 8, 124]
Monitor for proteinuria - weekly for 2 months and then monthly thereafter [1, 8]. Transient proteinuria (and occasionally haematuria) are not indications for cessation of therapy (and may be a feature of WD pre-treatment) but persistent heavy proteinuria (>2 g/d) should lead to cessation [8, 124]
Always check spot- and 24h urine protein pre-treatment [124]
Counsel the patient on the awareness and identification of blood disorders. Inform doctor immediately if sore throat, infection, non-specific illness, unexplained bruising or bleeding, purpura, mouth ulcers or rashes occur [1, 8, 124].
Take on an empty stomach at least 1 hour before food [1, 124].
In Wilson's disease, interaction between penicillamine and pyridoxals leading to increased excretion of vit. B6 is a theoretical possibility. Supplemental pyridoxine may be given [2, 8, 124].
Avoid concurrent administration of any drug with penicillamine (including pyridoxine, and especially zinc salts) [124].
25 % of patients demonstrate side effects and toxic reactions, of which 50 % of these patients require cessation of therapy [2].
Well-controlled patients WD or cystinuric patients on penicillamine often resent having to attend for monthly FBC and urine monitoring. The BNF recognises that "Longer intervals may be adequate in [each condition]." Shared care guidelines should reflect this flexibility. GPs should be advised by the WD or Cystinuria specialist team as to the frequency of monitoring appropriate to the individual patient. In some UK WD centres, patients are only monitored at their annual visit [124].

Paediatric Drug Information

Indication: **Wilson Disease**

Dose: **1 month – 11 years:** initially 10 mg/kg/day, orally, in 2 divided doses, increasing at 2-week intervals if tolerated to 20 mg/kg/day, orally, in 2 divided doses, maximum of 2 grams a day [1, 2, 8]. The usual adult maintenance dose is 1 gram a day; some predominantly hepatologically affected patients may require a higher dose [124]

Give concomitant pyridoxine, 10 mg, orally, ONCE a day [8].

Child 12 – 17 years: 20 mg/kg/day, orally, in 2 divided doses [1, 2]. Usual maintenance dose is 0.75 – 1 gram/day, orally, in 2 divided doses, maximum of 2 grams a day [1, 2]. The usual adult maintenance dose is 1 gram a day; some predominantly hepatologically affected patients may require a higher dose [124]

Give concomitant pyridoxine, 25mg, orally, ONCE a day [2].

Indication: **Cystinuria**

Dose: Initially, 5 mg/kg/day, orally, for 1 week [1, 2, 8], then increase gradually to 20 – 30 mg/kg/day, orally, in 2 divided doses, [1, 2, 8]. Adjust dose to maintain urinary cysteine < 200 mg/L [8] or 24-hour urinary cysteine < 1 mmol/L [1]. The usual adult maintenance dose is 0.5 – 1.5 grams/day, maximum of 3 grams/day [1, 124]. Ensure adequate fluid intake [1]. Long-term administration of daily doses significantly greater than 1 gram a day may lead to significant skin changes (*cutis laxa* and *elastosis perforans serpiginosa*) [124].

Adult Drug Information

Indication: **Wilson Disease**

Dose: 1.5 – 2 grams/day, orally, in 2 divided doses, adjusted according to response [10].
The usual adult maintenance dose is 1 gram a day, orally in 2 divided doses; some predominantly hepatologically affected patients may require more. After some years of treatment it may be possible to reduce the dose to 0.75 gram/day [2, 10, 124]
Minimum dose: 500 mg/day (1), Maximum dose: 2grams/day [2, 10]
A dose of 2 grams a day should not be continued for more than 1 year [10]
In the elderly, a dose of 20 mg/kg in divided dose should be used, similar to paediatric dosing [10]
To improve tolerability, consider starting at 250 mg/day, orally, in divided doses, increasing in 250 mg increments every 4 – 7 days [2]

Give concomitant pyridoxine, 25mg, orally, ONCE a day [2]

Indication: **Cystinuria (treatment)**

Dose: 1 – 3 grams/day, orally, in 3 – 4 divided doses; adjust dose to maintain urinary cysteine < 200 mg/L[2, 10]. The usual adult maintenance dose is 0.5 – 1.5 grams/day. Doses up to 4 grams a day have been used [2]. Long-term administration of daily doses significantly greater than 1 gram a day may lead to significant skin changes (*cutis laxa* and *elastosis perforans serpiginosa*) [124].

Indication: **Cystinuria (prophylactic)**

Dose: 0.5 – 1 gram/day, orally, at bedtime, adjusting to maintain urinary cysteine < 300 mg/L [10]. Maintain adequate fluid intake (3 L/day) [10]. For elderly patients, the minimum dose to maintain urinary cysteine <200mg/L is recommended [10].

PYRIDOXAL-5-PHOSPHATE (P5P/PLP)

Action: Active vitamin B_6 vitamer (active co-factor involved in over 140 reactions for neurotransmitter metabolism [2, 9]

Indication: Pyridox(am)ine 5'-phosphate oxidase (PNPO) deficiency [2, 9]

Preparation & supplier details: 50 mg tablets (50 tablets); Solgar (U)
25 mg tablets (90 tablets); Nutri Advanced brand (U)
50 mg capsules (100 capsules); Mawdsley's (U), Clinigen (U)

Funding notes: in tariff/PbR

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescriptions

Additional information: Round dose to quarter or half of tablet which can then be crushed and dispersed in water [8]
Not very soluble in water, therefore 10 mL may be needed per tablet for dissolution [8]
Sudden respiratory arrest and profound hypotension can occur, therefore commence treatment within working hours and always ensure adequate resuscitation equipment is available, *i.e.* ideally initiate on HDU/NICU/PICU [8]
Blood pressure, pulse, respiratory rate, oxygen saturation should be observed at baseline and then every 15 minutes for 3 hours following the first dose [8]
Use immediately after preparation of a dose to avoid photodegradation [125]
Monitor LFTs (transaminases) and use lowest effective dose [2, 126]

Paediatric Drug Information

Dose: 30 – 60 mg/kg/day, orally, in 4 – 6 divided doses [2, 8, 9, 126, 127]
Round dose to quarter or half a tablet [8]

Adult Drug Information

Dose: Limited information – Consult paediatric information above

PYRIDOXINE
(Vitamin B_6)

Action: Co-factor precursor where the active co-factor is involved in over 140 reactions for neurotransmitter metabolism [2, 9]

Indication:
Pyridoxine responsive homocystinuria (cystathionine β-synthase (CBS) deficiency) [2, 9, 128]
Non-pyridoxine responsive homocystinuria (cystathionine β-synthase (CBS) deficiency)
Pyridoxine Dependent Epilepsy (PDE), also known as Antiquitin deficiency [2, 9]
Pyridoxine responsive Ornithine aminotransferase (OAT) deficiency [2, 9]
Primary hyperoxaluria type I [2, 129]
Prevention of pyridoxine deficiency in the treatment of Wilson disease with penicillamine [2]
Non-ketotic hyperglycinaemia (genotype dependent) [2]
Hyperprolinaemia type II [2, 9]
X-linked sideroblastic anaemia [2]

Preparation & supplier details:
10 mg (packs of 28) and 50 mg tablets (packs of 28); AAH Pharmaceuticals
50 mg/mL injection; South Devon Healthcare NHS Trust

Funding notes: in tariff/PbR

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescriptions

Additional information:
Tablets can be quartered, halved and crushed and dispersed in water
IV pyridoxine: risk of cardiovascular collapse, resuscitation facilities must be readily available [8]

Risk of reversible peripheral neuropathy with long term, high doses of pyridoxine, therefore dose should remain less than 300 mg/day where possible [2], certainly less than 500 mg a day in children [128] and 1 gram in adults [128, 130]

Paediatric Drug Information

Indication: **Assessment of pyridoxine responsiveness in homocystinuria (cystathionine β-synthase (CBS) deficiency)**

Dose: All ages including neonate: 10 mg/kg/day, orally, in 2 divided doses (minimum of 100 mg/day, maximum of 500 mg/day) for a maximum of 6 weeks [1, 2, 128, 131]

Indication: **Pyridoxine responsive homocystinuria (CBS deficiency) maintenance dose**

Dose: Following assessment of responsiveness, gradually adjust to lowest dose that achieves tHcy < 50 micromole/L [128]

Indication: **Partial pyridoxine responsive homocystinuria (CBS deficiency) maintenance dose**

Dose: Following assessment of responsiveness, gradually adjust to lowest dose that achieves tHcy < 50 micromole/L in addition to diet and betaine [2, 128]

Indication: **Pyridoxine Dependent Epilepsy (PDE), also known as Antiquitin deficiency**

Dose: Initially by slow IV injection over 5 minutes, 100 mg, repeated daily for up to 3 days, with concurrent EEG monitoring to assessment [1, 2, 8, 9,183]
For maintenance dose convert to oral, generally in the range of 50 – 100 mg ONCE a day [1, 8] but adjusting as necessary. Maintenance 5-30mg/kg/day (max 500mg/day; infants 30mg/kg/day, max 300mg) [183]. Doses up to 30 mg/kg/day may be required [1, 2, 9] maximum of 1 gram/day in divided doses [1, 2, 8]

If IV route not appropriate, then 200 mg, daily, in divided doses, as a therapeutic trial for up to 7 days, adjusting the dose to a maintenance dose as above [8]

To prevent breakthrough seizures, double dose in the first 3 days of an intercurrent infection [2]

Indication: **Pyridoxine responsive Ornithine aminotransferase (OAT) deficiency [2, 9]**

Dose: 200 – 500 mg/day, orally in divided doses [2, 9]

Indication: **Primary hyperoxaluria type I**

Dose: 3 – 5 mg/kg/day, orally, in divided doses, increasing to 15 mg/kg/day in divided doses [129]
Only 10 – 40 % of patients will respond (dependent on genotype) [129]

Indication: **Prevention of pyridoxine deficiency in the treatment of Wilson disease with penicillamine**

Dose: Child 1 month – 11 years: 10 mg, orally, ONCE a day [1, 8]
Child 11 – 17 years: 25 mg, orally, ONCE a day [2]

Indication: **Non-ketotic hyperglycinaemia (genotype dependent)**

Dose: Dose not specified

Indication: **Hyperprolinaemia type II**

Dose: Epilepsy may respond to 50 mg, orally ONCE a day [2, 9]. Doses of 10 mg/kg/day, orally in divided doses can be used, maximum of 500 mg [9].

Indication: **X-linked sideroblastic anaemia**

Dose: Initially, 300 mg/day, orally, in 2 divided doses, followed by a maintenance dose of 100 mg, orally ONCE daily [2]

Adult Drug Information

Indication: **Assessment of pyridoxine responsiveness in homocysteinuria (cystathionine β-synthase (CBS) deficiency)**

Dose: 10 mg/kg/day, orally, in 2 divided doses, rounded to the nearest tablet, (maximum of 500 mg/day) for a maximum of 6 weeks [1, 2, 128]

Indication: **Pyridoxine responsive homocystinuria (CBS deficiency) maintenance dose**

Dose: Following assessment of responsiveness, gradually adjust to lowest dose that achieves tHcy < 50 micromole/L [128]

Indication: **Partial pyridoxine responsive homocystinuria (CBS deficiency) maintenance dose**

Dose: Following assessment of responsiveness, gradually adjust to lowest dose that achieves tHcy < 50 micromole/L in addition to diet and betaine [2, 128]

Indication: **Hyperhomocystinuria [9, 128]**

Dose: 100 mg, orally, ONCE a day [9]

Indication: **Pyridoxine Dependent Epilepsy (PDE), also known as Antiquitin deficiency [2, 9]**

Dose: Maintenance dose in the range of 50 – 100 mg ONCE a day [8] but adjusting as necessary. Doses up to 30 mg/kg/day may be required [2, 9] maximum of 1 gram/day in divided doses [1, 2, 8].

Indication:	**Pyridoxine responsive Ornithine aminotransferase (OAT) deficiency** [2, 9]
Dose:	200 – 500 mg/day, orally in divided doses [2, 9]
Indication:	**Prevention of pyridoxine deficiency in the treatment of Wilson's disease with penicillamine**
Dose:	25 mg, orally, ONCE a day [2]

RIBOFLAVIN
(Vitamin B_2)

Action: Co-enzyme in a number of different enzyme systems [2, 8]

Indication:
Variants of Electron transfer Flavoprotein Defects (ETF/ETF-DH) causing Multiple acyl-CoA dehydrogenase deficiency (MADD) (Glutaric aciduria type II) [2, 9]
Riboflavin responsive complex I deficiency [2, 8]
Brown-Vialetto-van-Laere syndrome [2]
Short chain acyl-CoA dehydrogenase deficiency (SCADD) [2]
RFVT1 riboflavin transporter deficiency [2]
FAD transporter defect & FAD synthase deficiency [2]
Dihydrolipoamide dehydrogenase deficiency [2]
L-2-hydroxyglutaric aciduria [2]
Trimethylaminuria (TMA) [2]
Methylenetetrahydrofolate reductase (MTHFR) deficiency (677TT genotype) [2, 132, 133]
Carnitine induced fishy body odour [134]

Preparation & supplier details:
50 mg capsules (100 capsules); Lamberts **(U)**
100mg tablets (pack of 100) by Nature's Bounty via Clinigen (U)
No IV preparation available

Funding notes: in tariff/PbR

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescriptions

Additional information:
Open capsules and disperse contents in water
Can discolour urine yellow (harmless) [1]
May interfere with laboratory analysis of other tests (inform lab of riboflavin supplementation) [8]

Paediatric Drug Information

Indication: **Multiple acyl-CoA dehydrogenase deficiency (MADD) (Glutaric aciduria type II)**

Dose: **All ages, including neonates:** 50 mg, orally, THREE times a day [2, 9].

Indication: **Riboflavin responsive complex I deficiency (caused by ACAD9 deficiency)**

Dose: 50 mg, orally, TWICE to THREE times a day [2, 135]. Doses of 400 mg/day in divided doses have been used [2, 8, 9]

Indication: **Brown-Vialetto-van-Laere syndrome (Riboflavin Transporter (RFVT) 2 & 3 defects)**

Dose:
RFVT3: 10 mg/kg/day, orally in divided doses [2]
RFVT2: 50 mg/kg/day, orally, in divided doses, maximum of 1.5 grams/day [2]

Indication: **Short chain acyl-CoA dehydrogenase deficiency (SCADD); RFVT1 riboflavin transporter deficiency; FAD transporter defect & FAD synthase deficiency; Dihydrolipoamide dehydrogenase deficiency; L-2-hydroxyglutaric aciduria; Trimethylaminuria (TMA)**

Dose: No dose specified, consider an empirical dose of 100 – 400 mg/day, orally, in divided doses [2]

Indication: **Fishy body odour associated with levocarnitine therapy**

Dose: 50 mg, orally TWICE a day [134]

Indication:	**Methylenetetrahydrofolate reductase (MTHFR) deficiency**
Dose:	1.6 mg, orally ONCE a day (from results in trial [132, 133]), maximum of 10 mg/day [9]. In clinical practice a minimum dose of 50 mg, orally ONCE a day is used.

Adult Drug Information

Dose:	Limited information – Consult paediatric information above

SACROSIDASE

Action: Yeast-derived form of the enzyme sucrase breaks down sucrose in the body.

Indication: **Congenital sucrase-isomaltase deficiency (CSID)**[188]

Preparation & supplier details: 11,600units/ml x60ml bottles (invertase), Newcastle Specials production line.
2x 118ml bottle pack available (sucraid), Optum Frontier therapies (USA).
2ml single-use container packs available (for patients of body weight >15Kg), Optum Frontier therapies (USA).

Funding notes: IFR

Suggested local formulary status: Red- Hospital only

Additional information: Stored in refrigerator. Refrigerated storage for invertase brand not usually required.[190]
Half dose to be taken before meals and remainder during meals.
Invertase available from UK and Sucraid brand available from USA manufacturer may have different dosing and storage requirements.

Paediatric Drug Information

Indication: As per above

Dose: Limited information- consult product literature

Adult Drug Information

Indication: As per above

Dose: Limited information- consult product literature

SAPROPTERIN (BH_4)

Action: Synthetic replacement of tetrahydrobiopterin (BH_4), a cofactor of the hydroxylases for phenylalanine, tyrosine and tryptophan [2, 136]

Indication: Responsive forms of Phenylketonuria (PKU) (Phenylalanine Hydroxylase (PAH) Deficiency) [2]
Tetrahydrobiopterin deficiency, *e.g.* Guanosine triphosphate cyclohydrolase I (GTPCH) deficiency; 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency [1, 2, 9, 136]

Preparation & supplier details: 100 mg dispersible tablets (30, 120 and 240 tablets) [Kuvan©]; BioMarin International Ltd. Teva Ltd.

Funding notes: Commissioned by NHSE for Adults and Children with phenylketonuria, via Blueteq.[184]
Commissioned for Adults and Children with tetrahydrobiopterin BH4 deficiencies via Blueteq.[184]

Suggested local formulary status: Red – hospital only

Additional information: 100 mg of sapropterin dihydrochloride (equivalent to 77 mg of sapropterin) [136]
The daily dose should be rounded to the nearest multiple of 100 mg (tablet) [136]
Take with food/meals to maximise absorption [136]
Refer to the dosing tables in the Summary of Product Characteristics (SPC)
Tablets should be dissolved in water (see SPC for volumes) and be taken within 20 minutes [1]
For use in PKU, it is important conduct an appropriate trial of responsiveness. There is a consensus pathway for commencing Sapropterin on BIMDG website. Genetic testing can help identify those who will not be responsive (those with 2 null mutations). It is important to ensure patients are taking maximum tolerated PHE exchanges prior to testing. International guidelines on response testing have been published [138]

Paediatric Drug Information

Indication: **Responsive forms of Phenylketonuria (PKU) (Phenylalanine Hydroxylase (PAH) Deficiency)**

Dose: Initially, 10 mg/kg, orally, ONCE a day, in the MORNING, with breakfast, adjusted according to blood phenylalanine and tyrosine levels [2, 136]. Usual maintenance dose is 5 – 20 mg/kg/day, orally, adjusted according to response [1, 2, 136]

Refer to the dosing tables in the Summary of Product Characteristics

Indication: **Tetrahydrobiopterin deficiency**

Dose: 2 – 5 mg/kg, orally, ONCE a day, in the MORNING, with breakfast, adjusted according to response [1, 136]. Maximum dose is 20 mg/kg/day [1, 136]. Total daily dose may be taken in 2 – 3 divided doses [1]

Adult Drug Information

Indication: **Responsive forms of Phenylketonuria (PKU) (Phenylalanine Hydroxylase (PAH) Deficiency) and tetrahydrobiopterin deficiency**

Dose: As per paediatric dosing [10, 136]

Indication: **Maternal Phenylketonuria (PKU)**

Dose: As per paediatric dosing and strict dietary control. See NHSE commissioning policy E12/P/a for further information [139]

SELEGILINE

Action: Monoamine-oxidase-B inhibitor [2, 10]

Indication: Adjunct to therapy with 5-hydroxytryptophan and co-careldopa/L-DOPA in tetrahydrobiopterin (BH_4) defects *e.g.* Guanosine triphosphate cyclohydrolase I (GTPCH) deficiency; 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency, dihydropterin reductase (DHPR) deficiency [2]

Preparation & supplier details: 5 mg, 10 mg tablets (100 tablets)

Funding notes: in tariff/PbR

Suggested local formulary status: Red – hospital only

Additional information: Caution of the cheese reaction: acute hypertensive crisis can occur when high dose selegiline is given with tyramine rich foodstuffs *e.g.* mature cheese, salami, yeast extracts (Marmite, Bovril *etc.*), fermented foods (beers, lagers and wines) [10]
The aim for the addition of selegiline is to reduce the dose and frequency of amine replacement medication, improve residual symptoms and prevent diurnal variation [2]
Side effects of levodopa may increase with the introduction of selegiline – consider reducing the concurrent dose of levodopa by 10 – 30 % in steps of 10 % every 3- 4 days [10]

Paediatric Drug Information

Indication: Tetrahydrobiopterin (BH_4) defects: Guanosine triphosphate cyclohydrolase I (GTPCH) deficiency; 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency, dihydropterin reductase (DHPR) deficiency [2]

Dose: 0.1 – 0.25 mg/kg/day, orally, in 3 – 4 divided doses [2]. Give alongside co-careldopa and 5-hydroxytryptophan [2]. Maximum dose of 10 mg/day [10].

Adult Drug Information

Dose: Limited information – Consult paediatric information above

SODIUM BENZOATE

Action:

Ammonia scavenger – provides an alternative pathway for the detoxification of ammonia by combining with glycine to form hippuric acid. Hippuric acid has high renal clearance, thereby reducing blood ammonia [2]
Reduction of glycine levels in Non-Ketotic hyperglycinaemia (NKH) [2]
Reduction of glycine levels for guanidinoacetate synthesis in Guanidinoacetate methyltransferase (GAMT) deficiency [2]

Indication:

Hyperammonaemia due to Urea Cycle Defects (UCDs) of which include: Ornithine Transcarbamylase (OTC) deficiency, Carbamoylphosphate synthase I (CPSI) Deficiency, Citrullinaemia type I, Arginosuccinic aciduria (ASA), Citrullinaemia type II (Citrin deficiency), N-Acetyl glutamate synthase (NAGs) deficiency [2, 8]
Hyperammonaemia due to Fatty Oxidation Disorders (FAODs), Organic Acidurias [2, 8, 9]
Non-Ketotic hyperglycinaemia (NKH) [2, 8, 9]
Guanidinoacetate methyltransferase (GAMT) deficiency [2]
Hyperammonemia of unknown or other causes

Preparation & supplier details:

500 mg/5 mL oral solution (100 mL); Veriton Pharma **(U)**
1.5g/5ml oral solution, (U), IPS Pharma, Nova labs
500 mg tablets (100); Veriton Pharma **(U)**
2 gram/5 mL solution for injection (5 mL x 10); Veriton Pharma **(U)**

Funding notes:

in tariff/PbR

Suggested local formulary status:

Injection	Red – hospital only
Oral liquid and tablets	Amber – hospital to initiate, GP to continue repeat prescriptions

Additional information:

Gastrointestinal side effects (nausea, vomiting and reflux) are common and can be reduced by giving smaller doses more frequently; with feeds/food (less soluble in acidic drinks); and with the use of concurrent acid suppressant medications [1, 8]
Caution when using in neonates as can cause kernicterus [8, 9]
Contains significant amounts of sodium (7mmols sodium per 1 gram of sodium benzoate), care in heart and/or renal failure [8, 9]. Monitor U & Es and blood pressure.
Injection can be given orally [8]
Intravenous Y-site compatibility with sodium benzoate, sodium phenylbutyrate and arginine at 50 mg/mL in 10 % glucose [8, 140, 141]
Intravenous admixture compatibility with sodium phenylbutyrate [141]
500 mg tablets (Veriton Pharma) contain nil carbohydrate and are preferred in the ketogenic diet (crush and disperse tablets).
1 mmol of nitrogen is *theoretically* removed by 1 mmol of sodium benzoate [1, 8]
Sodium benzoate oral solution contains Propylene Glycol 18mg/ml[184]

Paediatric Drug Information

Indication:

Acute treatment of hyperammonaemia in OTC deficiency and CPSI deficiency

Dose:

Child (all ages): Generally, if unwell but tolerating orally, can consider increasing dose from regular dose (maximum of 500 mg/kg/day), divided into 2 hourly doses to prevent nausea and vomiting [142]. If requires IV treatment, give loading dose of 250 mg/kg as an IV infusion over 90 minutes (if naïve to drug), followed by 250 mg/kg/day continuous IV infusion [142].
Follow Individualised Patient Plan from Metabolic specialist or BIMDG Emergency Guideline [142].

Indication:	**Acute treatment of hyperammonaemia in citrullinaemia and ASA**
Dose:	**Child (all ages):** Generally, if unwell but tolerating orally, can consider increasing dose from regular dose (maximum of 500 mg/kg/day), divided into 2 hourly doses to prevent nausea and vomiting [143]. If requires IV treatment, give loading dose of 250 mg/kg as an IV infusion over 90 minutes (if naïve to drug), followed by 250 mg/kg/day (max 500 mg/kg/day) continuous IV infusion [143]. Follow Individualised Patient Plan from Metabolic specialist or BIMDG Emergency Guideline [143].
Indication:	**Acute hyperammonaemia due to Propionic Acidaemia (PA) & Methylmalonic Acidaemia (MMA)**
Dose:	**Child (all ages):** 250 mg/kg/day, (max 500mg/kg/day), as a continuous intravenous infusion [144]. Follow Individualised Patient Plan form Metabolic Specialist or BIMDG Emergency Guideline
Indication:	**Acute hyperammonaemia due to N-acetylglutamate (NAGs) deficiency**
Dose:	**Child (all ages):** If tolerating orally, double the patient's normal dose of sodium benzoate [145] Would not give loading if already on it: If requires IV treatment, give 250 mg/kg as an IV infusion over 90 minutes followed by 250 mg/kg/day continuous IV infusion (maximum of 500mg/kg/day) [145]. Follow Individualised Patient Plan or BIMDG Emergency Guideline
Indication:	**Acute hyperammonaemia due to Hyperornithinaemia, Hyperammonaemia, Homocitrullinuria (HHH) and Lysinuiric Protein Intolerance (LPI)**
Dose:	**Child (all ages):** 250 mg/kg/day, as a continuous intravenous infusion [146]. Follow Individualised Patient Plan or BIMDG Emergency Guideline
Indication:	**Maintenance dose to control hyperammonaemia in Urea Cycle Defects (UCDs)**
Dose:	150 – 500 mg/kg/day, orally, in 3 - 4 divided doses [1, 2, 9]. Maximum of 12 grams a day [1], higher (18 grams/day) capping doses have been used anecdotally.
Indication:	**Non-Ketotic hyperglycinaemia (NKH)**
Dose:	250 – 750 mg/kg/day, orally, in 3 – 6 divided doses, maximum 12 grams/day [2, 9]
Indication:	**Guanidinoacetate methyltransferase (GAMT) deficiency**
Dose:	100 mg/kg/day, orally in 3 – 6 divided doses maximum 16 grams/day [2, 38]

Adult Drug Information

Indication:	**Acute treatment of hyperammonaemia in OTC deficiency, CPSI deficiency, citrullinaemia, ASA arginase deficiency, NAGs deficiency**
Dose:	250 mg/kg/day continuous IV infusion [147] Follow Individualised Patient Plan or BIMDG Emergency Guideline [147]
Indication:	**Maintenance dose to control hyperammonaemia in Urea Cycle Defects (UCDs)**
Dose:	250 mg/kg/day, orally, in 3 - 4 divided doses [2, 9]. Maximum of 12 grams a day [1], higher (18 grams/day) capping doses have been used anecdotally.
Indication:	**Non-Ketotic hyperglycinaemia (NKH)**
Dose:	250 – 750 mg/kg/day, orally, in 3 – 6 divided doses, maximum 12 grams/day [2, 9]

Indication:	**Guanidinoacetate methyltransferase (GAMT) deficiency**
Dose:	100 mg/kg/day, orally in 3 – 6 divided doses maximum 16 grams/day [2, 38]

SODIUM BICARBONATE

Action: Alkalinising agent - increases blood pH

Indication: Metabolic and/or renal acidosis [1]

Preparation & supplier details: 500 mg (6 mmol) capsules, (100 capsules); AAH Pharmaceuticals
600 mg (7 mmol) tablets, (100 capsules); AAH Pharmaceuticals
8.4 % (1 mmol/ml) oral solution (100 mL); AAH Pharmaceuticals (3-day expiry after opening)
8.4 % (1 mmol/mL) oral solution (100 mL); Mandeville Medicines **(U)** (7-day expiry after opening)

Funding notes: in tariff/PbR

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescriptions

Additional information: Unlicensed liquid has 7-day expiry after opening vs. 3-day expiry for licensed
Capsules can be opened and contents, dispersed in water.
Monitor pH and electrolytes [1]

Paediatric Drug Information

Dose: **Child (all ages):** 1 – 2 mmol/kg/day, orally, in divided doses, adjusted according to response [1, 8]

For intravenous dosing and administration, consult local protocol

Adult Drug Information

Dose: Approx. 57 mmol/day, orally, in divided doses [10], *i.e.*, 18 mmols (3 x 500 mg capsules), orally, THREE times a day adjusted according to response

For intravenous dosing and administration, consult local protocol

SODIUM DICHLOROACETATE (DCA)

Action: Dichloroacetate is a structural analogue of pyruvate and inhibits pyruvate dehydrogenasekinase (PDHK/E1 kinase) activity, thereby retaining any residual E1 kinase activity of the pyruvate dehydrogenase complex (PDHC) in its active (dephosphorylated form). Ultimately, PDHC remains in its active form [2]

Indication: Primary lactic acidosis [2]
Pyruvate Dehydrogenase Complex (PDHC) deficiency [1, 2]

Preparation & supplier details: 50 mg/mL powder for reconstitution for oral solution (200 mL); Xeal Pharma(U)

Funding notes: in tariff/PbR

Suggested local formulary status: Red – hospital only

Additional information: Only available orally (No IV preparation)
May cause polyneuropathy with prolonged use [1, 2]
Can affect oxalate metabolism (unknown frequency) [2]
Excipients include: sodium benzoate, aspartame, sodium saccharin
3-month expiry from date of manufacture.
To be used in conjunction with thiamine and ketogenic diet for PDHC deficiency [2]
Phenylbutyrate in combination with sodium dichloroacetate was shown to increase PDHC activity in mice acting as a chaperone. *Nb.* Phenylbutyrate is not commissioned for this indication [2]

Paediatric Drug Information

Indication: **Primary Lactic Acidosis and Pyruvate Dehydrogenase Complex (PDHC) deficiency**

Dose: 25 mg/kg/day, orally in 2 divided doses [2]
or
50 mg/kg/day, orally in 4 divided doses, adjusted according to response and increasing to 200 mg/kg/day if necessary [1]

Adult Drug Information

Dose: Limited information – Consult paediatric information above

SODIUM D,L-3-HYDROXYBUTYRATE

Action: Replaces deficient endogenous ketone body production in Multiple acyl-CoA dehydrogenase deficiency (MADD) (Glutaric aciduria type II) [2]
Alternative fuel source, allowing a reduction in carbohydrate intake for those with Glycogen Storage Disease type III (GSDIII) [2]

Indication: Glycogen Storage Disease type III (GSDIII)
Multiple acyl-CoA dehydrogenase deficiency (MADD) (Glutaric aciduria type II)

Preparation & supplier details: Powder (50 gram); Veriton Pharma (Special Products Ltd.) **(U)**
Local Manufacturing Unit can make powder in to 100 mg/mL oral solution **(U)**

Funding notes: in tariff/PbR

Suggested local formulary status: Red – hospital only

Additional information: Only available orally (No IV preparation)
Possibly protects against cardiomyopathy in GSDIII [2]
May improve cardiomyopathy and leukodystrophy in MADD (Glutaric aciduria type II) [2]
The isomer, L-3-hydroxybutyrate, does not occur naturally but is provided by the DL racemic mixture [2]
Anecdotal (G. Gillett & T. Hopkins, Sheffield) use of Butane-1,3-diol as an alternative to sodium D,L-3 hydroxybutyrate when it is unavailable, or when such high doses are needed, the sodium load is too high. It is sodium free and pH neutral.

Paediatric Drug Information

Indication: **Glycogen Storage Disease type III (GSDIII)**

Dose: Refer to: Derks, T.G.J, Smit, G.P.A., 2015. Dietary management in glycogen storage disorder disease type III: what is the evidence? *J Inherit Metab Dis* 38: 545 – 550 [148]

Indication: **Multiple acyl-CoA dehydrogenase deficiency (MADD) (Glutaric aciduria type II)**

Dose: 300 – 600 mg/kg/day, orally, in 5 - 8 divided doses [2]. Doses up to 900 mg/kg/day in three divided doses have been used [149]

Adult Drug Information

Dose: Limited information – Consult paediatric information above

SODIUM PHENYLBUTYRATE

Action: Ammonia scavenger – phenylbutyrate, a pro-drug, is metabolised to phenylacetate, which combines with glutamine to form phenylglutamine which has high renal clearance. This is an alternative pathway for the detoxification of ammonia and thereby reduces blood ammonia [2, 150]

Indication: Hyperammonaemia due to Urea Cycle Defects (UCDs) of which include: Ornithine Transcarbmylase (OTC) deficiency, Carbamoylphosphate synthase I (CPSI) Deficiency, Citrullinaemia type I, Arginosuccinic aciduria (ASA), Citrullinaemia type II (Citrin deficiency), N-Acetyl glutamate synthase (NAGs) deficiency [2]
Hyperammonaemia due Fatty Acid Oxidation Disorders (FAODs), Acidurias [2, 9]
Hyperammonemia of unknown or other cause

Preparation & supplier details: 483 mg/g [Pheburane] granules, (packs of 174 g); Eurocept International.
250 mg/mL powder for reconstitution for oral suspension (100 mL); Veriton Pharma (Special Products) **(U)**
2 gram/10 mL solution for injection (10 mL x 10 amps); Veriton Pharma (Special Products) **(U)**

Funding notes: NHSE commissioned/PbR excluded (all forms) [3]

Suggested local formulary status: Red – hospital only

Additional information: Injection can be given orally [8]
Gastrointestinal side effects (nausea, vomiting, abdominal pain and reflux) are common [1] and can be reduced by: giving smaller doses more frequently; with feeds/food; and with the use of concurrent acid suppressant medications [1, 8]
Contains a significant amount of sodium: 500 mg of sodium phenylbutyrate provides 2.7 mmol of sodium [8]
Risk of hypernatremia, therefore monitor U & Es, blood pressure and use cautiously in renal and/or cardiac failure [8, 151]
Refer to respective Summary of Product Characteristics (SPC) for detailed information on the use of Ammonaps granules and Pheburane granules
Intravenous Y-site compatibility with sodium benzoate, sodium phenylbutyrate and arginine at 50 mg/mL in 10 % glucose [8, 141, 151]
Intravenous admixture compatibility with sodium benzoate [141]
2 mmol of Nitrogen is *theoretically* removed by 1 mmol of sodium phenylbutyrate [8, 9]

Paediatric Drug Information

Indication: **Acute treatment of hyperammonaemia in OTC deficiency and CPSI deficiency**

Dose: **Child (all ages):** Generally, if unwell but tolerating orally, increase dose from regular dose (maximum of 500 mg/kg/day), divided into 2 hourly doses to prevent nausea and vomiting [142]. If patient requires IV treatment, give 250 mg/kg as an IV infusion over 90 minutes followed by 250 mg/kg/day continuous IV infusion [142].
Follow Individualised Patient Plan or BIMDG Emergency Guideline [142].

Indication: **Acute treatment of hyperammonaemia in citrullinaemia and ASA**

Dose: **Child (all ages):** Generally, if unwell but tolerating orally, increase dose from regular dose (maximum of 500 mg/kg/day), divided into 2 hourly doses to prevent nausea and vomiting [143]. If patient requires IV treatment, give 250 mg/kg as an IV infusion over 90 minutes followed by 250 mg/kg/day continuous IV infusion [143]
Follow Individualised Patient Plan or BIMDG Emergency Guideline [143]

Indication: **Acute hyperammonaemia due to N-acetylglutamate (NAGs) deficiency**

Dose: **Child (all ages):** If tolerating orally, double the patient's normal dose of sodium phenylbutyrate [145]
If patient requires IV treatment, give 250 mg/kg as an IV infusion over 90 minutes followed by 250 mg/kg/day continuous IV infusion [10]. Follow Individualised Patient Plan or BIMDG Emergency Guideline

Indication: **Acute hyperammonaemia due to Hyperornithinaemia, Hyperammonaemia, Homocitrullinuria (HHH) and Lysinuiric Protein Intolerance (LPI)**

Dose: **Child (all ages):** 250 mg/kg/day, as a continuous intravenous infusion [146]. Follow Individualised Patient Plan or BIMDG Emergency Guideline

Indication: **Maintenance dose to control hyperammonaemia in Urea Cycle Defects (UCDs)**

Dose: **Neonate and child (<20 kg)**
250 mg/kg/day, orally, in 3 - 4 divided doses, with food/feeds [1, 2, 8, 9]. Doses of up to 600 mg/kg/day have been used [150]
Child (>20 kg)
5 g/m^2/day, orally, in 3 – 4 divided doses, with food/feeds [1, 2, 8, 9]. Maximum dose 12 g/day [1] . Doses of up to 13 g/m^2/day have been used, maximum of 20 grams/day [2, 150]

Adult Drug Information

Indication: **Maintenance dose to control hyperammonaemia in Urea Cycle Defects (UCDs)**

Dose: 9.9 – 13 g/m^2/day, orally, in 3 – 4 divided doses, with food/feeds [1, 150]. Maximum of 20 grams/day [1, 150].

Indication: **Acute treatment of hyperammonaemia in OTC deficiency, CPSI deficiency, citrullinemia, ASA arginase deficiency, NAGs deficiency**

Dose: 250 mg/kg/day continuous IV infusion [147]
Follow Individualised Patient Plan or BIMDG Emergency Guideline [147]

THIAMINE
(Vitamin B_1)

Action: As a co-factor and to overcome lack of thiamine transporters in certain indications [2]

Indication: Thiamine responsive variants of: Maple Syrup Urine Disease (MSUD) [1, 2, 9], Pyruvate Dehydrogenase Complex (PDHC) deficiency [2, 9], Complex I deficiency [2]
Thiamine transporter II deficiency (Biotin-Responsive Basal Ganglia Disease) [2, 9, 19] and Mitochondrial TPP transporter deficiency [2]
Thiamine-responsive megaloblastic anaemia (Rogers Syndrome) [9]

Preparation & supplier details: 50 mg and 100 mg tablets, (100 tablets); AAH Pharmaceuticals
100 mg/mL solution for injection, (6 x 1 mL) (Teofarma, Switzerland) import via Clinigen (U)
100mg/2ml solution for injection (5x2ml) (Bevitine, France) import via Mawdlesy (U)

Funding notes: PbR/in tariff

Suggested local formulary status: Green – secondary or primary care initiation

Additional information: Crush and disperse tablets in water – oral liquid not indicated
If IV thiamine not available, consider using Pabrinex preparation (which contains other B vitamins and Vitamin C), as this will probably be suitable.
Serious allergic reactions/anaphylaxis can occur with IV administration of thiamine and as such, it should be administered over 30 mins [152] and resuscitation facilities should be available when given via the IV route [1]
Injection may contain phenol – avoid in neonates [1, 152]

Paediatric Drug Information

Indication: **Thiamine responsive Maple Syrup Urine Disease (MSUD)**

Dose: **Neonate & Child (all ages)** 5 - 10 mg/kg/day, orally [1, 9]. Dose range usually 50 – 1200 mg/day orally, in divided doses [2]

Indication: **Thiamine responsive Pyruvate Dehydrogenase Complex (PDHC) deficiency and Complex I deficiency (Congenital Lactic Acidosis)**

Dose: **Neonate:** 50 – 200 mg, orally or by intravenous infusion over 30 mins, ONCE DAILY, can be given in 2 – 3 divided doses [1].
Child: 100 – 300 mg, orally or by intravenous infusion over 30 mins, ONCE DAILY, can be given in 2 – 3 divided doses [1, 9]. Oral doses up to 1200 – 2000 mg can be used [1, 2]

Indication: **Thiamine transporter II deficiency (Biotin-Responsive Basal Ganglia Disease) [2, 9, 19]**

Dose: 100 – 400 mg/day, orally, in 2 – 3 divided doses. Doses up to 1.5g can be used [2, 19]

Indication: **Mitochondrial TPP transporter deficiency [2]**

Dose: 100 – 600 mg/day, orally, in 2 – 3 divided doses [2]

Indication: **Thiamine-responsive megaloblastic anaemia (Rogers Syndrome)**

Dose: 25 – 100mg/day, orally [2]

Adult Drug Information

Indication:	**Thiamine responsive Maple Syrup Urine Disease (MSUD)**
Dose:	Dose range usually 50 – 1200 mg/day orally, in divided doses [2]
Indication:	**Thiamine responsive Pyruvate Dehydrogenase Complex (PDHC) deficiency and Complex I deficiency**
Dose:	100 – 300 mg, orally, ONCE DAILY, can be given in 2 – 3 divided doses [1, 9]. Oral doses up to 1200 – 2000 mg can be used [1, 2]
Indication:	**Thiamine-responsive megaloblastic anaemia (Rogers Syndrome)**
Dose:	50 – 100 mg/day, orally [9, 153]

TRIENTINE (Dihydrochloride & Tetrahydrochloride)

Action: Chelating agent that aids the elimination of copper from the body by forming a stable complex that is renally excreted [2, 154]

Indication: Wilson 's disease [1, 2, 9, 154] Second line option for those intolerant to or have a contra-indication to penicillamine [155]

Preparation & supplier details: Trientine tetrahydrochloride 150 mg tablets [Cuprior] (packs of 72); gmp-orphan United Kingdom Ltd.
Trientine dihydrochloride 250 mg hard capsules [Tiollomed] (packs of 100); Tillomed Laboratories Ltd.

Funding notes: NHSE commissioned/PbR excluded [3]

Suggested local formulary status: Red – hospital only

Additional information:
Take on an empty stomach (at least 1 hour before or 2 hours after food) [156]
Take at least 1 hour apart from other medicinal products [156]
Tetrahydrochloride tablets (150 mg of trientene base) are scored so they can be halved (dose can be rounded to half tablets) [156]
Trientine dihydrochloride 250 mg = 167 mg of trientine base [154]
Trientine dihydrochloride capsules are not directly interchangeable with trientine tetrahydrochloride tablets
Treatment may affect iron metabolism (iron-deficient red cell indices, normal ferritin) – this usually responds to short courses of supplementation with a ferrous salt [2, 124]
Completion of Blueteq forms is mandatory before the prescribing and supply of trientine [157]
Any salt (dihydrochloride or tetrahydrochloride) of trientine is commissioned/funded by NHSE, but the product with the lowest acquisition cost is preferred [157]
There is concern that there may not yet be sufficient evidence to justify the lower dose of free base recommended by the manufacturers of trientine tetrahydrochloride [124, 158]. See reference 11 for further information (PKWP response, e.g. bioequivalence with dosing prior to high-fat meals).
Any NHSE Patient Access Scheme is likely to represent the lowest acquisition cost. The advice of NHSE-embedded pharmacists should be sought [155, 157]

Paediatric Drug Information

Dose: **Using trientine dihydrochloride capsules (dose expressed in *salt*)**

Child > 5 years of age
20 mg/kg/day rounded to the nearest 250 mg capsule of trientine dihydrochloride given in 2 – 3 divided doses, adjusting according to response [154]. The recommended initial dose of trientine dihydrochloride capsule is usually 500 – 1250 mg (2 – 5 capsules)/day [154].

Dose: **Using trientine tetrahydrochloride tablets (dose expressed in *base*) [156]**

Child 5 – 17 years
225 – 600 mg (1½ to 4 tablets) per day, orally, in 2 – 4 divided doses adjusted, according to response [156]

Adult Drug Information

Dose: **Using trientine dihydrochloride capsules (dose expressed in *salt*)**

1 gram – 2 grams per day, orally in 2 – 4 divided doses, adjusted according to response [154].

Return to contents

Dose:

Using trientine tetrahydrochloride tablets (dose expressed in *base*)

450 – 975 mg (3 to 6½ tablets) per day, in 2 to 4 divided doses, adjusted according to response [156]

VELAGLUCERASE ALFA
(VPRIV®)

Action: Enzyme Replacement Therapy (ERT) – recombinant glucocerebrosidase [1, 2, 159]

Indication: Gaucher Disease Type I and 3 [1, 2, 9, 159,230]

Preparation & supplier details: 400 units powder for solution for solution [VPRIV©]; Takeda UK
Funding notes: Commissioned by NHS England via national LSD centres [3]

Suggested local formulary status: Red – hospital only

Additional information: Consider pre-treatment with antihistamines, antipyretics and/or corticosteroids to prevent infusion related reactions (IRRs) [159]
Store in the refrigerator [159]
Monitor IgG antibody concentrations if IRRs occur and/or there is a loss or lack of effect with velaglucerase alfa [1]

Paediatric Drug Information

Dose: **Child 4 – 17 years:** initially 60 units/kg every 2 weeks, by intravenous infusion [1, 159], adjusted according to response to 15 – 60 units/kg every 2 weeks [1, 159]
Unlicensed at younger ages

Administration: IV over 60 minutes. Consult local protocol or Summary of Product Characteristics (SPC)

Adult Drug Information

Dose: Initially 60 units/kg every 2 weeks, by intravenous infusion [10, 159] , adjusted according to response to 15 – 60 units/kg every 2 weeks [10, 159]

Administration: Consult local protocol or Summary of Product Characteristics (SPC)

VESTRONIDASE ALFA

Action: Enzyme Replacement Therapy (ERT) – recombinant human beta-glucuronidase [178, 179]

Indication: Mucopolysaccharidosis VII (MPS VII) (Sly disease)

Preparation & supplier details: 2 mg/mL concentrate for solution for infusion [Mepsevii©]; Ultragenyx Pharmaceuticals

Funding notes: Commissioned for infantile MPS VII as per urgent policy statement 210401UPS[218]

Suggested local formulary status: Red – hospital only

Additional information: Pre-treatment with a non-sedating antihistamine, with or without an should be administered 30 – 60 mins before infusion [178]
Store in the refrigerator [178]
High sodium content – each vial dosed with corresponding volume of sodium chloride 0.9 % dilution fluid provides 35.5 mg of sodium. Use is therefore cautioned in those on sodium-controlled diets, in heart failure, renal failure [178]
Each vial contains 17.8 mg of sodium [178]
Do not administer if patient has an acute febrile or respiratory illness [178]

Paediatric Drug Information

Dose: 4 mg/kg by intravenous infusion EVERY TWO WEEKS [178]. Maximum dose 283 mg [178]

Administration: Consult local protocol or Summary of Product Characteristics (SPC)

Adult Drug Information

Dose: 4 mg/kg by intravenous infusion EVERY TWO WEEKS [178]. Maximum dose 283 mg [178]

Administration: Consult local protocol or Summary of Product Characteristics (SPC)

VIGABATRIN

Action: Increases levels of gamma-aminobutyric acid (GABA) in the brain through irreversible inhibition of the enzyme GABA transaminase. GABA transaminase is responsible for the breakdown of GABA [2, 160]

Indication: Succinic semialdehyde dehydrogenase deficiency

Preparation & supplier details: 500 mg film-coated tablets and 500 mg granules for oral solution (100 tablets & 50 sachets) [Sabril®]. 100mg and 500mg soluble tablets (100 tablets) [Kigabeq®].

Funding notes: In tariff/PbR

Suggested local formulary status: Amber

Additional information: Unproven benefit – monitor carefully (irreversible visual field defects possible) [2]
Visual defect testing required before initiating treatment and at 6 monthly intervals [1]
Counsel patient and family to report any new visual symptoms that develop. These can occur from 1 month to several years after starting [1, 160]
Granules may be dissolved in water, fruit juice or milk and administered straight away. Soluble tablets dissolve in 5-10ml water. If granules and soluble tablets are unavailable, film-coated tablets can be crushed and disperse in water or squash OR crushed and mixed with soft food (unlicensed use) [1, 8]
Granules can be mixed with a small amount of water and given rectally if needed (unlicensed use) (same dose) [1, 8]
Reduce dose in renal impairment (<60 mL/min) [1]

Paediatric Drug Information

Dose: Initially 30-50mg/kg/day (max 500mg/day) orally in two divided doses. To be increased according to response. Usual maintenance: 60-80mg/kg/day in two divided doses. Max of 150mg/kg/day or 3g/day (whichever is lowest)[1]. Doses of 100mg/kg/day have been used in case reports of SSADHD[229]. However, due to visual field defects the max recommended dose is 3g/day.

Adult Drug Information

Dose: 1 gram, orally in TWO divided doses, adjusted according to response in steps of 500 mg every week to a maximum of 3 grams/day in TWO divided doses [10]

VITAMIN A (as palmitate)

Action: Free radical scavenger [18]

Indication: Abetalipoproteinemia
Other causes of vitamin A deficiency

Preparation & supplier details: Dalivit multivitamin oral drop (25 mL); AAH Pharmaceuticals
Abvit oral solution 10,000 units/mL; Sterling Pharmaceuticals Ltd.
100,000units / 2mL injection (6) **(U)**; Durbin PLC

Funding notes: In tariff/PbR

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescriptions

Additional information: Dalivit contains 5000 units per 0.6 mL [1]. Also contains Ascorbic acid, ergocalciferol, nicotinamide, pyridoxine, riboflavin and thiamine [1]
Excessive doses may be teratogenic and so should be avoided in pregnancy [1]
High doses can be associated with acute toxicity (rough, dry skin; hepatomegaly, elevated erythrocyte sedimentation rate (ESR); elevated alkaline phosphatase concentration) [1]
Avoid in renal impairment

Paediatric Drug Information

Indication: **Vitamin A deficiency** [1]

Dose: **Neonates – 11 months:**
5000 units, orally, ONCE a day [1]
Child 1 month – 17 years:
10,000 units, orally, ONCE a day [1]
Higher doses may be required [1] Take with or after food [1]

Adult Drug Information

Indication: **Abetalipoproteinemia**

Dose: 100 – 400 units/kg/day [161]

VOLANESORSEN (Waylivra)

Action: Antisense oligonucleotide designed to inhibit the formation of apoC-III, enabling metabolism of triglycerides through an LPL-independent pathway [175]

Indication: Indicated as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate[175]

Preparation & supplier details: Pre-filled syringe containing 285mg of Volanesorsen in 1.5mL [175] [Waylivra®]; Akcea Therapeutics.

Funding notes: Commissioned according to commercial arrangements[227].

Suggested local formulary status: Red – hospital only

Additional information:
Only start treatment if baseline platelet count is > 140 x 10^9/L [175]
Platelet count monitoring during treatment is required at least every 2 weeks if platelet count is normal – consult SPC for monitoring frequency if platelet count is < 140 x 10^9/L [175]
Consult SPC for dose adjustment for in thrombocytopenia (< 140 x 10^9/L)
285mg volanesorsen = 300mg volanesorsen Sodium [175]
Store in the fridge [175]
Volanesorsen can be removed from fridge and stored at room temperature (< 30 °C) for up to 6 weeks [175]. It must be discarded if not used within 6 weeks after the first removal from refrigerated storage [175]
Give injection on same day each week [175]
In the case of a missed dose, give the missed dose as soon as possible within 48 hours of scheduled time. If it cannot be given within the 48 hours, then the missed dose should be skipped and next dose be given at the next planned day of the week [175].

Paediatric Drug information: Adult use only.

Adult Drug Information

Dose: 285 mg by subcutaneous injection ONCE EVERY WEEK for 3 months, then reduced to 285 mg by subcutaneous injection EVERY 2 WEEKS thereafter [175]. Review and adjust dose according to serum triglyceride levels- consult product literature[228].

Discontinue treatment in patients with a reduction in serum triglycerides < 25 % or who fail to achieve serum triglycerides below 22.6 mmol/L after 3 months on volanesorsen 285 mg weekly [175].

After 6 months of treatment, consider increasing frequency to 285 mg WEEKLY if response is inadequate in terms of serum triglyceride reduction and if platelet count is in normal range [175]. Patients should be re-down titrated to 285 mg EVERY 2 WEEKS if the 285 mg ONCE WEEKLY dose does not provide significant additional triglyceride reduction after 9 months [175].

ZINC ACETATE

Action: Zinc prevents the absorption of copper ions [1]

Indication: Wilson's Disease [1, 2]

Preparation & supplier details: 25 mg and 50 mg capsules (packs of 250); Recordati Rare Diseases UK Ltd.

Funding notes: In tariff/PbR

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescriptions

Additional information:

Patients should be treated initially with a chelating agent because zinc has a slow onset of action. When transferring from chelating treatment to zinc maintenance therapy, chelating treatment should be co-administered for 2–3 weeks until zinc produces its maximal effect [1, 162]

Concurrent dosing must be avoided (trientine and penicillamine may chelate zinc) [124]
Take on an empty stomach (1 hour before or 2 hours after food) [1, 162]
Transient gastric irritation may be reduced if first dose is taken mid-morning or with a little protein [1, 162]
Zinc acetate may cause less GI disturbance than sulphate [2, 124]
Monitor FBCs and cholesterol whilst on treatment in addition to plasma copper and urinary copper concentration [1, 162]
Reduce dose in pregnancy [1, 162]

Capsules may be opened and mixed with water, (can also use syrup- or sugar-flavoured water [1, 162]

Paediatric Drug Information

Dose:

Doses expressed as elemental zinc [1]

Child 1 – 5 years:	25 mg, orally, TWICE a day [1, 162]
Child 6 – 15 years (< 57 kg):	25 mg, orally, THREE times a day [1, 162]
Child 6 – 15 years (> 57 kg):	50 mg, orally, THREE times a day [1, 162]
Child 16 – 17 years:	50 mg, orally, THREE times a day [1, 162]

Adult Drug Information

Dose:

Dose expressed as elemental zinc [1]
50 mg, orally, THREE times a day, adjusted according to response [10, 162]

ZINC SULPHATE MONOHYDRATE

Action: Zinc prevents the absorption of copper ions (WD) and increases zinc in body (AE) [1]

Indication: Wilson Disease (WD) [1, 2]
Acrodermatitis Enteropathica (AE) [1]

Preparation & supplier details: 125 mg effervescent tablets (90 tablets), AAH Pharmaceuticals

Funding notes: In tariff/PbR

Suggested local formulary status: Amber – hospital to initiate, GP to continue repeat prescriptions

Additional information: 45 mg of elemental zinc = 125 mg of zinc sulphate monohydrate = ONE effervescent tablet [1]
Take with food [1]. This reduces the efficacy of zinc salts as treatment for WD, but lessens gastro-intestinal adverse effects [124]
Monitor urinary copper excretion in Wilson Disease [2]
Not licensed for Wilson Disease or Acrodermatitis Enteropathica
Accumulation may occur in renal impairment [1]
Monitoring serum copper is necessary when using zinc for treatment of AE as deficiency can occur (reduce dose of zinc) [2]

Paediatric Drug Information

Indication: **Acrodermatitis Enteropathica (AE)**

Dose: **Dose expressed as elemental zinc**
1 – 2 mg/kg/day, orally in 2 divided doses, adjusting dose as necessary [1]. Total daily dose may be given in 3 divided doses to improve tolerance [1].
Dose may need to be increased during growth spurts [2]
Post-pubertal requirements may be lower [2]

Adult Drug Information

Indication: **Wilson Disease**

Dose: Usual maintenance dose: 375mg (135 mg elemental zinc), orally, in 3 divided doses *i.e.* 125 mg (45 mg of elemental zinc), orally, THREE times a day [124]

Indication: **Acrodermatitis Enteropathica (AE)**

Dose: **Dose expressed as elemental zinc**
45 – 90 mg of zinc/day, orally, in 2 – 3 divided doses
Dose may need to be increased during pregnancy and lactation (up to 180 mg/day of elemental zinc) [2]

APPENDIX 1: Medications to avoid or use with caution in inherited metabolic disorders – further information

Sodium valproate & valproic acid

Sodium valproate and valproic acid should be avoided in following Inherited metabolic disorders (IMDs):

- Urea cycle defects (UCDs)
- Organic acidurias
- Fatty acid oxidation disorders (FAOs)
- Non-ketotic hyperglycinaemia (NKH)
- Mitochondrial diseases
- Carnitine transporter defects

Sodium valproate and valproic acid can cause hyperammonaemia [1, 81] by decreasing the functionality of the urea cycle *i.e.* the metabolic pathway involved in detoxification of ammonia, through inhibition of, n-acetyl-glutamate synthase [163]. For this reason, sodium valproate and valproic acid should be avoided in the following inborn errors of metabolism where hyperammonaemia can occur *i.e.* UCDs, organic acidurias, FAOs.

Sodium valproate and valproic acid should also be avoided in Non-ketotic hyperglycinaemia (NKH) [2], as inhibition of the Glycine Cleavage System (GCS) and can result in increased glycine concentrations in plasma and cerebrospinal fluid (CSF), causing paradoxical seizures [2].

Sodium valproate should be avoided for the treatment of seizures in those with mitochondrial diseases or where a mitochondrial disease is suspected. There is some evidence valproate can cause inhibition of complexes I and IV in the respiratory transport chain of mitochondria [164].

Valproate, as a weak organic acid can bind free carnitine, thereby causing carnitine insufficiency [79]. Valproate should be avoided in those with carnitine transporter defects and organic acidaemia [79].

Aminoglycosides (*e.g.* gentamicin, tobramycin and amikacin)

Aminoglycosides have been associated with mitochondrial toxicity and mitochondrial inhibition *in vitro* [165]. Evidence suggests an increased risk of aminoglycoside associated ototoxicity in patients with mitochondrial mutations, including in cases where patients aminoglycoside serum levels were within therapeutic range.[189]

Aspartame

Aspartame is a sweetener used in some preparations of medicines. Aspartame (L-aspartyl-L-phenylalanine methyl ester) [2] is a source of phenylalanine and sources of phenylalanine should be avoided in those with Phenylketonuria (PKU) [2].

If it is not possible to avoid aspartame in a medicine then the amount of aspartame the patient will receive will need to be calculated. Contact your pharmacy department or medicines information department to ascertain this information.

Depending on the patient,

- the aspartame may be of such a small quantity that PKU dietary adjustment is not required
- the short term use of an aspartame containing medication will not be clinically significant
- PKU dietary adjustment will be required to account for aspartame content.

Corticosteroids

Corticosteroids are known to increase protein turnover and thereby increase nitrogen and ammonia load. The use of corticosteroids is not contraindicated, but the potential for increased ammonia concentration should be borne in mind if corticosteroids are used in patient groups with the following diseases:

- Urea cycle defects
- Organic acidurias
- Fatty acid oxidation disorders .

- This is a theoretical consideration. In practice corticosteroids are safely used in patients with such disorders

Probenacid

Probenacid is known to reduce the urinary excretion of phenylacetylglutamine (PAGN) [60]. PAGN is a metabolite of sodium phenylbutyrate and glutamine and causes a reduction in plasma ammonia [60]. Reduced urinary excretion of PAGN can therefore cause upstream accumulation of ammonia as there is reduced clearance [60].

Pivmecillinam

Pivemecillinam and other pivalate based antibiotics should be avoided in patients with carnitine transporter deficiencies because the pivalate moiety of this antibiotic binds carnitine and promotes the renal excretion of carnitine [2]. Maternal use and early neonatal use of pivemecillinam and other pivalate based antibiotics can interfere with newborn screening for Isovaleric acidaemia (IVA) causing false positive results [160]. These phenomena can also be observed with other weak organic acids (*e.g.* benzoate) [40].

Propofol

Propofol is recommended to be avoided in patients with mitochondrial disorders, or at least be given in reduced concentrations due to its depressant effect on the mitochondria [9, 166]. Propofol also has a risk of propofol infusion syndrome particularly after prolonged infusions of more than 48 hours, and for this reason it is not recommended for use in children under 16 receiving intensive care [1, 167]. It is proposed that this may be a result of the depressant effects that propofol has on the mitochondria [168]. The propofol infusion syndrome mimics mitochondrial cytopathies, and includes symptoms of rhabdomyolysis [167, 168]. It has been reported that in children with mitochondrial disorders, even short term use of propofol may be associated with delayed recovery and the need for ICU admission [168, 169]. Propofol is a lipophilic drug and therefore formulated in a lipid base, namely, refined soya-bean oil. The European Pharmacopeia (EP) specifies that the fatty acids that comprise soya bean oil primarily have a chain length of C14 or greater. Therefore, the propofol formulation used is predominately a long-chain triglyceride. Based on a small dataset of published data, propofol as a single bolus at the induction appears safe in children with well controlled medium-chain acyl-CoA dehydrogenase deficiency (MCADD) [40]. It is recommended to avoid using in long chain fatty acid oxidation disorders such as LCHAD and VLCADD, and in patients with MCADD who are unwell and decompensated [170].

Lactose

Lactose is an excipient commonly used a variety of pharmaceutical preparations such as tablets, capsules and parenteral preparations [171]. Lactose is hydrolysed into glucose and galactose and therefore poses a risk for those with galactosaemia [171]. Pharmaceutical preparations containing lactose should be used with caution in children with galactosaemia. If a preparation containing lactose is being used then the amount of lactose contained per dose should be ascertained from the manufacturer and the amount per day calculated. This information should be discussed with the consultant and dietitian. Generally, a preparation containing the lowest amount of lactose should be used for a shortest time possible [172]. For most medications, lactose (particularly for adult patients) the amount of is unlikely to be significant [172]. However this should always be checked and discussed with the specialist inherited metabolic disease team.

Lactulose

Lactulose contains high amounts of lactose and galactose and is contraindicated in galactosaemia [172]. See lactose above for further information.

Sorbitol & Fructose

Sorbitol and fructose are excipients used as sweeteners in oral pharmaceutical preparations; and sorbitol is used as a peptide stabiliser in some pharmaceutical parenteral preparations [173]. Sorbitol is rapidly converted *in vivo* to fructose by sorbitol dehydrogenase in the liver and so safety concerns regarding fructose also apply to sorbitol [173]. Fructose and sorbitol are avoided in patients with hereditary fructose intolerance (HFI) which is also known as fructose 1-phosphate aldolase B deficiency

[173]. Patients with HFI develop a natural defence mechanism against fructose and sorbitol by vomiting from any ingestion [173]. This defence mechanism is bypassed when sorbitol is inadvertently administered *via* a parenteral route [173]. Sorbitol should be avoided in patients with HFI, especially parenteral preparations as there is a risk of hepatic decompensation [40, 173]. However, some preparations contain very low amounts of sorbitol (8 – 16 mg per dose) and can be given to these patients with careful consideration [173]. This should always be checked and discussed with the specialist inherited metabolic disease team.

Food items or medicines that contain fructose, sucrose, glycerol, and/or sorbitol, should also be avoided in individuals with Fructose-1, 6- bisphosphatase deficiency, especially during acute crisis in infancy or early childhood.

Detailed information can be found in the European Medicines Agency: Information for the package leaflet regarding fructose and sorbitol used as excipient in medicine products for human use.

The following excipients may contain fructose or can be metabolised into fructose:	***The following excipients do not contain or yield fructose (not-exhaustive):***
Corn syrup / high-fructose corn syrup / isoglucose	Corn starch
Fructose	Dextrose / maltodextrin / glucose
Maltitol (E965)	Lactose
Polydextrose (E1200)	Maltose
Polysorbate-80 (E433) /-20 (E432) /-40 (E434) /-60 (E435) /-65 (E436)	Saccharin (E954)
Sorbitol (E420) / sorbitan / sorbitan esters (E491, E492, E493, E494, E495, E496)	
Stevia / steviol / steviol glycosides (E960)	
Sucralose (E955)	
Sucrose / saccharose	

Further general information:

- **"Sugar-free" medication** are not preferable by default, as these formulations may contain artificial sweeteners which can be metabolised into fructose. Check the tables above carefully.
- **Injectable vaccines** commonly contain polysorbate-80, but are given infrequently and contain such a small quantity that they can be safely prescribed and administered. Some **oral vaccines** contain large amounts of sucrose.
- **Injectable amiodarone** contains large quantities of polysorbate-80

Medications in patients with mitochondrial disease

Clinical guidance is often sought when prescribing drugs for patients with primary mitochondrial disease. Theoretical considerations concerning drug safety in patients with mitochondrial disease may lead to unnecessary withholding of a drug in a situation of clinical need. A modified Delphi technique, by a panel of 16 experts in mitochondrial medicine, pharmacology, and basic science from six different countries aimed to develop consensus on safe medication use in patients with a primary mitochondrial disease. This publication is available here [165] , with a lay summary available here [174]

Glucose Transporter-1 Deficiency (GLUT1 deficiency syndrome)

The following drugs should be avoided in GLUT1 deficiency syndrome [2] as they are known to inhibit the glucose 1 (GLUT1) transporter in the blood brain barrier (BBB):

- Phenobarbital
- Diazepam
- Chloral hydrate
- Theophylline
- Caffeine
- Alcohol

APPENDIX 2: Medications & the Ketogenic diet

What is a Ketogenic Diet?

A ketogenic diet is a dietetic management option for children and adults with intractable epilepsy not responding to anti-epileptic drugs (AEDs), GLUT1 deficiency syndrome or pyruvate dehydrogenase deficiency. A Ketogenic Diet aims to achieve a steady state of ketosis using a diet that is:

- very high in fat and
- severely restricted in carbohydrate content.

Medications and the Ketogenic Diet

The excipient content of medications (particularly liquid preparations) is an unrecognised source of carbohydrate so can contribute significantly to carbohydrate (sugar) intake. The use of medications in liquid form is widespread in paediatrics and in patients with gastrostomy tubes.

*If the carbohydrate content of medications is not considered then ketosis can be compromised. *

Pharmaceutical Care Points for patients on Ketogenic Diets

Consider the following points:

- Are newly prescribed medications necessary?
- Can any medications be stopped or their dose reduced?
- Minimise the sugar and carbohydrate content of intravenous drugs.
    - *E.g.* avoid using glucose as a diluent for IV drug administration - use sodium chloride where possible.
- Avoid using oral liquids, syrups and chewable tablets as they often contain more carbohydrate than other formulations
- Take care with liquids labelled as **"sugar-free"**. These can contain sweeteners and can be an unrecognised source of carbohydrate. Generally, sugar-free liquids can contribute greatly as a carbohydrate source.
- For details of excipients that ARE and AREN'T sources of carbohydrate, see table 2.
- If in doubt if an excipient is a carbohydrate source, a useful rule of thumb is
    - *"substances ending '-ose' and '-ol' are usually converted to glucose in the body (cellulose is an exception and is suitable)"*
- Contact the pharmaceutical manufacturer to obtain carbohydrate content/excipient content and quantity present in medication.
- Medications in suppository form are a useful non-carbohydrate source alternative to consider.
- Switch medications from liquid to tablet form (if clinically appropriate).
- Liaise with the patient's specialist ketogenic diet dietitian or doctor for further information.

Switching medications from liquid to tablet form

When switching to tablet form consider the following:

- Does the patient have an enteral feeding tube?
    - If so, what tube do they have? *i.e.* NGT, PEG, PEJ, JEJ
    - What size is the tube?
    - Where is the medicine absorbed and is this compatible with their tube?

This will help determine if the tablet can be crushed or dispersed for administration via the tube.

- If the dose prescribed is not equal to a whole tablet, is it appropriate to administer an aliquot?
    - *E.g.* Drugs that are not soluble in water will not uniformly disperse in a given amount of water and so an aliquot may not be an accurate approach to dosing. It may be more accurate to halve or quarter the tablet and then crush and disperse.

Table 2: Excipients and their carbohydrate status

Excipients that ARE a carbohydrate source	Excipients that are NOT a carbohydrate source
Sugars: dextrose, fructose, glucose, lactose, sucrose & sugar	Cellulose
Starches: cornstarch, pregelatinised starch, sodium starch glycolate	Carboxymethylcellulose
Sweeteners such as: Sorbitol, mannitol, xylitol, isomalt, erythritol	Hydroxymethylcelluose
Alcohol	Microcrystalline cellulose
Glycerin	Polyethylene glycol
Hydrogenated Starch Hydrolysates (HSH)	Magnesium stearate
Ascorbic acid	Aspartame
	Saccharine
	Asulfamine potassium (K)

APPENDIX 3: Medications available *via* Individual Funding Requests (IFRs) only

Uridine (triacetate)

Action: Oral pro-drug that replenishes Uridine Monophosphate (UMP), a necessary component of RNA [2, 180]

Indication: UMP Synthase Deficiency (Hereditary Orotic Aciduria) [2]

Preparation & supplier details: Xuriden 2-gram oral granules (30 x 2 gram); Wellstat Therapeutics (US Import) **(U)**

Funding notes: Not commissioned

Suggested local formulary status: Red – hospital only

Additional information: Monitor urinary orotic acid [9] - adjust dose to maintain lowest output of orotic acid [2]

Paediatric Drug Information

Dose: 60 - 120 mg/kg/day, orally, ONCE daily [181]. Maximum of 8 grams a day [181]
100 – 150 mg/kg/day, orally, in divided doses, if using uridine powder [2, 9]. Maximum of 8 grams a day [181]

Adult Drug Information

Dose: 60 - 120 mg/kg/day, orally, ONCE daily [181]. Maximum of 8 grams a day [181]
100 – 150 mg/kg/day, orally, in divided doses, if using uridine powder [2, 9]. Maximum of 8 grams a day [181]

Triheptanoin

Action:	Anaplerotic substrate [2]
Indication:	Long Chain Fatty Acid Oxidation Disorders (FAODs) such as Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (VLCAD) [2] Pyruvate Carboxylase deficiency [2]
Preparation & supplier details:	Ultragenyx Pharmaceuticals
Funding notes:	Not routinely commissioned, IFR approval required [3]
Suggested local formulary status:	Red – hospital only

Paediatric Drug Information

Indication:	**Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (VLCAD)**
Dose:	4 grams/kg/day, orally, in divided doses to provide 30% of total calories [2]
Indication:	**PC deficiency**
Dose:	4 grams/kg/day, orally, in divided doses to provide 30% of total calories [2]

Further information

Vockley, J., Charrow, J., Ganesh, J., Eswara, M., Diaz, G.A., Enns, G.M., Marsden, D.L., 2015. Response to Compassionate Use of Triheptanoin in Infants With Cardiomyopathy Due to Long Chain Fatty Acid Oxidation Defects (LC-FAODs). *J Inherit. Metab. Dis.* P349

REFERENCES

1. COMMITTEE, JOINT FORMULARY. British National Formulary for Children (BNFc). 2019 [cited 2019 7th November]; Available from: https://bnfc.nice.org.uk.

2. SAUDUBRAY, JEAN-MARIE, BAUMGARTNER, MATTHIAS R., and WALTER, JOHN HUGH, *Inborn metabolic diseases : diagnosis and treatment*. 2016.

3. NHSENGLAND. Medicines not reimbursed through national prices and directly commissioned by NHS England, . 2019 [cited 2019 29th April]; Available from: https://www.england.nhs.uk/wp-content/uploads/2019/04/nhs-england-drugs-list-v14.1.pdf. .

4. (TAKEDA), SHIRE PHARMACEUTICALS LTD. Replagal 1 mg/mL, concentrate for solution for Infusion - Summary of Product Characteristics (SPC). 2019 2019 7th November]; Available from: https://www.medicines.org.uk/emc/product/9186#.

5. SANOFI-GENZYME. Myozyme 50 mg, powder for concentrate for solution for infusion - Summary of Product Characteristics (SPC). 2019 [cited 2019 26th October]; Available from: https://www.medicines.org.uk/emc/medicine/19030.

6. SANOFI-GENZYME. Myozyme 50 mg, powder for concentrate for solution for infusion - Summary of Product Characteristics (SPC). 2019 [cited 2019 26th October]; Available from: https://www.medicines.org.uk/emc/medicine/19030.

7. CHAKRAPANI, A., 2010. , *Guidelines for the Management of Infantile Pompe Disease*. 2010, NHS: Available on request.

8. COMMITTEE, PAEDIATRIC FORMULARY. Evelina London Paediatric Formulary. 2019 [cited 2019; Available from: http://cms.ubqo.com/public/d2595446-ce3c-47ff-9dcc-63167d9f4b80.

9. ZSCHOCKE, JOHANNES, et al., *Vademecum metabolicum : diagnosis and treatment of inborn errors of metabolism*. 2011, Friedrichsdorf; [Stuttgart]: Milupa Metabolics : Schattauer.

10. COMMITTEE, JOINT FORMULARY. British National Formulary (BNF). 2019 [cited 2018 16th August]; Available from: https://bnf.nice.org.uk.

11. ATAXIAUK. Management of the ataxias: towards best clinical practice. . 2009; Available from: https://www.acpin.net/pdfs/Ataxia_Guidelines.pdf.

12. BURNETT, J. R., HOOPER, A. J., and HEGELE, R. A., *Abetalipoproteinemia*, in *GeneReviews((R))*, M.P. ADAM, et al., Editors. 1993, University of Washington, Seattle, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.: Seattle (WA).

13. PERETTI, NOEL, et al. *Guidelines for the diagnosis and management of chylomicron retention disease based on a review of the literature and the experience of two centers*. Orphanet journal of rare diseases, 2010. **5**, 24 DOI: 10.1186/1750-1172-5-24.

14. NORTH-LEWIS, P., *Vitamins in Cholestasis Guideline*. 2018, Leed's Children's Hospital: Leeds.

15. LTD., ALEXION PHARMA UK. Strensiq (Asfotase alfa) solution for injection - Summary of Product Characteristics (SPC) 2019 [cited 2019 30th October]; Available from: https://www.medicines.org.uk/emc/product/7991/smpc

16. NICE. Highly specialised technologies guidance [HST6]: Asfotase alfa for treating paediatric-onset hypophosphatasia. 2017 [cited 2019 30th October].

17. LTD., RECORDATI RARE DISEASES UK. Cystadane 1-gram oral powder - Summary of Product Characteristics (SPC). 2020 [cited 2020 20th April]; Available from: https://www.medicines.org.uk/emc/medicine/20803.

18. SAUDUBRAY, J. M., VAN DEN BERGHE, GEORGES, and WALTER, JOHN, *Inborn metabolic diseases : diagnosis and treatment.* 2012.

19. TABARKI, B., AL-HASHEM, A., and ALFADHEL, M., *Biotin-Thiamine-Responsive Basal Ganglia Disease*, in *GeneReviews((R))*, M.P. ADAM, et al., Editors. 1993, University of Washington, Seattle University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.: Seattle (WA).

20. LTD., KYOWA KIRIN. Crysvita solution for subcutaneous injection – Summary of Product Characteristics (SPC). 2019 [cited 2019 7th December]; Available from: https://www.medicines.org.uk/emc/product/9779.

21. NICE. Highly Specialised Technologies guidance (HST8): Burosumab for treating X-linked hypophosphataemia in children and young people. 2018 [cited 2019 7th December]; Available from: https://www.nice.org.uk/guidance/hst8.

22. LTD., RECORDATI RARE DISEASES UK. Carbaglu 200 mg dispersible tablets - Summary of Product Characteristics (SPC). 2019 [cited 2019 5th November]; Available from: https://www.medicines.org.uk/emc/product/6234/smpc.

23. CLAYTON, P., *RE: BIMDG Formulary - Final checks - disorders of bile acid and cholesterol metabolism.*, W.A. BATTEN, MURPHY, E.,, Editor. 2019.

24. NHS, ENGLAND. Clinical Commissioning Policy: Cholic acid and chenodeoxycholic acid for treating inborn errors of bile acid synthesis (all ages) - NHS England Reference: 170127P. 2019 [cited 2020 2nd May]; Available from: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2019/07/Clinical-Commissioning-Policy_Cholic-acid-and-chenodeoxycholic-acid-for-treating-inborn-errors-of-bile-acid-sy.pdf.

25. BIOSCIENCES, LEADIANT. Chenodeoxycholic acid Leadiant 250 mg hard capsules - Summary of Product Characteristics. 2017 [cited 2020 2nd May]; Available from: https://www.ema.europa.eu/en/documents/product-information/chenodeoxycholic-acid-leadiant-epar-product-information_en.pdf.

26. (SPMPU), ST. MARY'S PHARMACEUTICAL UNIT, *Product Specification – Cholesterol oral suspension 150 mg/mL (100 mL).* ST. MARY'S PHARMACEUTICAL UNIT (SPMPU), Editor. 2019.

27. CENTRE, NATIONAL HORIZON SCANNING. Cholic acid (Orphacol) for inborn errors of primary bile acid synthesis- first line. 2014 [cited 2016 21st September]; Available from: http://www.io.nihr.ac.uk/report/cholic-acid-orphacol-for-inborn-errors-of-primary-bile-acid-synthesis-first-line/.

28. CTRS, LABORATOIRES. Orphalcol 250 milligram capsules - Summary of Product Characteristics (SPC). 2013 [cited 2016 21st September]; Available from: https://www.medicines.org.uk/emc/medicine/30114.

29. PARIKH, SUMIT, et al., *A modern approach to the treatment of mitochondrial disease.* Current treatment options in neurology, 2009. **11**(6): p. 414-430.

30. AJAGBE, B. O., OTHMAN, R. A., and MYRIE, S. B., *Plant Sterols, Stanols, and Sitosterolemia.* J AOAC Int, 2015. **98**(3): p. 716-723.

31. MERKENS, L. S., et al., *Sitosterolemia*, in *GeneReviews(®)*, M.P. ADAM, et al., Editors. 1993, University of Washington, Seattle Copyright © 1993-2020, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.: Seattle (WA).

32. DESCHAMPS, P., et al., *The saga of copper(II)–l-histidine.* Coordination Chemistry Reviews, 2005. **249**(9): p. 895-909.

33. RAI, V., *FW: Copper histidine information Ref. no.: 110924*, W.A. BATTEN, Editor. 2015.

34. SARGEANT, A, *Copper histidine supply for 2019*, W.A. BATTEN, Editor. 2019: 2018.

35. LEMONDE, H., *RE: BIMDG Formulary Review*, W.A. BATTEN, MURPHY, E.,, Editor. 2019.

36. VAIRO, F. P. E., et al., *A systematic review and evidence-based guideline for diagnosis and treatment of Menkes disease.* Mol Genet Metab, 2019. **126**(1): p. 6-13.

37. SIDU, S., MARCH, G.,, *Datasheet: Creatine Monohydrate Powder*, in *Available on request*, V. PHARMA, Editor. 2011, Veriton Pharma: Surrey.

38. STOCKLER-IPSIROGLU, S., et al., *Guanidinoacetate methyltransferase (GAMT) deficiency: outcomes in 48 individuals and recommendations for diagnosis, treatment and monitoring.* Mol Genet Metab, 2014. **111**(1): p. 16-25.

39. SCHWAHN, B, *RE: cPMP availability.*, W.A. BATTEN, MURPHY, E.,, Editor. 2020.

Return to contents

40. SCHWAHN, B, *RE: PAPERS TO REVIEW: Metabolic CRG Agenda for Meeting to be held on the 16th Jan.2020*, W.A. BATTEN, MURPHY, E.,, Editor. 2020.

41. SCHWAHN, B. C., et al., *Efficacy and safety of cyclic pyranopterin monophosphate substitution in severe molybdenum cofactor deficiency type A: a prospective cohort study.* Lancet, 2015. **386**(10007): p. 1955-63.

42. INC, PERRIGO NEW YORK, *Perrigo Dextromethorphan Polistirex Extended-Release Oral Suspension Drug Facts*, P.N.Y. INC, Editor. 2012.

43. S., ARTHUR. Neonatal & Paediatric Pharmacist Group (NPPG) Newsletter No. 61. 2016 [cited 2020 21st June]; 61:[Newsletter]. Available from: http://nppg.org.uk/wp-content/uploads/2019/12/NPPG-61-amended.pdf.

44. 44-661, GOOD NEIGHBOR PHARMACY, *COUGH GELS- dextromethorphan hbr capsule, liquid filled Amerisource Bergen*. 2017.

45. HEALTHCARE, PFIZER CONSUMER. Robitussin Dry Cough Medicine – Summary of Product Characteristics. 2016 [cited 2018 15th June]; Available from: https://www.medicines.org.uk/emc/product/3878/smpc.

46. CHALLIS, B. G., et al., *Adult-onset hyperinsulinaemic hypoglycaemia in clinical practice: diagnosis, aetiology and management.* Endocr Connect, 2017. **6**(7): p. 540-548.

47. NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE (NICE), 2017. . Eliglustat for treating type 1 Gaucher disease: Highly specialised technologies guidance [HST5]. 2017 [cited 2019 30th November]; Available from: https://www.nice.org.uk/guidance/hst5/chapter/3-The-technology

48. SANOFI-GENZYME. Summary of Product Characteristics (SPC) – Cerdelga 84 mg hard capsules. 2019; Available from: https://www.medicines.org.uk/emc/product/2615

49. FROM:, BIOMARIN EUROPE LTD. ACCESSED ONLINE ON 09/08/2018 AVAILABLE, *Summary of Product Characteristics (SPC) for Vimizim (elosulfase alfa) solution for concentrate for infusion.* . 2014.

50. BATTEN, W., *Clinical Guideline – Elosulfase alfa (Vimizim) – Prescribing and administration.* , U.H.B.N.F. TRUST, Editor. 2017.

51. LEXICOMP, *UpToDate – Ezetimibe: Paediatric Drug Information:* . 2018.

52. CAPPUCCIO, G., et al., *Pearls & oy-sters: familial epileptic encephalopathy due to methylenetetrahydrofolate reductase deficiency.* Neurology, 2014. **83**(3): p. e41-4.

53. KNOWLES, L., MORRIS, A. A., and WALTER, J. H., *Treatment with Mefolinate (5-Methyltetrahydrofolate), but Not Folic Acid or Folinic Acid, Leads to Measurable 5-Methyltetrahydrofolate in Cerebrospinal Fluid in Methylenetetrahydrofolate Reductase Deficiency.* JIMD Rep, 2016. **29**: p. 103-107.

54. ZSCHOCKE, JOHANNES; HOFFMANN, GEORG F.; BURLINA, ALBERTO B.; NYHAN, WILLIAM L.; F. K. SCHATTAUER VERLAGS; , *Vademecum metabolicum: Manual of metabolic paediatrics, 2019*

55. WONG, S. Y., et al., *Oral D-galactose supplementation in PGM1-CDG.* Genet Med, 2017. **19**(11): p. 1226-1235.

56. KNIFFIN, C.L. Congenital Disorder of Glycosylation Type IIn (CDG2N). . 2015 [cited 2019 21st November]; Available from: https://www.omim.org/entry/616721?search=slc39a8&highlight=slc39a8

57. PARK, J. H., et al., *SLC39A8 Deficiency: A Disorder of Manganese Transport and Glycosylation.* Am J Hum Genet, 2015. **97**(6): p. 894-903.

58. DÖRRE, K., et al., *A new case of UDP-galactose transporter deficiency (SLC35A2-CDG): molecular basis, clinical phenotype, and therapeutic approach.* J Inherit Metab Dis, 2015. **38**(5): p. 931-40.

59. 29/04/2019., BIOMARINN INTERNATIONAL LTD. ACCESSED:, *Summary of Product Characteristics (SPC) – Naglazyme 1 mg/mL concentrate for solution for infusion.* 2011.

60. LTD., SWEDISH ORPHAN BIOVITRUM (SOBI), *Summary of Product Characteristics (SPC) – Ravicti 1.1g/mL oral liquid.* . 2018.

61. AGENCY, EUROPEAN MEDICINES, *Assessment report - Ravicti International non-proprietary name: glycerol phenylbutyrate.* . 2015.

62. NEELEMAN, ROCHUS A., et al., *Heme as an initial treatment for severe decompensation in tyrosinemia type 1.* Genetics in Medicine, 2020. **22**(2): p. 437-438.

63. (BIMDG), BRITISH INHERITED METABOLIC DISEASE GROUP. BIMDG Adult Emergency Adult Plan Acute Porphyria. 2017 [cited 2019 29th April]; Available from: http://www.bimdg.org.uk/store/guidelines/Acute_Porphyria_Emergency_Management_BIMDG_FINAL_256730_15122017.pdf.

64. STEIN, P., et al., *Best practice guidelines on clinical management of acute attacks of porphyria and their complications.* Ann Clin Biochem, 2013. **50**(Pt 3): p. 217-23.

65. WOODLAND, G., UKMI. Medicines Q&A: How should haem arginate (human hemin) be administered in the management of acute porphyria? . 2018 [cited 2019 29th April]; Available from: https://www.sps.nhs.uk/articles/how-should-haem-arginate-human-hemin-be-administered-in-the-management-of-acute-porphyria/

66. MEDUSA), INJECTABLE MEDICINES GUIDE. Injectable Medicines Guide – Intravenous Paediatric Haem arginate. 2018 2019]; 15th May]. Available from: http://www.injguide.nhs.uk/IVGuideDisplay.asp.

67. LABORATOIRES STEROP NV, *Hydroxocobalamin 10 mg/2 mL Package Leaflet: Information for the user*, in *Available on request.* 2016.

68. CARRILLO-CARRASCO, N., et al., *Hydroxocobalamin dose escalation improves metabolic control in cblC.* J Inherit Metab Dis, 2009. **32**(6): p. 728-731.

69. HUEMER, M., et al., *Guidelines for diagnosis and management of the cobalamin-related remethylation disorders cblC, cblD, cblE, cblF, cblG, cblJ and MTHFR deficiency.* J Inherit Metab Dis, 2017. **40**(1): p. 21-48.

70. BAUMGARTNER, MATTHIAS R., et al., *Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia.* Orphanet Journal of Rare Diseases, 2014. **9**(1): p. 130.

71. (TAKEDA), SHIRE PHARMACEUTICALS LTD. Summary of Product Characteristics (SPC) – Elaprase 2 mg/mL concentrate for solution for infusion. 2018 [cited 2019 10th May]; Available from: https://www.medicines.org.uk/emc/product/9184

72. GENZYME, SANOFI. Summary of Product Characteristics (SPC) – Cerezyme 200-unit powder for concentrate for solution for infusion. . 2018 [cited 2019 09/05/2019]; Available from: https://www.medicines.org.uk/emc/product/9764/

73. GENZYME, SANOFI. Summary of Product Characteristics (SPC) – Aldurazyme 100 units/mL concentrate for solution for infusion. 2018 [cited 2019 10th May]; Available from: https://www.medicines.org.uk/emc/product/216

74. JOÃO SILVA, M., et al., *Pyruvate dehydrogenase deficiency: identification of a novel mutation in the PDHA1 gene which responds to amino acid supplementation.* Eur J Pediatr, 2009. **168**(1): p. 17-22.

75. PATEL, K. P., et al., *The spectrum of pyruvate dehydrogenase complex deficiency: clinical, biochemical and genetic features in 371 patients.* Mol Genet Metab, 2012. **106**(3): p. 385-94.

76. (BIMDG), BRITISH INHERITED METABOLIC DISEASE GROUP. Adult Emergency Management Urea Cycle Defects. 2018 [cited 2019 10th May]; Available from: http://www.bimdg.org.uk/store/guidelines/ADULT_UCD-rev_2015_422170_09012016.pdf

77. (BIMDG), BRITISH INHERITED METABOLIC DISEASE GROUP. Hyperammonaemia: Urea Cycle Disorders OTC and CPS deficiencies. . 2017 [cited 2019 10th May]; Available from: http://www.bimdg.org.uk/store/guidelines/ER-UCD1-v4_852010_09092016.pdf.

78. (BIMDG), BRITISH INHERITED METABOLIC DISEASE GROUP. Hyperammonaemia: Urea Cycle Disorders Citrullinaemia and Arginosuccinic Aciduria. . 2017 [cited 2019 10th May]; Available from: http://www.bimdg.org.uk/store/guidelines/ER-UCD2-v4_403123_09092016.pdf

79. SCHWAHN, B. , *RE: PAPERS FOR REVIEW: Metabolic CRG Agenda for Meeting to be held on the 16th January 2020.*, W.A. BATTEN, MURPHY, E.,, Editor. 2020.

80. (BIMDG), BRITISH INHERITED METABOLIC DISEASE GROUP. Hyperammonaemia in Urea Cycle Disorders – NAGs deficiency. 2017 [cited 2019 10th May]; Available from: http://www.bimdg.org.uk/store/guidelines/ER-NAGSv4_936070_09092016.pdf

81. (BIMDG), BRITISH INHERITED METABOLIC DISEASE GROUP. Undiagnosed Hyperammonaemia: Diagnosis and immediate management. 2017 [cited 2019 10th May]; Available from: http://www.bimdg.org.uk/store/guidelines/Hyperammonaemiaand_manage_2016_415469_09092016.pdf

82. EL-HATTAB, A. W., ALMANNAI, M., and SCAGLIA, F., *Arginine and citrulline for the treatment of MELAS syndrome.* J Inborn Errors Metab Screen, 2017. **5**.

83. KOGA, Y., et al., *L-arginine improves the symptoms of strokelike episodes in MELAS.* Neurology, 2005. **64**(4): p. 710-2.

84. PAVLU-PEREIRA, H., FLORINDO, C., SILVA, M.J., TAVARES DE ALMEIDA, I., LEANDRO, P., RIVERA, I., VICENTE J.B., *O-035 Exploring stabilising small molecules as a potential chaperone therapy for pyruvate dehydrogenase complex deficiency.*, in *Society for the Study of Inborn Errors of Metabolism*. 2015, J Inherit Metab Dis: Lyon. p. S35 – S378.

85. LHEUREUX, P. E., et al., *Science review: carnitine in the treatment of valproic acid-induced toxicity - what is the evidence?* Crit Care, 2005. **9**(5): p. 431-40.

86. ROSSI, A., FECAROTTA, S., DELLA CASA, R., ROMANO, R., ZUPPALDI, C., STRISCIUGLIO, P., PARENTI, G.,, *P-184 Efficacy of Riboflavin supplementation in carnitine-induced fish odour syndrome.* . Journal of Inherited Metabolic Diseases, 2018. **41**: p. S124.

87. EL-HATTAB, A. W., *Systemic Primary Carnitine Deficiency*, in *GeneReviews(®)*, M.P. ADAM, et al., Editors. 1993, University of Washington, Seattle, Copyright © 1993-2020, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.: Seattle (WA).

88. (BIMDG), BRITISH INHERITED METABOLIC DISEASE GROUP. Methylmalonic Acidaemia – Acute Decompensation. 2017 [cited 2019 12th May]; Available from: http://www.bimdg.org.uk/store/guidelines/ER-MMA-v4_141428_09092016.pdf

89. (BIMDG), BRITISH INHERITED METABOLIC DISEASE GROUP. Isovaleric Acidaemia – Acute Decompensation. 2016 [cited 2019 12th May]; Available from: http://www.bimdg.org.uk/store/guidelines/ER-IVA-v4_101727_09092016.pdf

90. (BIMDG), BRITISH INHERITED METABOLIC DISEASE GROUP. Propionic Acidaemia – Acute Decompensation. 2017 [cited 2019 12th May]; Available from: http://www.bimdg.org.uk/store/guidelines/ER-PA-v4_887167_09092016.pdf

91. (BIMDG), BRITISH INHERITED METABOLIC DISEASE GROUP. Adult Emergency Management - Propionic Acidaemia. . 2018 [cited 2019 13th May]; Available from: http://www.bimdg.org.uk/store/guidelines/ADULT_PA-rev_2015_672411_09012016.pdf

92. (BIMDG), BRITISH INHERITED METABOLIC DISEASE GROUP. Adult Emergency Management – Methylmalonic Acidaemia. 2018 [cited 2019 12th May]; Available from: http://www.bimdg.org.uk/store/guidelines/ADULT_MMA-rev_2015_808601_09012016.pdf.

93. PHARMACEUTICAL PRESS & MEDICINES COMPLETE, 2019. ACCESSED ONLINE ON 13/05/2019. , *Martindale: The Complete Drug Reference.*, P. PRESS, Editor. 2019.

94. BABIKER, M., ROGERS, R., . Clinical Guideline: Levodopa trial in children suspected to have dopamine responsive dystonia. . 2018 [cited 2019 13th May]; Available from: http://nww.avon.nhs.uk/dms/download.aspx?did=19260.

95. PFEFFER, GERALD, et al., *Treatment for mitochondrial disorders.* Cochrane Database of Systematic Reviews, 2012(4).

96. RODRIGUEZ, M. C., et al., *Beneficial effects of creatine, CoQ10, and lipoic acid in mitochondrial disorders.* Muscle Nerve, 2007. **35**(2): p. 235-42.

97. MAESAKA, H., et al., *Hyperalaninemia hyperpyruvicemia and lactic acidosis due to pyruvate carboxylase deficiency of the liver; treatment with thiamine and lipoic acid.* Eur J Pediatr, 1976. **122**(2): p. 159-68.

98. BYRD, D. J., et al., *Neonatal pyruvate dehydrogenase deficiency with lipoate responsive lactic acidaemia and hyperammonaemia.* Eur J Pediatr, 1989. **148**(6): p. 543-7.

99. NICOLSON, G. L., *Mitochondrial Dysfunction and Chronic Disease: Treatment With Natural Supplements.* Integr Med (Encinitas), 2014. **13**(4): p. 35-43.

100. ANALYTICS, GREENWOOD VILLAGE (CO): TRUVEN HEALTH. Lipoic acid. In: In Depth Answers [database on internet]. 2019 [cited 2019 16th May]; Available from: www.micromedexsolutions.com.

101. NUTRICIA. Pure Amino Acid Powders: L-isoleucine. . 2019 [cited 2019 13th May]; Available from: http://www.nutricia.ie/products/view/pure_amino_acid_powders#

102. VITAFLO. Leucine 100. 2019 [cited 2019 18th December]; Available from: https://www.nestlehealthscience.co.uk/asset-library/documents/vitaflo/datacards%202018%20-%2019/l0420_dc3_uk_0417%20leucine%20app.pdf

103. NUTRICIA. Pure Amino Acid Powders: L-leucine. . 2019 [cited 2019 13th May]; Available from: https://www.nutriciahcp.com/adult/products/L-Leucine/

104. NUTRICIA. Pure Amino Acid Powders: L-lysine. 2019 [cited 2019 13th May]; Available from: http://www.nutricia.ie/products/view/pure_amino_acid_powders#

105. HYLAND, K., et al., *Oral phenylalanine loading in dopa-responsive dystonia.* A possible diagnostic test, 1997. **48**(5): p. 1290-1297.

106. VAN GINKEL, W. G., et al., *The Effect of Various Doses of Phenylalanine Supplementation on Blood Phenylalanine and Tyrosine Concentrations in Tyrosinemia Type 1 Patients.* Nutrients, 2019. **11**(11).

107. DE KONING, T. J., et al., *Congenital microcephaly and seizures due to 3-phosphoglycerate dehydrogenase deficiency: outcome of treatment with amino acids.* J Inherit Metab Dis, 2002. **25**(2): p. 119-25.

108. DE KONING, T. J., et al., *Prenatal and early postnatal treatment in 3-phosphoglycerate-dehydrogenase deficiency.* Lancet, 2004. **364**(9452): p. 2221-2.

109. NUTRICIA. Pure Amino Acid Powders: L-valine. 2019 [cited 2019 13th May]; Available from: http://www.nutricia.ie/products/view/pure_amino_acid_powders#

110. LTD., RECORDATI RARE DISEASES UK. Summary of Product Characteristics – Cystagon 150 mg hard capsules. 2017 [cited 2019 20th May]; Available from: https://www.medicines.org.uk/emc/product/6237/

111. INC., LEXICOMP. UpToDate: Tiopronin – drug information. 2019 [cited 2019 20th May]; Available from: https://www.uptodate.com/contents/tiopronin-drug-information?sectionName=Pediatric&topicId=10287&search=tiopronin&usage_type=panel&anchor=F12595418&source=panel_search_result&selectedTitle=1~6&kp_tab=drug_general&display_rank=1#F12595418

112. PHARMACAL, MISSION. Summary of Product Characteristics – Thiola (tiopronin) tablets. 2019 [cited 2019 20th May]; Available from: https://www.thiola.com/sites/default/files/2018-09/thiola_pi_unhighlighted_thl_t9360r0617.pdf

113. AMICUS THERAPEUTICS EUROPE LTD. Summary of Product Characteristics (SPC) – Galafold 123 mg hard capsules. 2016 [cited 2019 20th May]; Available from: https://www.ema.europa.eu/en/documents/product-information/galafold-epar-product-information_en.pdf

114. ACTELION PHARMACEUTICALS UK LTD. Summary of Product Characteristics (SPC) – Zavesca (miglustat) 100 mg hard capsules. . 2018 [cited 2019 20th May]; Available from: https://www.medicines.org.uk/emc/product/39/smpc

115. LTD., ACTELION PHARMACEUTICALS UK, *Actelion Medical Information: Attached is the response to your inquiry UK18-00039*, W. BATTEN, Editor. 2018.

116. NUTRITION WAREHOUSE LTD. Summary of Product Characteristics (SPC) - Nicotinamide 100 mg tablets. 2006 [cited 2019 20th May]; Available from: http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1533269397496.pdf

117. (SOBI), SWEDISH ORPHAN BIOVITRUM LTD. Summary of Product Characteristics (SPC) – Orfadin 10 mg hard capsules. 2019 [cited 2019 3rd June]; Available from: https://www.medicines.org.uk/emc/product/10052/

118. (SOBI), SWEDISH ORPHAN BIOVITRUM LTD. Summary of Product Characteristics (SPC) – Orfadin 4 mg/mL oral suspension. . 2019 [cited 2019 3rd June]; Available from: https://www.medicines.org.uk/emc/product/6927#

119. INTRONE, W. J., et al., *A 3-year randomized therapeutic trial of nitisinone in alkaptonuria.* Mol Genet Metab, 2011. **103**(4): p. 307-14.

120. GUIDE, INJECTABLE MEDICINES. Injectable Medicines Guide (Medusa) – Octreotide. 2016 [cited 2019 31st July]; Available from: http://www.injguide.nhs.uk/IVGuideDisplay.asp

121. INC., LEXICOMP. UpToDate: Vitamin B5 (Pantothenic acid): Drug Information. Topic 10191. Version 69.0. . 2019 [cited 2019 3rd June]; Available from: https://www.uptodate.com/contents/vitamin-b5-pantothenic-acid-drug-information?search=pantothenic%20acid&source=panel_search_result&selectedTitle=1~24&usage_type=panel&kp_tab=drug_general&display_rank=1

122. CLARKE, S. L., et al., *Barth syndrome.* Orphanet J Rare Dis, 2013. **8**: p. 23.

123. BELL, CAROLYN L. and GRAZIANO, FRANK M., *The safety of administration of penicillamine to penicillin-sensitive individuals.* Arthritis & Rheumatism, 1983. **26**(6): p. 801-803.

124. GILLETT, G., *RE: National Metabolic Formulary – please forward to Joan.*, W. BATTEN, Editor. 2020.

125. WILSON, M.P., *0-068: Developments in the diagnosis and treatment of PNPO deficiency.* J Inherit Metab Dis, 2016. **39**.

126. COMAN, D., et al., *PNPO Deficiency and Cirrhosis: Expanding the Clinical Phenotype?* JIMD Rep, 2016. **25**: p. 71-75.

127. HOFFMANN, G. F., et al., *Pyridoxal 5'-phosphate may be curative in early-onset epileptic encephalopathy.* J Inherit Metab Dis, 2007. **30**(1): p. 96-9.

128. MORRIS, A. A., et al., *Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency.* J Inherit Metab Dis, 2017. **40**(1): p. 49-74.

129. COCHAT, PIERRE and BASMAISON, ODILE, *Current approaches to the management of primary hyperoxaluria.* Archives of Disease in Childhood, 2000. **82**(6): p. 470-473.

130. TOXBASE. Pyridoxine hydrochloride (pyridoxine). . 2017 [cited 2019 22nd July]; Available from: https://www.toxbase.org/poisons-index-a-z/p-products/pyridoxine/

131. (BIMDG), BRITISH INHERITED METABOLIC DISEASE GROUP. HCU Clinical Management Guidelines – v1.2. 2017 [cited 2019 3rd June]; Available from: http://www.bimdg.org.uk/store/enbs//HCU_clinical_management_guidelines_v12_Jan_2017_105750_25042017.pdf

132. WILSON, C. P., et al., *Blood pressure in treated hypertensive individuals with the MTHFR 677TT genotype is responsive to intervention with riboflavin: findings of a targeted randomized trial.* Hypertension, 2013. **61**(6): p. 1302-8.

133. MCNULTY, H., STRAIN, J. J., and WARD, M., *Riboflavin lowers blood pressure in hypertensive people with the MTHFR 677TT genotype.* Arch Public Health, 2014. **72**(Suppl 1): p. K2.

134. *Oral Presentations.* Journal of Inherited Metabolic Disease, 2018. **41**(1): p. 1-36.

135. HAACK, T. B., et al., *Exome sequencing identifies ACAD9 mutations as a cause of complex I deficiency.* Nat Genet, 2010. **42**(12): p. 1131-4.

136. LTD., BIOMARINN INTERNATIONAL. Summary of Product Characteristics (SPC) for Kuvan 100 mg soluble tablets. 2013 [cited 2019 9th June]; Available from: https://www.ema.europa.eu/en/documents/product-information/kuvan-epar-product-information_en.pdf

137. WARD, J. , *Re: Funding for Sapropterin for PTPS deficiency*, H. LEMONDE, Editor. 2018.

138. MUNTAU, ANIA C., et al., *International best practice for the evaluation of responsiveness to sapropterin dihydrochloride in patients with phenylketonuria.* Molecular Genetics and Metabolism, 2019. **127**(1): p. 1-11.

139. ENGLAND, NHS. Clinical Commissioning Policy: Sapropterin (Kuvan) for Phenylketonuria: Use in Pregnancy. Commissioning policy E12/P/a. 2013 [cited 2019 18th December]; Available from: https://www.england.nhs.uk/wp-content/uploads/2013/04/e12-p-a.pdf.

140. GUIDE, INJECTABLE MEDICINES. Injectable Medicines Guide (Medusa) – sodium benzoate version 4. 2016 [cited 2019 31st July]; Available from: http://www.injguide.nhs.uk/IVGuideDisplay.asp

141. WILLIAM, BATTEN, HANNAH, BATECHELOR, and DANIELA, MONTI, *P2P Stability study of a mixed system of sodium benzoate and sodium phenylbutyrate in intravenous (iv) infusion fluids.* Archives of Disease in Childhood, 2018. **103**: p. e1 - e1.

142. (BIMDG), BRITISH INHERITED METABOLIC DISEASE GROUP. Hyperammonaemia – Urea Cycle Disorders OTC and CPS deficiencies. . 2017 [cited 2019 20th June]; Available from: http://www.bimdg.org.uk/store/guidelines/ER-UCD1-v4_852010_09092016.pdf

143. (BIMDG), BRITISH INHERITED METABOLIC DISEASE GROUP. Propionic Acidaemia – Acute Decompensation. . 2017 [cited 2019 20th June]; Available from: http://www.bimdg.org.uk/store/guidelines/ER-PA-v4_887167_09092016.pdf

144. (BIMDG), BRITISH INHERITED METABOLIC DISEASE GROUP. Propionic Acidaemia – Acute Decompensation. . 2017 [cited 2019 20th June]; Available from: http://www.bimdg.org.uk/store/guidelines/ER-PA-v4_887167_09092016.pdf

145. BIMDG), BRITISH INHERITED METABOLIC DISEASE GROUP. Hyperammonaemia – NAGs deficiency. . 2017 [cited 2019 20th June]; Available from: http://www.bimdg.org.uk/store/guidelines/ER-NAGSv4_936070_09092016.pdf

146. (BIMDG), BRITISH INHERITED METABOLIC DISEASE GROUP. Hyperammonaemia due to transport defects HHH syndrome and LPI. . 2017 [cited 2019 20th June]; Available from: http://www.bimdg.org.uk/store/guidelines/ER-HHH-LPI-v4_474932_09092016.pdf

147. (BIMDG), BRITISH INHERITED METABOLIC DISEASE GROUP. Adult Emergency Management of Urea Cycle Defects including OTC deficiency, CPS1 deficiency, citrullinaemia, arginosuccinic aciduria, arginase deficiency, NAGs deficiency 2015 [cited 2019 20th June]; Available from: http://www.bimdg.org.uk/store/guidelines/ADULT_UCD-rev_2015_422170_09012016.pdf

148. DERKS, T. G. and SMIT, G. P., *Dietary management in glycogen storage disease type III: what is the evidence?* J Inherit Metab Dis, 2015. **38**(3): p. 545-50.

149. LTD., SPECIAL PRODUCTS, *Data Sheet: Sodium D,L-3-hydroxybutyrate*. 2006, Available on request from the company.

150. IMMEDICA. Summary of Product Characteristics (SPC)- Ammonaps 500 mg tablets. 2019 [cited 2020 6th September]; Available from: https://www.medicines.org.uk/emc/product/10986/smpc.

151. GUIDE, INJECTABLE MEDICINES. Injectable Medicines Guide (Medusa) – sodium phenylbutyrate. . 2016 [cited 2019 31st July]; Available from: http://www.injguide.nhs.uk/IVGuideDisplay.asp

152. GUIDE, INJECTABLE MEDICINES. Injectable Medicines Guide (Medusa) – Thiamine version 4. . 2017 [cited 2019 31st July]; Available from: http://www.injguide.nhs.uk/IVGuideDisplay.asp

153. OISHI, K. and DIAZ, G. A., *Thiamine-Responsive Megaloblastic Anemia Syndrome*, in *GeneReviews(®)*, M.P. ADAM, et al., Editors. 2017, University of Washington, Seattle, Copyright © 1993-2020, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.: Seattle (WA).

154. LTD., TILLOMED LABORATORIES. Summary of Product Characteristics (SPC) – Trientine dihydrochloride Tillomed 250 mg capsules, hard. . 2020 [cited 2019 27th June]; Available from: https://www.medicines.org.uk/emc/product/11626/smpc.

155. ENGLAND, NHS. Clinical Commissioning Policy: Trientine for Wilson Disease (all ages) NHS England Reference: 170094P. 2018 [cited 2019 27th June]; Available from: https://www.england.nhs.uk/wp-content/uploads/2018/12/Trientine-for-Wilson-disease-all-ages-1.pdf

156. LTD., GMP-ORPHAN UNITED KINGDOM. Summary of Product Characteristics (SPC) – Cuprior 150 mg film-coated tablets. 2017 [cited 2019 27th June]; Available from: https://www.medicines.org.uk/emc/product/10100#DOCREVISION

157. TIBBS, C., *NHS England Circular RE: Trientine for Wilson Disease (all ages) NHS England Reference: 170094P.*, N. ENGLAND, Editor. 2019.

158. AGENCY, EUROPEAN MEDICINES, *CHMP assessment report, Cuprior, EMA/308946/2017 Procedure No. EMEA/H/C/004005/0000*, in *Procedure No. EMEA/H/C/004005/0000*. 2017.

159. LTD., SHIRE PHARMACEUTICALS. Summary of Product Characteristics (SPC) – VPRIV 400 units powder for solution infusion. . 2018 [cited 2019 18th July]; Available from: https://www.medicines.org.uk/emc/product/9187#

160. SANOFI. Summary of Product Characteristics (SPC) – Sabril 500 mg film coated tablets. 2018 [cited 2019 17th July]; Available from: https://www.medicines.org.uk/emc/product/4279/

161. BURNETT JR, HOOPER AJ, HEGELE RA. . , *Abetalipoproteinemia.* GeneReviews® [Internet], 2018.

162. LTD., RECORDATI RARE DISEASES UK. Summary of Product Characteristics (SPC) – Wilzin 25 mg hard capsules. . 2019 [cited 2019 22nd July]; Available from: https://www.medicines.org.uk/emc/product/6245/smpc

163. AIRES, C. C., et al., *New insights on the mechanisms of valproate-induced hyperammonemia: inhibition of hepatic N-acetylglutamate synthase activity by valproyl-CoA.* J Hepatol, 2011. **55**(2): p. 426-34.

164. HROUDOVA, J. and FISAR, Z., *Activities of respiratory chain complexes and citrate synthase influenced by pharmacologically different antidepressants and mood stabilizers.* Neuro Endocrinol Lett, 2010. **31**(3): p. 336-42.

165. DE VRIES, M. C., et al., *Safety of drug use in patients with a primary mitochondrial disease: An international Delphi-based consensus.* J Inherit Metab Dis, 2020. **43**(4): p. 800-818.

166. MARSH, S. I, *Neuromuscular disorders and anaesthesia. Part 2: specific neuromuscular disorders.* Cont Edu Anaesth Crit Care and Pain, 2011. **11**: p. 119 - 123.

167. *Meyler's side effects of drugs. 6 6*. 2006, Amsterdam: Elsevier.

168. DRIESSEN, J. J., *Neuromuscular and mitochondrial disorders: what is relevant to the anaesthesiologist?* Curr Opin Anaesthesiol, 2008. **21**(3): p. 350-5.

169. FARAG, EHAB, et al., *Metabolic Acidosis due to Propofol Infusion.* Anesthesiology, 2005. **102**(3): p. 697-698.

170. ALLEN, C., PERKINS, R., and SCHWAHN, B., *A retrospective review of anesthesia and perioperative care in children with medium-chain acyl-CoA dehydrogenase deficiency.* Paediatr Anaesth, 2017. **27**(1): p. 60-65.

171. EMA), EUROPEAN MEDICINES AGENCY. Information for the package leaflet regarding lactose used as an excipient in medicinal products for human use. 2018 [cited 2019 16th October]; Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-information-package-leaflet-regarding-lactose-used-excipient-medicinal-products-human-use_en.pdf

172. SHAW, VANESSA, *Clinical paediatric dietetics*. 4th Edition ed. 2016.

173. PRODUCTS., EUROPEAN MEDICINES AGENCY (EMA); COMMITTEE FOR HUMAN MEDICINAL. Information for package leaflet regarding fructose and sorbitol used as excipient in medicinal products for human use. 2017 [cited 21st January 2020]; Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/information-package-leaflet-regarding-fructose-sorbitol-used-excipients-medicinal-products-human-use_en.pdf

174. (IMP), INTERNATIONAL MITO PATIENTS. LIST OF MEDICINES TO BE USED WITH CAUTION IN PRIMARY MITOCHONDRIAL DISEASE [online]. 2020 [cited 2020 22nd February]; Available from: https://www.mitopatients.org/mitodisease/list-of-medicines.

175. THERAPEUTICS, AKCEA. Summary of Product Characteristics - Waylivra 285mg solution for injection in pre-filled syringe. 2019 [cited 2019 5th July]; Available from: https://www.ema.europa.eu/en/documents/product-information/waylivra-epar-product-information_en.pdf.

176. (MHRA)., MEDICINES HEALTHCARE REGULATORY AGENCY. Early access to medicines scheme (EAMS) scientific opinion: Volanesorsen as a treatment of adult patients with familial chylomicronaemia syndrome. 2018; Available from: https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-scientific-opinion-volanesorsen-as-a-treatment-of-adult-patients-with-familial-chylomicronaemia-syndrome

177. NICE), NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. Volanesorsen for treating familial chylomicronaemia syndrome [ID1326]. . 2020 [cited 2019 18th July]; Available from: https://www.nice.org.uk/guidance/indevelopment/gid-hst10015

178. PHARMACEUTICALS., ULTRAGENYX. Summary of Product Characteristics (SPC) – Mepsvii concentrate for solution for infusion. . 2018 [cited 2019 17th July]; Available from: https://www.ema.europa.eu/en/documents/product-information/mepsevii-epar-product-information_en.pdf

179. SERVICE, SPECIALIST PHARMACY. Vestronidase alfa. 2019 [cited 2019 17th July]; Available from: https://www.sps.nhs.uk/medicines/vestronidase-alfa/

180. (SPS), SPECIALIST PHARMACY SERVICE. Uridine Triacetate. 2019 [cited 2019 18th July]; Available from: https://www.sps.nhs.uk/medicines/uridine-triacetate/

181. CORPORATION, WELLSTAT THERAPEUTICS. Summary of Product Characteristics (SPC) for Xuriden (uridine triacetate) oral granules. 2015 [cited 2019 17th July]; Available from: https://www.xuriden.com/FPI.pdf

182. Prescribing Information: Nulibry, Sentyl Therapeutics Inc. 2021. Available from: nulibry-prescribing-information-v2.pdf

183. SAUDUBRAY, JEAN-MARIE, BAUMGARTNER, MATTHIAS R., and WALTER, JOHN HUGH, *Inborn metabolic diseases : diagnosis and treatment*. 2022

184. Veriton Pharma data sheet 2019

185. Amryt Pharmaceuticals. Myalepta 3 mg powder for solution for injection - Summary of Product Characteristics (SPC). 2022 [cited 2022 28th November]. Available from: https://www.medicines.org.uk/emc/product/11182

186. NHS England. Clinical Commissioning Policy [170095P]: Metreleptin for congenital leptin deficiency (all ages). 2018 [cited 2022 28th November]. Available from: https://www.england.nhs.uk/publication/metreleptin-for-congenital-leptin-deficiency-all-ages/

187. NICE. Highly specialised technologies guidance [HST14]: Metreleptin for treating lipodystrophy. 2021 [cited 2022 28th November]. Available from: https://www.nice.org.uk/guidance/hst14/resources/metreleptin-for-treating-lipodystrophy-pdf-50216258848453

188. Treem WR, McAdams L, Stanford L, Kastoff G, Justinch C, Hyams J. Sacrosidase therapy for Congenital Sucrase-Isomaltase Deficiency. J Pediatr. Gatrpemterol Nutr. 1999; 28 (2): 137-142.

189. Medicines and Healthcare Products Regulatory Agency. Aminoglycosides (gentamicin, amikacin, tobramycin, and neomycin): increased risk of deafness in patients with mitochondrial mutations. Jan 2021. Available from: https://www.gov.uk/drug-safety-update/aminoglycosides-gentamicin-amikacin-tobramycin-and-neomycin-increased-risk-of-deafness-in-patients-with-mitochondrial-mutations

190. Newcastle Specials NHS Pharmacy Production and Quality Control Unit.2023.

191. Sovereign Medical. Carglumic Acid Waymade 200 mg Dispersible Tablets. 2021 [cited 2022 8th April]; Available from: https://www.medicines.org.uk/emc/product/11814/smpc.

192. Eurocept International bv. Ucedane 200 mg dispersible tablets. 2020 [cited 2022 8th April]; Available from: https://www.medicines.org.uk/emc/product/11441/smpc

193. Cipaglucosidase alpha with Miglustat for treatment of Late onset pompe disease. August 2023. (Online). Available from: Overview | Cipaglucosidase alfa with miglustat for treating late-onset Pompe disease | Guidance | NICE. (Accessed August 2023).

194. Amicus Therapeutics. EAMS Information for HCP Cipaglucosidase alfa and Miglustat. Accessed online on 15/02/2023 available from: Cipaglucosidase alfa with miglustat in the treatment of late-onset Pompe disease - GOV.UK (www.gov.uk)

195. Sanofi. Summary of Product Characteristics (SPC) for Nexviadyme (Avalglucosidase alfa) 100mg powder for concentrate for solution for infusion. Accessed online on 14/02/2023 available from: Nexviadyme | European Medicines Agency (europa.eu)

196. NICE Technology appraisal guidance [TA821] Avalglucosidase alfa for treating Pompe Disease. Accessed online on 14/02/2023, available from www.nice.org.uk/guidance/ta821

197. SANOFI. Praluent 150mg solution for injection in pre-filled pen. 2022 [cited 2023 31st March]; Available from https://www.medicines.org.uk/emc/product/8093/smpc#gref

198. NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE (NICE), 2016. Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia [TA393]. 2016 [cited 2023 31st March]; Available from https://www.nice.org.uk/guidance/ta393

199. NHSENGLAND. Medicines not reimbursed through national prices and directly commissioned by NHS England. 2022 [cited 2023 28th March]; Available from: https://www.england.nhs.uk/publication/nhs-england-drugs-list/

200. NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE (NICE), 2016. Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia [TA394]. 2016 [cited 2023 28th March]; Available from https://www.nice.org.uk/guidance/ta394

201. NHS England, 2016. NHS England statement on evolocumab for the treatment of homozygous familial hypercholesterolaemia. Specialised Services Circular 1649 2016-09-13

202. NHSENGLAND. Medicines not reimbursed through national prices and directly commissioned by NHS England, . 2022 [cited 2023 28th March]; Available from: https://www.england.nhs.uk/publication/nhs-england-drugs-list/

203. Amryt Pharmaceuticals DAC, 2022. *Summary of Product Characteristics Lojuxta® 5mg 10mg 20mg hard capsules*. Accessed 08/04/23 Available from: https://www.medicines.org.uk/emc/product/9669/smpc

204. British National Formulary, Pharmaceutical Press: Accessed online on: 08/04/2023. Available from: https://bnf.nice.org.uk/

205. NHSE, 2018. *Clinical Commissioning Policy: Lomitapide for treating homozygous familial hypercholesterolaemia*. Accessed online on 08/04/2013. Available from: https://www.england.nhs.uk/wp-content/uploads/2018/07/1679-lomitapide.pdf

206. NHS England, 2019. Medicines not reimbursed through national prices and directly commissioned by NHS England, Versionhttps://www.england.nhs.uk/wp-content/uploads/2019/04/nhs-england-drugs-list-v14.1.pdf 14.. Accessed 08/04/2013.

207. Sacks et al, 2013. *Severe hypertriglyceridemia with Pancreatitis. Thirteen Years' treatment with lomitapide*. JAMA intern Med published online December 23, 2013. doi:10.1001/jamainternmed.2013.13309.

208. Zydus France S.A.S. Nulibry 9.5mg powder for solution for injection – Summary of Product Characteristics (SPC) 2023; available from https://www.ema.europa.eu/en/medicines/human/EPAR/nulibry

209. Saudubray, 2011, Inborn Metabolic Diseases: Diagnosis and Treatment, 5th Edition, Springer

210. ZSCHOCKE, JOHANNES, et al., Vademecum metabolicum : diagnosis and treatment of inborn errors of metabolism, 5th Edition. 2021, Thieme; [Stuttgart]: Nutricia GmbH, Erlangen.

211. Chiesi Ltd. Summary of Product Characteristics (SPC) for pegunigalsidase alfa (Elfabrio®) solution for injection. Accessed online on 25/10/2023 available from: https://www.medicines.org.uk/emc/product/14960

212. NICE technology appraisal guidance [TA915], Pegunigalsidase alfa for treating Fabry disease. Accessed online on 25/10/2023, available from : https://www.nice.org.uk/guidance/ta915

213. Chiesi Ltd. FDA prescribing information for Elfabrio® (pegunigalsidase alfa-iwxj) injection, for intravenous use. Accessed online 25/10/2023, available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761161s000lbl.pdf

214. Padidela, R., Yates, R., Benscoter, D., McPhail, G., Chan, E., Nichani, J., Mughal, M.Z., Myer, C., Narayan, O., Nissenbaum, C. and Wilkinson, S., 2020. Characterization of tracheobronchomalacia in infants with hypophosphatasia. Orphanet Journal of Rare Diseases, 15, pp.1-9.

215. All Wales Medicines Strategy Group (AWMSG), 2022. Mercaptamine bitartrate Procysbi. [online] Available from https://awttc.nhs.wales/accessing-medicines/medicine-recommendations/mercaptamine-bitartrate-procysbi1/ Accessed 17/01/2023

216. Makuloluwa, A.K and Shams, F., 2018. Cysteamine hydrochloride eye drop solution for the treatmemt of corneal cystine crystal deposits in patients with cystinosis: an evidence-based review. Clinical Opthamology (Aukland, NZ), 12, p227

217. Baumgartner, M.R., Hörster, F., Dionisi-Vici, C., Haliloglu, G., Karall, D., Chapman, K.A., Huemer, M., Hochuli, M., Assoun, M., Ballhausen, D. and Burlina, A., 2014. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. Orphanet journal of rare diseases, 9(1), pp.1-36

218. Update reference to the commissioning policy instead NHS England » Urgent clinical commissioning policy statement: Vestronidase alfa for Mucopolysaccharidosis Type VII (MPS, Sly syndrome) (infantile)

219. Padidela, R., Cheung, M.S., Saraff, V. and Dharmaraj, P., 2020. Clinical guidelines for burosumab in the treatment of XLH in children and adolescents: British paediatric and adolescent bone group recommendations. Endocrine Connections, 9(10), p.1051

220. Wortmann, S.B., Van Hove, J.L., Derks, T.G., Chevalier, N., Knight, V., Koller, A., Oussoren, E., Mayr, J.A., van Spronsen, F.J., Lagler, F.B. and Gaughan, S., 2020. Treating neutropenia and neutrophil dysfunction in glycogen storage disease type Ib with an SGLT2 inhibitor. Blood, 136(9), pp.1033-1043.

221. Grünert, S.C., Derks, T.G., Adrian, K., Al-Thihli, K., Ballhausen, D., Bidiuk, J., Bordugo, A., Boyer, M., Bratkovic, D., Brunner-Krainz, M. and Burlina, A., 2022. Efficacy and safety of empagliflozin in glycogen storage disease type Ib: Data from an international questionnaire. Genetics in Medicine, 24(8), pp.1781-1788.

222. Boulanger, C., Stephenne, X., Diederich, J., Mounkoro, P., Chevalier, N., Ferster, A., Van Schaftingen, E. and Veiga-da-Cunha, M., 2022. Successful use of empagliflozin to treat neutropenia in two G6PC3-deficient children: Impact of a mutation in SGLT5. Journal of inherited metabolic disease, 45(4), pp.759-768.

223. Bidiuk, J., Gaciong, Z.A. and Sobieraj, P., 2022. The overall benefits of empagliflozin treatment in adult siblings with glycogen storage disease type Ib: one year experience. Archives of Medical Science: AMS, 18(4), p.1095.

224. Makrilakis, K., Barmpagianni, A. and Veiga-da-Cunha, M., 2022. Repurposing of Empagliflozin as a Possible Treatment for Neutropenia and Inflammatory Bowel Disease in Glycogen Storage Disease Type Ib: A Case Report. Cureus, 14(7).

225. Grünert, S.C., Elling, R., Maag, B., Wortmann, S.B., Derks, T.G., Hannibal, L., Schumann, A., Rosenbaum-Fabian, S. and Spiekerkoetter, U., 2020. Improved inflammatory bowel disease, wound healing and normal oxidative burst under treatment with empagliflozin in glycogen storage disease type Ib. Orphanet journal of rare diseases, 15, pp.1-8.

226. COMMITTEE, JOINT FORMULARY. British National Formulary (BNF). 2023. Empagliflozin monograph. Available from: https://bnf.nice.org.uk.

227. NICE Highly specialised technologies appraisal guidance. [HST13]. Volenesorsen for treating familial chylomicronaemia syndrome, Oct 2020. [Accessed Feb 2024]. Available from: 1 Recommendations | Volanesorsen for treating familial chylomicronaemia syndrome | Guidance | NICE

228. COMMITTEE, JOINT FORMULARY. British National Formulary (BNF). 2023. Volanesorsen monograph. Available from: https://bnf.nice.org.uk.

229. Gropman, A., 2003. Vigabatrin and newer interventions in succinic semialdehyde dehydrogenase deficiency. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*, *54*(S6), pp.S66-S72.

230. Reference : Hughes, D., et al 2015. Standard Operating Procedure for the treatment of type 3 Gaucher Disease with enzyme replacement therapy. Paper copy available from authors.

231. Amgen Ltd. Repatha SureClick -Summary of Product Characteristics. 2022 [cited 2023 28th March]; Available from https://www.medicines.org.uk/emc/medicine/30628#gref