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Mapping challenges in the accessibility of treatment products for urea cycle disorders: A survey of European healthcare professionals

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Abstract

Current management guidelines for urea cycle disorders (UCDs) offer clear strategies, incorporating both authorized and non-authorized medicinal products (including intravenous formulations and products regulated as food). These varying product categories are subject to specific accessibility challenges related to availability, reimbursement, and pricing. The aim of this study is to identify potential obstacles to optimal UCD treatment implementation in European clinical practice. A survey aimed at metabolic healthcare professionals (HCPs) managing patients with UCDs in Europe was disseminated through the European Reference Network for Hereditary Metabolic Disorders and the European registry and network for intoxication type metabolic diseases. Forty-eight survey responses were collected from 21 European countries. In 16 of these countries, at least one metabolic HCP reported challenges in accessing UCD products. Reimbursement issues were reported for most

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products (8/10), including both authorized and non-authorized products. Availability-related challenges were also reported for 8/10 products, although unavailability was limited to non-authorized products. Prices impacted accessibility for all authorized products (3/3) and one non-authorized IV product. The accessibility of UCD treatment products varied across Europe, although no clear regional variations could be discerned. Survey data revealed that metabolic HCPs experience challenges in accessing both authorized and non-authorized products for UCD management in the majority of European countries. This indicates that registering unauthorized products may not resolve all issues. Improved reimbursement policies and fair pricing models, as well as (adjusted) authorization procedures may help address these concerns, thereby optimizing treatment access for UCD patients.

KEYWORDS

(orphan) medicinal products, health care professional perspective, nutritional therapy, treatment access, urea cycle disorders

1 | INTRODUCTION

Urea cycle disorders (UCDs) are a group of rare inherited metabolic diseases (IMDs) wherein deficiencies in urea cycle functioning result in impaired removal of toxic ammonia from the body. In the "classic" UCDs, enzymes in the cycle itself are affected: carbamoylphosphate synthetase 1 deficiency (MIM#237300), ornithine transcarbamoylase deficiency (OTCD, MIM#311250), argininosuccinate synthetase 1 deficiency (MIM#215700), argininosuccinate lyase deficiency (MIM#207900), and arginase 1 deficiency (ARG1D, MIM#207800). Three additional disorders are also regarded UCDs as dysfunction of the urea cycle causes the main symptoms: In *N*-acetylglutamate synthase deficiency (NAGSD, MIM#237310), urea cycle dysfunction is caused by impaired *N*-acetylglutamate-dependent CPS1 activation. In hyperornithinemia-hyperammonemia-homocitrullinuria syndrome (MIM #238970), urea cycle dysfunction is caused by a deficient mitochondrial ornithine uptake (ORNT1/SLC25A15), affecting the OTC reaction. In citrin deficiency (MIM#603471; MIM#605814), the function of citrin (an aspartate/glutamate transporter in mitochondria) is impaired, resulting in insufficient cytosolic aspartate as a substrate for the ASS1 reaction.[1]

The clinical manifestations of these UCDs are highly variable and can range from mild to life-threatening, affect various organs, and can follow recurrently acute, acute-on-chronic, and chronic progressive disease courses.[2,3] The management approach for UCDs can be broadly categorized by two phases: treatment of acute decompensations and long-term management.[4] During acute decompensation, the primary goal is to rapidly reduce ammonia levels, which can be achieved by administration of intravenous (IV) nitrogen scavengers, i.e., sodium benzoate alone or together with sodium phenylacetate. This is combined with arginine-HCl IV, intended to restore deficiencies, activate CPS1 and hence to support the urea cycle. Dysfunctional arginine formation means its supplementation becomes essential to all UCDs except ARG1D. Sufficient caloric intake to promote anabolism should be provided concomitantly, and protein intake should be stopped for no longer than 24–48 h to prevent endogenous protein breakdown. Hemodialysis or hemofiltration should be considered in patients with plasma ammonia levels above 250 μmol/L to prevent severe neurological sequelae.[4,5] For long-term management, oral sodium benzoate and/or sodium or glycerol phenylbutyrate can be given to reduce nitrogen load. Arginine is supplemented (except for ARG1D) and in the mitochondrial UCDs carbamoylphosphate synthetase 1 deficiency, OTCD, and hyperornithinemia-hyperammonemia-homocitrullinuria syndrome, citrulline can be (additionally) supplemented. In NAGSD, oral *N*-carbamoylglutamate can substitute *N*-acetylglutamate and is used both in the acute setting and as long-term monotherapy.[4]

While current management guidelines[4] offer clear treatment strategies, their real-world application can be hindered by accessibility of essential products. This was worryingly illustrated by a survey on UCD treatment implementation in Germany and Austria: emergency medication was found to be unavailable in 34% of responding hospitals.[6] As of yet, it is unclear whether this is also the case in other European countries. Inaccessibility of treatment products can have dire consequences; in a French cohort of UCD patients, one patient died after

TABLE 1 Overview of urea cycle disorder management products and their current regulatory status in the European Union.

Regulatory category	Active ingredient(s)	Trade name(s)
Authorized medicinal products	Glycerol phenylbutyrate	Ravicti[a,8]
	N-Carbamoylglutamate	Carbaglu[b,9], Ucedane[10]
	Sodium phenylbutyrate	Ammonaps[11], Pheburane[b,12]
Non-authorized intravenous products	Arginine	n/a
	Sodium benzoate	n/a
	Sodium benzoate/phenylacetate	Ammonul[c]
	Sodium phenylbutyrate	n/a
Non-authorized oral products	Arginine	n/a
	Citrulline	n/a
	Sodium benzoate	n/a

[a]Active designation as orphan medicinal product.
[b]Designated orphan medicinal product upon introduction, orphan designation since expired.
[c]Not authorized in Europe, but has been granted a marketing authorization in the United States.

receiving only hemofiltration since nitrogen scavengers were unavailable.[7] Access to UCD treatment products may be impacted by their regulatory status, which, in Europe, varies from orphan medicinal products to products that have not been formally authorized as medicines, such as compounded (IV) formulations and food products (i.e. food supplements and foods for special medical purposes, see Table 1 for an overview).

Reliance on non-authorized (food) products is often necessary in the management of IMDs. Nutritional therapy products can be critical to improving metabolic stability in these disorders and while these products are routinely used, they have rarely been authorized for this purpose.[13,14] As a result, treatment products fall into regulatory categories ranging from food to (orphan) medicine, which can impact their availability, suitability, pricing and reimbursement—potentially reducing treatment access for patients with UCDs and other IMDs.[13,14] This study aims to assess the impact of these factors on the treatment of UCDs in European clinical practice. The objective is to identify potential obstacles to optimal treatment implementation, which can then be addressed to improve the medical management of UCDs and possibly provide insights for other IMDs facing similar challenges.

2 | METHODS

2.1 | Survey design and definitions

A cross-sectional survey was sent out to metabolic healthcare professionals (HCPs) managing adult and/or pediatric patients with UCDs in Europe. A predominantly closed-question questionnaire was designed, with five general demographic questions, three questions on UCD management and four sets of two questions each on product accessibility in UCD management. These addressed the occurrence of challenges in the accessibility of products in use in the (1) acute and (2) long-term setting, and inaccessible but desired products for the (3) acute and (4) the long-term setting. According to the World Health Organization, accessibility of a medicinal product is defined as both being *available* (i.e., can be found in a pharmacy or healthcare system) and being *affordable* (i.e., patients are financially able to obtain it, often through reimbursement).[15]

To analyze the accessibility of authorized (orphan) medicinal products, availability can be assessed by reviewing relevant marketing authorizations and affordability by analysis of national reimbursement decisions.[16,17] As discussed previously however, UCD management products include not only authorized (orphan) medicinal products but also products that were never authorized, such as food products and compounded formulations, as well as products only authorized outside of Europe. Therefore, analyzing the accessibility of UCD management products is more complex. Additionally, a third component is relevant to access to non-authorized treatment products: their suitability. Since these products are subject to different, less stringent manufacturing and quality requirements, it is important to consider if the available products are of sufficient quality and dosed appropriately for use in the treatment of a particular condition.[14]

To allow for the inclusion of all treatment products essential to managing UCDs, this study assessed their accessibility based on clinical practice itself. Therefore, we defined *accessibility* as the HCP's ability to utilize a treatment product for patient management in current clinical practice, considering *availability*, *affordability*, and *suitability*. If challenges in accessing a product were reported, respondents were then asked to specify the factor(s) responsible for complicating or preventing access: no or inconsistent availability, affordability (insufficient reimbursement and high pricing), and/or suitability (desired quality and dosing). These factors were thus evaluated from the perspectives of HCPs. The complete questionnaire is available in Supplementary Material S1.

TABLE 2 Reports of challenges in the accessibility of urea cycle disorder management products.

			Acute management	Long-term management
Austria	3	Pediatric[a] ($n = 3$)		
Belgium	3	Pediatric[a] ($n = 3$)	X	X
Czech Republic	2	Pediatric[a] ($n = 2$)	X	X
Denmark	1	Pediatric[a] ($n = 1$)		
France	1	Pediatric[a] ($n = 1$)		
Germany	6	Pediatric[a] ($n = 5$), internist ($n = 1$)	X	X
Greece	1	Pediatric[a] ($n = 1$)	X	
Hungary	1	Pediatric[b] ($n = 1$)	X	
Ireland	2	Pediatric ($n = 1$), internist[b] ($n = 1$)	X	
Italy	7	Pediatric[a] ($n = 6$), internist ($n = 1$)	X	
Latvia	1	Pediatric ($n = 1$)	X	X
Netherlands	3	Internist ($n = 2$), Pediatric ($n = 1$)	X	X
Norway	1	Pediatric ($n = 1$)		
Poland	1	Pediatric[a] ($n = 1$)	X	X
Portugal	2	Pediatric[a] ($n = 2$)	X	X
Slovakia	1	Pediatric[a] ($n = 1$)	X	
Slovenia	1	Pediatric ($n = 1$)		
Spain	7	Pediatric[a] ($n = 6$), internist ($n = 1$)	X	X
Sweden	1	Pediatric ($n = 1$)	X	
Switzerland	1	Pediatric[a] ($n = 1$)	X	X
UK	2	Internist ($n = 2$)		

Note: Green = No challenges reported. Red = Challenges in access reported.
[a]Also managing adult patients.
[b]/Clinical geneticist.

2.2 | Data collection

Responses were collected using the web-based survey software Castor EDC (Castor v2023.4.4.0). The survey was disseminated through the emailing list of both the European Reference Network for Hereditary Metabolic Disorders[18] (MetabERN) and the European registry and network for Intoxication type Metabolic Diseases[19] (E-IMD). Additionally, personal invitations were sent to metabolic experts from three countries (France, the United Kingdom, and Poland) that were not initially represented in the survey response, identified through prior international research collaborations by the authors. Response collection for the survey extended from September until December 2023.

2.3 | Statistical analysis

The results were analyzed and visualized using Microsoft Excel and R (version 4.3.2). All statistic tests used were descriptive. Normality was examined using quantile–quantile (Q–Q) plots and the Shapiro–Wilk test.

3 | RESULTS

A total of 48 unique completed survey responses from 43 healthcare centers in 21 European countries were collected, predominantly from metabolic pediatricians (83%, see Table 2). Five respondents completed the questionnaire twice, the first response was retained. It is of note that 65% ($n = 26$) of pediatricians in our survey reported managing both adult and pediatric UCD patients. The estimated number of patients with UCDs under management by the HCP ranged from 1 to 90 (median: 11), with a total of approximately 1000 UCD patients managed by surveyed HCPs. As expected based on UCD incidence data,[20] HCPs reported managing patients with OTCD most often, with 46 HCPs indicating they manage such cases, followed by management of argininosuccinate lyase deficiency ($n = 40$ HCPs) and argininosuccinate

TABLE 3 Access to urea cycle disorder management products per country: Usage and challenges.

Country	Product category, name									
	Authorized medicinal products			Non-authorized IV products				Non-authorized oral products		
	Glycerol phenylbutyrate (Ravicti)	*N*-carbamoylglutamate (Carbaglu, Ucedane)	Sodium phenylbutyrate (Ammonaps, Pheburane)	Arginine	Sodium Benzoate	Sodium Benzoate/phenylacetate (Ammonul)[a]	Sodium phenylbutyrate	Arginine	Citrulline	Sodium Benzoate
Belgium		X	X				X			
Czech Republic		X				X	X			
Germany	X		X			X				X
Greece					X		X			
Hungary					X	X	X			
Ireland			X	X	X		X			X
Italy							X			
Latvia		X		X	X	X	X	X		X
Netherlands	X					X				
Poland	X	X	X							
Portugal	X				X	X				
Slovakia				X		X				
Spain						X				X
Sweden						X				
Switzerland	X	X						X	X	

Note: Green = In use, no challenges reported. White = Not in use, no desired use reported. Orange = Available, challenges in accessibility reported. Red = Not available. Yellow = Reported as not available by some respondents, while others in same country report use.

[a]Not authorized in Europe, but imported from the US.

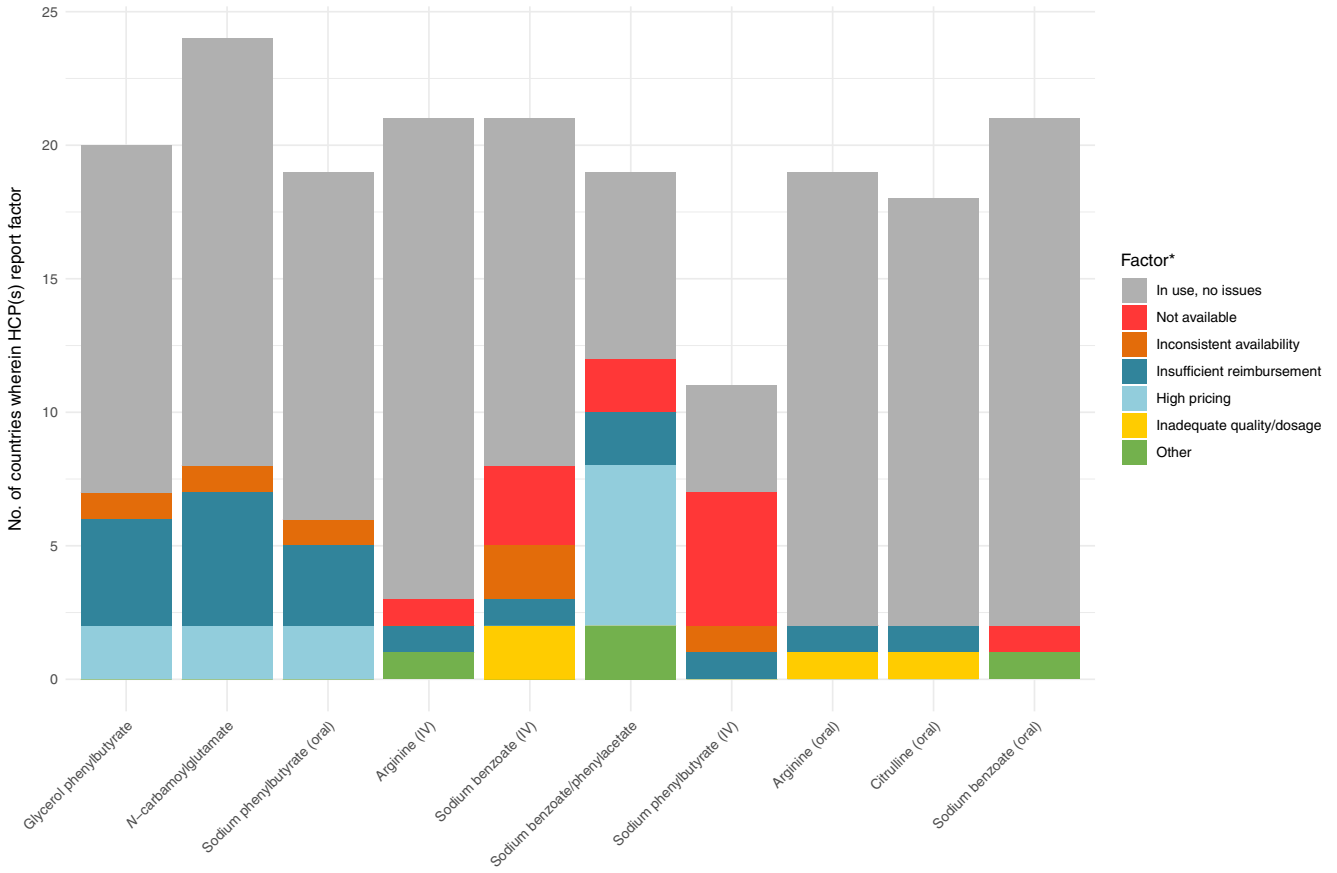

FIGURE 1 Reported factors impacting accessibility of urea cycle disorder (UCD) management products. *Multiple factors could be reported for one product, so totals may exceed the number of surveyed countries. HCPs, healthcare professionals; IV, intravenous.

synthetase 1 deficiency ($n = 35$ HCPs). Fewer HCPs reported managing patients with NAGSD ($n = 10$ HCPs), citrin deficiency ($n = 17$ HCPs), and ARG1D ($n = 17$ HCPs).

In 15/21 countries (71.4%), at least one metabolic HCP reported challenges in the accessibility of UCD management products (see Table 2). These countries encompass most Central and Eastern European (CEE) countries included in this survey (5/6: CZ, HU, LV, PL, SK), most Western European countries (7/8: AT, BE, CH, DE, FR, IE, NL), all Southern European (SE) countries (4/4: ES, GR, IT, PT), and one of the included Northern European countries (1/3: SE), outlined per product in Table 3. Challenges cited include no or inconsistent availability ($n = 18$), insufficient reimbursement ($n = 19$), high pricing ($n = 12$), and inadequate quality and/or dosing ($n = 4$) (see Figure 1). No challenges in access to UCD treatment products were noted by HCPs in Slovenia, Denmark, Norway, and the UK. National variation in accessibility was reported in three countries (CZ, ES, and IT).

For the authorized medicinal products (i.e. glycerol phenylbutyrate, *N*-carbamoylglutamate, and sodium phenylbutyrate), no unavailability was reported; however, inconsistent availability was reported by different single respondents from one specific country for each product (glycerol phenylbutyrate: NL; *N*-carbamoylglutamate: PL; and sodium phenylbutyrate: DE). Issues experienced in the use of authorized products mostly relate to insufficient reimbursement, as was reported by HCPs in 7/21 countries (30.4%). Financial strain on patients due to no or incomplete reimbursement of either glycerol phenylbutyrate or *N*-carbamoylglutamate were reported from HCPs in five countries (BE, CH, CZ, LV, and PL), three of them (BE, CH, and LV) also facing restricted access to *N*-carbamoylglutamate. Additionally, in five countries, HCPs reported hospitals paying for at least one of these products due to inadequate reimbursement (CH, CZ, DE, PL, and PT). Moreover, high pricing was mentioned as an obstacle by respondents in four countries (CH, DE, LV, and PL); for *N*-carbamoylglutamate, for instance, one respondent noted that it was too expensive to stock this

medicine in the hospital for emergency use, and another that its price meant that its usage was (too) restricted.

The availability of non-authorized intravenous products (i.e., arginine IV, sodium benzoate IV, sodium benzoate/phenylacetate IV, and sodium phenylbutyrate IV) appears to be most challenging in clinical practice. Instances of complete unavailability were noted for all four non-authorized IV products, with IV sodium phenylbutyrate impacted especially; unavailability impeding its usage was reported in five countries (BE, CZ, HU, IT, and LV). In Latvia, access to IV products seems particularly challenging, with only sodium benzoate/phenylacetate being available but not used due to a lack of reimbursement, leaving oral sodium phenylbutyrate as the only management option for acute decompensation. IV nitrogen scavengers are also difficult to access in Hungary, since sodium benzoate and sodium phenylbutyrate are not available as IV formulations and obtaining sodium benzoate/phenylacetate requires arranging individual reimbursement through the National Health Insurance Fund, with subsequent transportation taking up to 7 weeks.

Challenges relating to insufficient reimbursement were also reported for non-authorized IV products, although much less than for authorized products (in 3/21 countries: IE, LV, and NL). Notably, instances of pricing restricting product usage of non-authorized IV products were exclusively linked to sodium benzoate/phenylacetate (reported in DE, ES, HU, NL, PT, and SE). Additionally, product formulation was cause for concern in Portugal, where sodium benzoate IV was not available in the desired quality or dosage. Specific regulatory requirements may also hinder access to products in this category: in Slovakia, for instance, a permit is required every 6 months for the import of both arginine IV and sodium benzoate/phenylacetate, since they are unauthorized.

Non-authorized oral products (i.e. arginine, citrulline, and sodium benzoate) posed the least challenges. Only one instance of unavailability was reported: for oral sodium benzoate by an HCP in Spain. The issue of product quality was raised for both arginine and citrulline in Switzerland, as well as financial strain on the hospital due to insufficient reimbursement. No respondents noted challenges related to pricing for this group of products. The lack of a prepared formulation was raised by a respondent in Germany as challenging for pharmacists, as they have to encapsulate the substance for each individual patient.

4 | DISCUSSION

Access to specialized medication continues to be a challenge, particularly for patients affected by rare diseases like UCDs. In this study, survey data reveal that metabolic HCPs in the majority of European countries have experienced challenges accessing products for optimal UCD management, affecting both authorized and non-authorized products. In contrast to the availability issues with non-authorized IV products, no instances of complete unavailability were reported for authorized medicinal products. This may be explained by marketing authorization holders in the European Union (EU) carrying a legal responsibility for ensuring their products are available in the applicable markets.[21] Conversely, reimbursement and pricing, affecting affordability, appear to be the major challenges in accessing authorized medicinal products for UCD management in European clinical practice.

In our study, the accessibility of UCD treatment products was assessed by analyzing HCPs' reports on their usage, desired usage, and the challenges that impeded or complicated their utilization. Challenges were identified in the accessibility defined by either availability, affordability, and/or suitability of these products, similarly based upon HCPs' clinical evaluation of these factors. Consequently, a product was considered unavailable in a certain country if HCPs practicing there reported it so. When examining our findings on product availability, the reported availability of all authorized products aligns with a previous survey by Heard et al.; this study found that the three OMPs for UCDs were available in all included European countries except Bulgaria.[22] It is relevant to mention here that the latest marketing authorization for products included in our survey was granted in 2017, allowing a time frame for their introduction well beyond previously observed post-authorization availability delays of up to 1.6 years.[8–12,23]

The impact of reimbursement policies and high pricing on patient access to medicinal products for rare diseases such as UCDs across Europe has been well-documented.[16,17,24] In this survey, these factors were also most frequently reported as challenges to the accessibility of authorized medicinal products. They appear to affect the accessibility of non-authorized products to a lesser degree, with high pricing affecting accessibility noted only for sodium benzoate/phenylacetate, the only product in this category that does have a marketing authorization outside of Europe. This highlights a difficulty for improving patient access to UCD management products: obtaining a marketing authorization may improve the availability of IV products, but pricing will likely go up. This is especially true for products with an orphan designation and their pricing can remain high, with a recent study indicating pricing reductions for OMPs are gradual and limited.[25,26] This is exemplified by the multiple reports of pricing restricting the accessibility of *N*-

carbamoylglutamate in our survey, despite the marketing exclusivity of the original OMP ending over a decade ago and the availability of a generic alternative.[9,10]

At country level, access was most challenging in Latvia. Earlier research also showed that of the CEE countries, Latvia had the lowest number of reimbursed OMPs.[27] Reimbursement in Latvia is generally realized though a national reimbursement list, but there is also a special program for reimbursing medicines aimed at children with rare diseases, as well as a price-capped individual reimbursement policy.[28] This survey demonstrates that for managing the acute decompensation of UCDs in Latvia, the limited availability of IV products is worrisome. Although all countries included in this survey are considered high-income based on their gross national income per capita,[29] other research has indicated an equity gap in patient access to OMPs between Western and CEE countries.[30] Of the EU counties included in our survey, all CEE countries (CZ, HU, PL, SL, and SK) and 3/4 SE countries (ES, GR, and PT) have a gross national income below 90% of the EU average.[31]

In this survey, challenges in accessing UCD management products were reported in all SE countries, most CEE and Western European countries and one Northern European country. Although no clear regional variations in the factors impacting accessibility of UCD management products could be discerned, it seems that higher-income countries generally experience better access to UCD treatment products. The countries wherein no issues were reported (AU, DK, FR, NO, SV, and UK) are all higher income, with the exception of Slovenia.[29] However, some higher-income countries like Germany and Switzerland did report challenges, suggesting that factors beyond income, such as reimbursement policies and regulatory frameworks, may also play a significant role in determining access. Future research could examine both national and patient-level economic factors and their impact on access to non-authorized treatments for UCDs and other IMDs.

It should be noted, however, that recruitment through MetabERN and E-IMD may have resulted in an underrepresentation of HCPs from parts of Eastern Europe, likely with less access to treatment. Additionally, survey data are inherently subjective and the number of respondents per country varied, with the findings for several countries based on a single respondent. While variability was observed among the responses from three countries, two of these had much higher response rates. Sample size also limited certain subgroup analyses, including on accessibility in pediatric and adult populations separately, as few HCPs managed only adult patients.

Our design also means that accessibility issues which HCPs did not experience as problematic were likely not recorded. Local practices and guidelines might also omit unavailable products, especially if there are alternatives (e.g. nitrogen scavengers), leading to underreporting of their absence. In a recent French cohort of UCD patients, management varied by hospital, with only one center following international rather than local guidelines.[7] An example of national variation is the more frequent application of sodium phenylbutyrate in Germany, the Netherlands and the Czech Republic.[32] In countries where other nitrogen scavengers are prioritized, access issues related to sodium phenylbutyrate may be reported less, even if they contribute to its limited application. Employment of other treatment approaches such as liver transplantation could also have impacted the need for certain products and, consequently, our findings.

Additionally, HCPs' perspectives on what exactly constitutes (un)availability may have varied. It cannot be determined from this survey if reported unavailability means a product was actually not present in a national market or healthcare system, or if difficulties in procuring it resulted in its perceived unavailability. Similarly, intermittent shortages due to supply-chain disruptions that occurred longer ago may not have been captured due to recall bias. Comparing our finding to studies analyzing the availability of medicinal products based on more objective measures such as sales, prescription or reimbursement records can improve their validity. However, these often focus only on (O)MPs and exclude non-authorized products, meaning existing knowledge of their accessibility is sparse.[16,17,23,24] Thus, the present study does offer a relevant perspective on an often overlooked product category essential to the management of UCDs and many other IMDs.

This study highlights the European perspective, but UCD patients globally may face similar challenges. In Japan, IV phenylbutyrate is unavailable and patients purchase food-grade citrulline from the Japanese Society for Inherited Metabolic Diseases, reportedly reducing its use.[33,34] In the US, IV nitrogen scavenger therapy relies on sodium benzoate/phenylacetate as the only authorized option.[35] Access to oral citrulline and arginine may be more challenging, as sourcing and reimbursement of medical foods can be highly variable, with potentially high out-of-pocket costs.[36,37] In low- to middle-income countries like India and Pakistan, sodium phenylbutyrate, *N*-carbamoylglutamate, and nutritional therapies for IMDs are often unavailable, difficult to import, and/or inaccessible due to cost.[38,39]

The main objectives for improving patient access to UCD management products appear to be twofold: to increase and safeguard the availability of non-authorized

(IV) products, while also optimizing the pricing and reimbursement strategies for authorized medicinal products. To obtain central marketing authorization in the EU, applications must be submitted to the EMA for quality, efficacy and safety assessment, typically requiring large clinical trials. For rare diseases like UCDs, meeting these requirements is challenging.[40,41] The EMA therefore offers special incentives for OMPs and alternative authorization pathways are also available.[42–44] Conditional approval, for instance, is granted based on limited data with the requirement for additional post-marketing evidence.[43] Such an application may facilitate authorization for non-authorized products which have been used in UCD management for decades with well-documented effectiveness.

Alternatively, it has also been argued that common, food-related ingredients like arginine and citrulline, with effectiveness in rare diseases supported by open medical literature, should be considered as a separate regulatory category.[45] In oral form, these products are currently classified as foods, and since sodium benzoate is also available as a food preservative, this may explain why they are more accessible than the more tightly regulated pharmaceutical formulations for IV use.[14] A dedicated regulatory category and perhaps specialized authorization routes aimed at such well-established, never-authorized substances could be developed. Improving reimbursement policies to better align with such a category might also be required. Challenges in accessing (nutritional) treatments are likely present in other IMDs, such as vitamin-responsive IMDs, aminoacidopathies and organic acidurias, as many of these conditions similarly involve treatments that have long been used but remain unauthorized. Modifying regulations and reimbursement to better align with this clinical reality could improve patient access.

It should be carefully considered which non-authorized products stand to benefit from pursuing a marketing authorization in light of potential price increases, when compounded formulations or food products sometimes suffice.[14,46] This is supported by the limited concerns in this study regarding the suitability (quality and dosing) of non-authorized oral products, suggesting that HCPs generally find them adequately formulated for UCD treatment. It seems most appropriate to evaluate the necessity for authorization on a case-by-case basis by reviewing features related to a product's functioning in the treatment of IMDs. For subsequently authorized products, cost-based pricing models may help establish sustainable fair pricing, and improve affordability.[47] This may in turn positively impact reimbursement decisions and that is especially important following a less extensive authorization procedure similar to conditional approval, which can have the opposite effect.[24] For products already authorized, implementing national or EU policies that stimulate development of generic alternatives may help generate more competition, reducing generic pricing and improving their subsequent reimbursement.[48]

In conclusion, this survey revealed that access to products for medicinal UCD management is challenging in the majority of European countries. This indicates a potential disconnect between optimal treatment approaches, as captured in guidelines, and the clinical reality. The availability of non-authorized IV formulations can potentially be improved by (adjusted) authorization procedures based on their well-established use in clinical practice. Fair pricing models as well as improved reimbursement and generic policies offer the potential to further increase the accessibility of authorized medicinal products. It may thereby be possible to optimize access to medicinal UCD management in European clinical practice. This could also set an example for other IMDs, in which the accessibility of essential products can be similarly challenging.

AUTHOR CONTRIBUTIONS

C.H., A.B. and N.S. conceptualized the review. N.S. and A.B. designed the initial survey, which was further developed with the assistance of C.H., J.H., H.H. and M.W. The data collection and subsequent visualization was done by N.S. and A.B, with C.H. assisting with data interpretation. The original draft of the manuscript was prepared by N.S. A.B. supervised the project. All authors reviewed, edited, and approved the final manuscript for submission.

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CONFLICT OF INTEREST STATEMENT

Outside of submitted work, H.H. has received a grant for Metakids and has served on an advisory board for BioMarin. M.W. reports to be involved in pre-marketing studies with Ultragenyx and Moderna. Financial arrangements are made through the Erasmus MC. C.H. reports to be involved in pre-marketing studies with Genzyme, Protalix, and Idorsia. Financial arrangements are made through AMC Research BV. N.S. and A.B. have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, A.B., upon reasonable request.

ETHICS STATEMENT

Ethics approval was not required by our institution, as this study did not involve any patient related data or patient participation.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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