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Cases of drug repositioning in children's orphan drugs: Licenced drugs versus unlicenced magistral preparations

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ABSTRACT

Pharmacological treatments of several paediatric diseases are limited by the lack of medicinal products properly indicated for the children. A solution for overcoming such issue may be found in drug repositioning, based on an established clinical use of off-label medicines or extemporaneous preparations. This study aims to discuss the use of licenced products and magistral preparations, which can be compounded in hospital pharmacies, intended to treat rare diseases affecting childhood. A huge cost gap is observed between compounded and industrial drug products, suggesting a clear need in reconsidering the cost-effectiveness of repositioned products, and finding a balance between the manufacturers' economic sustainability and the patients' access to therapies.

1. Introduction

Drug repositioning is a strategy that involves molecules with a marketing authorisation (MA) for specific therapeutic indications and, therefore, with a well-known safety profile to regulatory agencies and scientific communities. In this case, the traditional process of drug discovery is sped up as it consists of the identification of a novel clinical use for drug substances. The advantages of this approach are linked to lowering the costs required for preclinical studies, and phase I and II clinical trials, while other costs, including regulatory and phase III clinical trials, generally remain comparable to those of new medicinal products [1]. In terms of availability on the market, repositioned drugs can reach the patient in 3–12 years, with an average cost of $300 million and an estimated success rate in terms of MA five times higher than for new compounds, ranging from 30% to as high as a potential 75% [2]. Until now, drug repositioning has been more frequently associated with a serendipitous discovery of a novel pharmacological activity of a molecule on new targets, leading to new possible indications of use, than with specific research insights based on the pharmacological mechanism of action of the molecule or the pathological pathways of the disease [1,3]. Data required to sustain a MA can differ significantly for the two cases and, consequently, the costs for the applicant.

Classical examples of repositioned drug substances are thalidomide for multiple myeloma or erythema nodosum leprosum, sildenafil for erectile dysfunction, minoxidil for alopecia, and amantadine for Parkinson's disease, while recently new therapeutic options able to save patients have been needed to face the COVID-19 outbreak [4].

Investing in drug repositioning also shows some risks for manufacturers. Most of drug products proposed for repositioning to treat COVID-19 have not been authorized, suggesting that carrying on a too-significant reduction of the current regulatory entry barriers in the future might yield a decline in quality and a waste of resources [5,6]. Moreover, patent protection could be weak increasing the risk for marketing authorisation holders (MAH) [1], particularly in the case of off-patent medicines having no economic incentives and a high risk that successful clinical trials could benefit competitors [7]. Finally, the availability of generic medicines can lead physicians to prescribe them off-label for the repurposed indication, reducing the market share of the

Abbreviations: AIFA, Agenzia Italiana del Farmaco; BNFC, British National Formulary for Children; CDCA, Chenodeoxycholic acid; CTX, Cerebrotendinous xanthomatosis; EDTA, Ethylenediaminetetraacetic acid; ELBW, Extremely low birth weight; EMA, European Medicines Agency; EPAR, European Public Assessment Report; HMA, Head of Medicines Agencies; HTA, Health Technology Assessment; MA, Marketing authorisation; MAH, Marketing authorisation holder; PIP, Paediatric investigation plan; PK, Pharmacokinetics; PPI, Proton pump inhibitor; STAMP, Safe and Timely Access to Medicines for Patients; VLBW, Very-low-body weight.

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authorized repositioned product and, therefore, the returns on investment [1]. However, it is noteworthy that the need for a unique formulation and/or dosage regimen that cannot easily be achieved with the available generics is a more favourable exception. Consequently, the MAH investment in research and development gradually shifted from "blockbuster" indications to "niche buster" (e.g., rare and ultra-rare diseases) for which regulatory authorities have introduced economic and data protection incentives to expand the available treatments [8].

The other ways to satisfy the clinical needs of patients (e.g., children) affected by diseases without a specifically indicated licenced medicinal product, such as in the case of rare diseases, is the off-label use of available industrial products and the compounding of magistral preparations. For the latter, the main example is when a formulation composition or pharmaceutical dosage form or strength is not yet available on the market to meet the specific clinical needs of patients. Off-label use medicines and magistral preparations can last as long as repositioned drugs have been authorized. Since such a process seems to have no effect on the benefit/risk balance of the treatment but a huge impact on the economic sustainability of the healthcare system due to the higher costs of licenced treatment, an important debate has emerged in the scientific community about the treatment cost-effectiveness of licenced medicinal products derived from drug repositioning [8–10].

In this context, the manuscript aims to discuss the use of licenced products and magistral preparations intended to treat rare diseases affecting childhood. The critical discussion is based on the analysis of medicines that are present on the market as licenced drugs and can be also compounded in a hospital pharmacy. Eight case studies of repositioned medicinal products intended to be used in infants and children were selected. Indeed, taking advantage of the expertise at the compounding laboratory of the hospital pharmacy of the Institute for Maternal and Child Health IRCCS Burlo Garofolo, the costs were compared to industrially available medicinal products. The discussion is also focused on analysing the price difference between market-authorized medicinal products and magistral preparations in Italy.

2. Methodology

Non-clinical and clinical data on selected authorized medicines were obtained from the European Public Assessment Reports (EPAR) available on the EMA and the Orpha.net portals, respectively [11,12]. To collect the scientific and clinical information about the drug usage and clinical practice before a medicinal product was authorized in the EU, peer-reviewed articles were searched on electronic databases PubMed, and Scopus®, using terms such as (*Drug AND *Rare disease) OR (Extemporaneous preparation AND *Drug). In the initial screen of the identified articles, a single researcher reviewed the title and abstract of each paper to filter out irrelevant literature and duplicates. The exclusion criteria were papers on the non-clinical use of drugs.

Treatment costs of industrial medicinal products were extrapolated in August 2022 from the database CODIFA based on the AIFA resolutions (e.g., ex-factory prices) published on *Gazzetta Ufficiale* (i.e., Italy Official Journal) and the costs of extemporaneous preparations were calculated based on the *Tariffa Nazionale* per *la vendita al pubblico dei medicinali* (i.e., National rate list of medicines), respectively [13,14]. Treatment costs of industrial medicinal products authorized in other European Countries was extrapolated by publicly available national databases [13,15–21].

Industrial products and extemporaneous preparations were compared based on pharmaceutical forms; to overcome differences in drug concentration or dosage, the costs of both industrial products and extemporaneous preparations were normalized by the milligrams of drug substance per unit of product.

3. Case studies

Eight drug substances (e.g., budesonide, caffeine, chenodeoxycholic acid, cholic acid, glycopyrronium, idebenone, midazolam, propranolol) used in the compounding laboratory of the hospital pharmacy of the Institute for Maternal and Child Health IRCCS Burlo Garofolo were selected since they have been authorized by EMA for specific orphan indications in paediatric patients, following a centralized procedure (Table 1). Non-clinical and clinical data on selected authorized medicines were reported in Table 2, whereas treatment costs of industrial medicinal products and extemporaneous preparations in Table 3 and Table 4, respectively.

3.1. Budesonide

Eosinophilic esophagitis is a relatively new disease since has been diagnosed for the first time in the early 90s, with an incidence of between 6 and 13 new cases per year per 100,000 inhabitants. It is characterized by a chronic immune/antigen-mediated oesophageal inflammatory disease associated with oesophageal dysfunction resulting from severe eosinophil-predominant inflammation [22]. The treatment is mainly based on dietary and pharmacological interventions [23]. Due to the scant palatability of the highly restricted diet, the marked weight loss and the high costs for the patient, the use of oral proton pump inhibitors (PPIs) and corticosteroids (e.g., budesonide) are often necessary to manage the disease symptoms. Inhaled budesonide can inhibit the maturation and activation of eosinophils through suppression of the release of their stimulating cytokines [24]. However, significant secondary side effects can occur due to the systemic drug absorption after pulmonary administration and by low patient adherence due to the complex use of the administration devices (e.g., metered-dose inhaler). Therefore, the interest in developing orally or topically applied therapeutics has risen for treating both adults and children [25–28].

In 2018, following an accelerated assessment, EMA authorized an orodispersible tablet containing 1 mg of budesonide for the treatment of eosinophilic oesophagitis in adults older than 18 years of age (Jorveza®) [29]. This follows the attribution of the orphan designation in 2013. As reported in Table 2, the preclinical and clinical data provided by the applicant included both bibliographic references and in vitro/in vivo studies. In particular, the clinical efficacy and safety have been demonstrated in two double-blind clinical trials (a phase-II study and phase-III one) enrolling up to a total of 160 adult patients.

In the case of magistral preparations of budesonide, formulative changes can be introduced in comparison to industrial formulation to personalise the treatment based on specific needs of patients. For example, published formulative studies discussed the criticisms connected to the compounding of extemporaneous preparations and their clinical efficacy [27,30,31]. Formulative changes have been useful for treating paediatric patients since they require adjustments in strength and dosage form in comparison to adults [32]. Since the preparation of orodispersible tablets is not feasible in a compounding laboratory due to the high complexity of the preparation methods, extemporaneous preparations are frequently formulated as a viscous suspension. In this context, the optimization of preparation viscosity is crucial for allowing it to adhere to the oesophagus mucosa, prolonging the drug release on site and drug absorption [33]. It is the case of the extemporaneous preparation made at the hospital pharmacy of IRCCS Burlo Garofolo, which consists in a viscous suspension of sterile water, stevia, disodium EDTA, glycerine, sodium benzoate, sodium saccharin, xanthan gum and budesonide in concentration of 1 mg/ml. Briefly, during preparation, the solid excipients are mixed and, then, glycerine and budesonide are added. Finally, the mixture is made up the volume with water. The final solution was packaged in a 60 ml sterile syringe.

3.2. Caffeine

Preterm new-borns are frequently affected by apnoea. If prolonged, they can lead to serious risks to patient health, including brain damage, dysfunctions of the gut or other organs, respiratory failures, and death. The prevalence of apnoea is estimated at 0.5–1.2 per 10.000 premature

Table 1
Repositioned medicinal products authorized by EMA following a centralized procedure for therapeutic indications relevant for childhood.

API	BRAND NAME OF LICENCED PRODUCTS	FIRST AUTHORIZED CLINICAL INDICATION	TYPE OF MA PATHWAY	TYPE OF MA APPLICATION (dossier)	REF.
Budesonide	Jorveza	Eosinophilic oesophagitis	Accelerated assessment	Art. 8.3 Dir. 2001/83/EC (complete)	[29]
Caffeine	Peyona (previously Nymusa)	Primary apnoea of premature in new-borns	Centralized procedure	Art. 10(a) Dir. 2001/83/EC (well-established use)	[34]
	Gencebok	Primary apnoea of premature in new-borns	Generic of a centrally authorized product, Article 3(3) of Regulation (EC) No. 726/2004	Art. 10(3) Dir. 2001/83/EC (hybrid)	[36]
Chenodeoxycholic acid	Chenodeoxycholic acid Leadiant	Cerebrotendinous xanthomatosis	Exceptional circumstances	Art. 10(3) Dir. 2001/83/EC (hybrid)	[42]
Cholic acid	Orphacol	3βHydroxy-Δ5-C27-steroid oxidoreductase deficiency or Δ4-3-Oxosteroid-5β-reductase deficiency	Exceptional circumstances	Art. 10(a) Dir. 2001/83/EC (well-established use)	[45]
Glycopyrronium	Sialanar	Sialorrhea in children and adolescents with conditions affecting nervous system	Paediatric use	Art. 10(a) Dir. 2001/83/EC (well-established use)	[52]
Idebenone	Sovrima	Friedreich's ataxia	Conditional approval[a]	Art. 8.3 Dir. 2001/83/EC (complete)	[59]
	Raxone	Leber's hereditary optic neuropathy (LHON)	Exceptional circumstances	Art. 10(3) Dir. 2001/83/EC (hybrid)	[56]
Midazolam	Buccolam	Acute (sudden) convulsive seizures in children and adolescents	Paediatric use	Art. 10(3) Dir. 2001/83/EC (hybrid)	[67]
Propranolol	Hemangiol	Infantile haemangioma	Paediatric use	Art. 8.3 Dir. 2001/83/EC (complete)	[72]

[a] Refused because the Benefit/risk balance has not been considered positive by the CHMP because data provided by the applicant are not consistent and robust enough.

new-borns [34]. However, most of infants weighing less than 1 kg at birth are affected by apnoea [35]. Caffeine, which is commonly present and assumed by foods (e.g., coffee), has been used in clinics since the 70s′ for prophylactic purposes and for treating apnoea of prematurity. It can antagonize adenosine receptors A1 and A2 in the Central Nervous System (CNS). It increases the sensitivity of receptors and probably also decreases the threshold of the medullary respiratory centre to CO_2. Such pharmacological mechanism permits to increase in minute ventilation and to decrease in the frequency of apnoeic episodes. The increase in respiratory rate and blood pH results in a reduced pCO_2 and improved function of the respiratory muscles in premature infants with recurrent apnoea. Before the commercial availability of industrially produced medicinal products (early '90s), caffeine solutions were prepared in hospital pharmacies. Only in 2003, a 20 mg/ml solution for intravenous infusion and oral solution (branded name: Nymusa®) received the orphan designation by EMEA (now EMA) for treating primary apnoea of premature new-borns. In 2009, the designation was translated into a formal MA by following a centralized procedure. The treatment regimen included a loading dose (20 mg/kg) by intravenous infusion and maintenance doses (5 mg/kg) every 24 h by infusions or oral administration. The medicinal product called Nymusa® was subsequently changed to Peyona® by the MAH. Previously, no medicines containing 20 mg/ml of caffeine had been approved in the EU for the treatment of neonatal apnoea; however, they have been present in the United States since 1998. Therefore, thanks to the extensive literature supporting the clinical use of caffeine, there was a well-established application of use. No ex-Novo pre-clinical and clinical studies were submitted in the authorisation dossier (Table 2). Ten years after the first MA, the period of market exclusivity of Peyona®, and the status of orphan medicine, ended, opening the market to copies. Gencebok®, a therapeutic equivalent medicinal product containing 10 mg/ml of caffeine citrate, was authorized in 2019 by following a hybrid application (Table 1) [36]. The lower pharmaceutical strength was developed to meet the clinical needs of new-borns weighing lower than 1500 g (i.e., very-low-body weight (VLBW)/extremely low birth weight (ELBW) infants). As well as Peyona®, non-clinical and clinical patterns of the medicinal product were based on literature data [37]. Moreover, considering the different pharmaceutical strengths (20 mg/ml versus 10 mg/ml) a biowaiver was claimed by the MAH to support the equivalence of the two products. Indeed, for parenteral aqueous solutions, bioequivalence studies can be waived if requirements of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) were met. In the case of Gencebok®, the product contains the same drug substance and no changes in the routes of administration, pharmaceutical form, therapeutic indications and recommended dosage regimen is present in comparison to Peyona®. Moreover, it is noteworthy that, according to the EPAR for Peyona®, the pharmacokinetics of the caffeine is linear within the range of the two strengths (10 mg/ml, 20 mg/ml). Pharmaceutically equivalent extemporaneous preparations can be easily compounded in hospital and community pharmacy settings. The standard composition of the extemporaneous preparation made at IRCCS Burlo Garofolo consists in sterile water, citric acid monohydrate and caffeine. The preparation protocol consists in the dissolution of all drug and excipients in the sterile water under magnetic stirrer to obtain a clear solution. The final solution has a pH between 1.6 and 1.8.

3.3. Chenodeoxycholic acid

Chenodeoxycholic acid (CDCA) was originally authorized in 1970 as a low-cost medicine for the treatment of gallstones. In the later 'eighties, clinical evidence suggested its beneficial use in treating patients with the hereditary metabolic disease cerebrotendinous xanthomatosis (CTX) [38]. CTX is a rare autosomal recessive disorder affecting children caused by mutations that block the first step of oxidation of the side-chain of sterol intermediates in the bile acid synthesis pathway. Based on the Opha.net portal more than 300 patients have been reported worldwide, with a prevalence of approximately 1/50,000 among Caucasians [39]. The main CTX clinical manifestations are juvenile cataracts, chronic diarrhoea, tendon xanthomas, and a broad range of neurological symptoms, including pyramidal and cerebellar signs, cognitive impairment, parkinsonism, and epilepsy [40]. Promoting the myelin synthesis in nerve fibres with residual unaffected axons, the CDCA stabilizes the CTX clinical symptoms, arresting the disease progression [40,41]. However, the lower the extent of irreversible structural damage to axons, the higher the efficacy of CDCA [40]. Consequently, the CDCA treatment should be started as early as possible to prevent neurological damage and deterioration in CTX. After significant neurological pathology is established, the effect of treatment is limited, and deterioration continues [41].

Based on these clinical findings, CDCA was authorized by the EMA as

Table 2
Non-clinical and clinical data included in the dossier submitted of analysed medicinal products for obtaining the marketing authorisation.

API	BRAND NAME OF LICENCED PRODUCTS	NON-CLINICAL DATA	CLINICAL DATA	REF.
Budesonide	Jorveza	– Literature data. – In vitro pharmacology safety study evaluating the effect of budesonide on hERG channels. – Local tolerance studies using the hamster cheek pouch model	*Pharmacokinetics/pharmacodynamics* – Phase I PK/PD study (25 enrolled healthy subjects, 12 enrolled patients) *Clinical efficacy and safety* – Literature data – Double-blind, double-dummy, randomised, 4 parallel groups, multi-centre, placebo-controlled, dose-finding, confirmatory phase II (76 enrolled patients) – Double-blind, randomised, 2 parallel groups, multi-centre, placebo-controlled, comparative, confirmatory, phase III (88 enrolled patients)	[29]
Caffeine	Peyona (previously Nymusa)	–Literature data.	*Pharmacokinetics/pharmacodynamics* –Literature data; no additional experimental data *Clinical efficacy and safety* –Literature data	[34]
	Gencebok	–Literature data.	*Pharmacokinetics/pharmacodynamics* – Literature data; biowaiver in comparison to Peyona. *Clinical efficacy and safety* – Literature data; no additional experimental data	[36]
Chenodeoxycholic acid	Chenodeoxycholic acid Leadiant	– Literature data. – Reproduction toxicity studies in rhesus monkey and baboon	*Pharmacokinetics/pharmacodynamics* – Literature data; no additional experimental data *Clinical efficacy and safety* – Two retrospective studies on patients (adults and children) – Enrolled patients: 35 + 28	[42]
Cholic acid	Orphacol	– Literature data.	*Pharmacokinetics/pharmacodynamics* – Literature data; no additional experimental data *Clinical efficacy and safety* – Literature data – 38 and 11 patients reports with 3β-HSD and Δ4-3-oxoR deficiencies, respectively	[45]
Glycopyrronium	Sialanar	– Literature data.	*Pharmacokinetics/pharmacodynamics* – Literature data (9 references,3 of them in children). – Bioequivalence study between test product and that used in published phase III clinical trials. *Clinical efficacy and safety* – Literature data on No. 6 clinical studies (No. 3 Phase III clinical trials, 214 enrolled patients)	[52]
Idebenone	Sovrima	– Literature data. – Additional Safety and Pharmacology studies, including two 28-day repeat-dose toxicity studies in rats and dogs, and genotoxicity tests	*Pharmacokinetics/pharmacodynamics* – Phase I clinical pharmacology program: 4 single- and multiple-dose studies, 4 interaction studies, 1 hepatic and 1 renal impairment study, 1 metabolism and disposition study, 1 single- and 1 multiple-dose study in children, adolescents, and adults with FRDA (total 239 enrolled subjects). *Clinical efficacy and safety* – Literature data (deriving from the original Alzheimer programme) – Phase IA, single-dose, dose-escalation pilot safety study (79 enrolled patients) – Phase IB, multiple-dose pilot safety study (15 enrolled patients) – Phase II dose-ranging, efficacy, and safety study (48 enrolled patients)	[59]
	Raxone	– Pharmacology and toxicology data are partially based on other already authorized products. – Primary pharmacology data in an animal model – Safety pharmacology studies (focused on potential cardiovascular effects) – Non-clinical pharmacokinetic studies on mice – Toxicology studies (genotoxicity)	*Pharmacokinetics/pharmacodynamics* – Four Phase I studies to investigate drug bioavailability with/without food intake (69 enrolled healthy subjects) *Clinical efficacy and safety* – Randomized, double-blind, placebo-controlled, parallel-group, pivotal phase II study (85 enrolled patients)	[56]

(*continued on next page*)

Table 2 (*continued*)

API	BRAND NAME OF LICENCED PRODUCTS	NON-CLINICAL DATA	CLINICAL DATA	REF.
			– Single-visit, observational follow-up study (60 enrolled patients among those included in the first study). – Phase II study (48 patients) and two Phase III studies on efficacy, safety, and tolerability studies (232 and 70 patients), which primarily served as supportive safety information.	
Midazolam	Buccolam	– Literature data.	*Pharmacokinetics/pharmacodynamics* – Literature data and in silico experimental data – Open-label, single-dose, sparse sampling PK study (50 enrolled children) *Clinical efficacy and safety* – Literature data	[67]
Propranolol	Hemangiol	– Literature data. – Toxicity study conducted in juvenile rats for determining the effect on reproductivity and development	*Pharmacokinetics/pharmacodynamics* – Single-centre, randomised, open-label, single-dose, 2-period crossover study. (Hemangiol vs conventional tablet; 12 enrolled healthy adults) – Two open-label, multicentre, repeated-dose studies (Hemangiol; 23 + 23 enrolled infants) *Clinical efficacy and safety* – A randomized, controlled, multidose, multicentre, adaptive phase II/III study (Hemangiol; 456 enrolled infants) – Multicentre, uncontrolled, open-label study (ongoing)	[72]

Table 3
Strengths, pharmaceutical form, reimbursement status in Italy, and price of analysed medicinal products [13].

API	MEDICINAL PRODUCTS	REIMBURSEMENT STATUS IN ITALY	STRENGTHS, PHARMACEUTICAL FORM	UNITS/VOLUME PER PACK	PRICE (€)	COST (€/mg/unit)
Budesonide	Jorveza	Reimbursed	1 mg, orodispersible tablet	90	335.70	3.730
Caffeine	Peyona (previously Nymusa)	Not reimbursed	20 mg/ml, solution for infusion and oral solution	1 ml, 10 vials	324.00	1.620
	Gencebok	Not reimbursed	10 mg/ml, solution for infusion and oral solution	1 ml, 50 vials	990.24	1.980
CDCA	Chenodeoxycholic acid Leadiant	Reimbursed	250 mg, capsule	100	13,995.00	0.559
Cholic acid	Orphacol	Reimbursed	50 mg, capsule	30	2430.00	1.620
Glycopyrronium	Sialanar	Not reimbursed	320 μg/ml, oral solution	250 ml	869.00	10.862
Idebenone	Raxone	Reimbursed	150 mg, tablet	180	6317.50	0.234
Midazolam	Buccolam	Reimbursed	10 mg, oral solution in a pre-filled syringe	4	81.77	2.044
Propranolol	Hemangiol	Reimbursed	3.75 mg/ml, oral solution	120 ml	180.50	0.401

Table 4
Strengths, pharmaceutical form, price of extemporaneous preparation equivalent to analysed industrial medicinal products. The cost of extemporaneous preparations was calculated based on Annexes A and B of *Tariffa Nazionale* per *la vendita al pubblico dei medicinali* (i.e., National rate list of medicines) [14].

API	STRENGTHS, PHARMACEUTICAL FORM	UNITS/VOLUME PER PACK	COST OF MAGISTRAL PREPARATION (€)	COST (€/mg/unit)
Budesonide	1 mg/ml, oral suspension	120 ml	48.60	0.405
Caffeine	20 mg/ml, oral solution	150 ml	21.85	0.007
CDCA	165 mg, capsule	100	29.32	0.002
Cholic acid	50 mg/ml, oral suspension	50 ml	16.25	0.007
Glycopyrronium	0.5 mg/ml, syrup	50 ml	28.05	1.122
Idebenone	300 mg, capsule	300	95.32	0.001
Midazolam	10 mg/ml, intranasal solution	10 ml	4.02	0.040
Propranolol	2 mg/ml, oral solution	150 ml	23.33	0.078

an orphan medicinal product for the treatment of CTX, applying the pathway for exceptional circumstances [42]. The medicinal product followed a hybrid application in agreement with art. 10(3) of Dir. 2001/83/EC (Table 1). Indeed, as shown in Table 2, the MA was supported by two retrospective clinical trials conducted in less than 73 patients among children and adults. No formal preclinical safety studies have been conducted, but the safety profile of CDCA was supported by the available literature data which revealed no special hazard for humans. At IRCCS Burlo Garofolo, magistral preparations of CDCA consist of capsules with personalized dose based on the needs of the paediatric patient. Their compounding starts from the manipulation of the industrial capsules for preparing of extemporaneous capsules of a suitable size for meeting clinical needs of paediatric patients.

3.4. Cholic acid

Cholic acid was used in clinics for the treatment of inborn errors in primary bile acid synthesis due to 3β-Hydroxy-Δ5-C27-steroid

oxidoreductase deficiency or Δ4-3-Oxosteroid-5βreductase deficiency in infants, children and adolescents aged 1 month to 18 years and adults (prevalence 0.06/10,000 in the EU). Both deficiencies are extremely rare genetic disorders and the oral administration of cholic acid can inhibit the production of hepatotoxic bile acid precursors and provide a stimulus for bile flow facilitating their hepatic clearance [43]. Cholic capsules had been compounded in France and used at *Bicêtre Hospital* from 1993 to 2007 [44]. During this period, the hospital pharmacy first and then the *Agence Générale des Équipements et Produits de Santé - Établissement Pharmaceutique des Hôpitaux de Paris* (AGEPS-EPHP) were successively authorized by French authorities as both manufacturing and batch release sites of the finished product. From 2002, capsules containing cholic acid also received the orphan designation by EMA. However, in October 2007, the AGEPS-EPHP signed an exclusive license agreement on the industrial development and commercialization with a private pharmaceutical company that started to manufacture cholic acid capsules, with the same composition and specifications, under the invented name Orphacol®. It has been supplied to French hospitals as Named-Patient Compassionate Use. In 2013, the company obtained a centralized MA following the regulatory pathway for products of well-established use (Table 1) [45]. Since the product has been used for over 10 years at the MA application, to demonstrate the efficacy and safety profiles of the products, preclinical or clinical data were substituted by about 30 publications dating back to 1987 (Table 2).

However, the availability of licenced product in form of capsules does not allow easy personalization of the dosage in function of the patient growth and his/her clinical outcome. For example, powder for an oral suspension containing 5% w/w of cholic acid has been compounded at hospital pharmacy of IRCCS Burlo Garofolo [46]. In absence of relevant stability issues of drug, the powder for oral suspension was preferred to facilitate the drug titration and to overcome potential difficulties of patient in swallowing the medicine. The excipients' composition of the powder for oral suspension consists in a mixture of hydroxyethylcellulose, aroma, citric acid monohydrate, fructose, neohesperidin, sodium saccharin, ammonium glycyrrhizinate, microcrystalline cellulose. The preparation protocol consists in the mixing of all drug and excipients in a mortar to obtain a homogeneous powder.

3.5. Glycopyrronium

The glycopyrronium is used both in adults and children for treating sialorrhea (chronic pathological drooling) [47,48]. Sialorrhea or drooling is the unintentional loss of saliva from the mouth which can have a significant and negative impact on the quality of life of patients, other than increasing the risk of dehydration. Although it is a normal phenomenon in infancy that regresses after the development of bulbar musculature and the neurological control of the tongue, drooling after 4 years is considered neurodevelopmentally abnormal [49]. If the prevalence of chronic drooling in childhood is up to 0.6%, it affects between a third to a half of young patients with quadriplegic cerebral palsy [50]. Due to its antimuscarinic action, glycopyrronium can inhibit competitively acetylcholine receptors on salivary glands, reducing the rate of salivation [51]. However, unlike other antimuscarinic drugs, glycopyrronium has a quaternary charge that limits its penetration of the blood-brain barrier and, therefore, the risk of CNS side effects. Intravenous, intramuscular, and oral glycopyrronium seems to reduce salivation in healthy adult volunteers; however, oral administration showed a delayed onset and longer duration of effects compared with the two injected formulations [51]. The use of glycopyrronium has been particularly diffused in the United Kingdom, so that it has been included in the British National Formulary for Children (BNFc) since the early 2000s.

A medicinal product (Sialanar®) containing glycopyrronium was authorized in 2016 following an MA application for paediatric use. The product was authorized specifically for children aged 2 to <18 years with neurological disorders. Taking advantage of the existing literature, the efficacy and safety profile of the product was mainly supported by bibliographic references back to the early '90s, which includes three phases III clinical trials (Table 2) [52]. They are limited to a bioequivalence study designed to compare the formulations in the literature (oral solution 1 mg/5 ml or 0.2 mg/ml) and the medicinal product (oral solution containing 400 μg/ml of glycopyrronium bromide, equivalent to 320 μg/ml of glycopyrronium). On the other side, pharmaceutically equivalent extemporaneous preparations (e.g., oral solution, syrup) can be easily compounded in hospital and community pharmacy settings. The excipients' composition consists in sodium nipagin, monobasic sodium phosphate monohydrate, sterile water, anhydrous dibasic sodium phosphate, sucrose and glycopyrronium. The preparation protocol consists in the dissolution of all drug and excipients in the sterile water under magnetic stirrer to obtain a clear solution. The final solution should have a pH < 6.

3.6. Idebenone

Idebenone is a synthetic analogue of coenzyme Q. Due to its antiradical scavenger activity, idebenone was originally investigated as a treatment for Alzheimer's disease and other cognitive defects [53] and granted the MA in Japan in 1986. However, results of clinical trials show a low efficacy in blocking the cognitive decline of the disease [54], and the medicinal product was withdrawn from the Japanese market in 1998. Since 2001, idebenone has been used for the treatment of Friedreich ataxia (prevalence 1/20,000 to 1/50,000), an inherited neurodegenerative disorder characterized by progressive gait and limb ataxia, dysarthria, dysphagia, oculomotor dysfunction, loss of deep tendon reflexes, pyramidal tract signs, scoliosis, and in some, cardiomyopathy, diabetes mellitus, visual loss and defective hearing [55]. It was also studied for Leber's hereditary optic neuropathy, which is another mitochondrial disorder characterized by acute or sub-acute painless vision loss of both eyes in a matter of weeks or a few months [56]. In 2004, idebenone received its first orphan designation for Friedreich ataxia by EMA. In 2007, two additional orphan designations were given for the treatment of Duchenne muscular dystrophy and Leber's hereditary optic neuropathy, respectively [57]. In particular, the second orphan designation was attributed to an idebenone-containing film--coated tablet (Raxone®), which was a reformulation of the existing originator product (Mnesis®). One year later, EMA refused the MA for a second product (Sovrima®) intended for treating Friedreich ataxia since it did not show a significant improvement compared with the placebo in the clinical outcomes [58,59]. Indeed, the EMA considered the scientific literature provided by the applicant weak in demonstrating a consistent clinical benefit of Sovrima®. In 2015, EMA authorized by exceptional circumstances the Raxone® for Leber's hereditary optic neuropathy. Taking advantage of the existing information, a hybrid application was followed by the MAH (Table 1). It is interesting to note that the applicant also included, for safety purposes, the clinical trials on Friedreich ataxia for providing additional supportive safety information (Table 2). On the other side, no medicinal product containing idebenone has been authorized yet for Duchenne muscular dystrophy, but its efficacy is documented by at least four clinical trials, two of which were supported by the same MAH of Raxone®, published from 2011 to 2015 [60–63].

At IRCCS Burlo Garofolo, magistral preparations of idebenone consist of capsules made of pregelatinized corn, magnesium stearate, micronized silica, micronized talc and a customized dose of active ingredient based on the needs of the paediatric patient. The dose was increased to 300 mg to fulfil the therapeutic need of four patients affected by Duchenne muscular dystrophy. Indeed, for such therapeutic indication, the regimen is set at 300 mg three times daily, which cannot be easily maintained by using available strengths of industrial medicinal products (e.g., Raxone®) in such patients.

3.7. Midazolam

Convulsive status epilepticus is the most common childhood neurological emergency and can lead to neurocognitive sequelae and death. Infants younger than 12 months have the highest incidence and frequency of the disease. In clinical practice, several pharmacological treatments are indicated in the case of status epilepticus. The first-line treatment is benzodiazepines such as lorazepam or diazepam, often administered intravenously in a hospital setting. In other cases, rectal administration (diazepam) is frequently used in an emergency in community and home settings, although it presents several practical disadvantages (e.g., the need to remove clothing, and social embarrassment). Midazolam has been used systemically administered to adults and children (including infants) in the EU and the USA since the early '80s as a sedative and in pre-anaesthesia and anaesthesia [64,65]. The development of oral formulations containing midazolam was also supported by published studies demonstrating good drug stability in compounded preparations [66].

In 2011, a mucosal solution of midazolam in a pre-filled syringe was authorized to the market under the trade name Buccolam® [67]. The applicant submitted a hybrid MA application for paediatric use for treating acute seizures in children aged from 3 months to <18 years known to have epileptic seizures. Seizures are a transient occurrence of signs and/or symptoms due to abnormal excessive and synchronous neuronal activity in the brain, and they are frequent in the first stage of a status epilepticus. Like previous cases, the preclinical and clinical data included in the dossier are mainly composed of bibliographic references (Table 2). Only in silico studies and a clinical trial on 50 children have been provided to support the determination of the pharmacokinetic and pharmacodynamic profile of the drug.

Hospital pharmacy of IRCCS Burlo Garofolo developed and routinely prepare an extemporaneous solution of midazolam for intranasal use. Compared to other technological solutions (e.g., rectal preparation), it permits an easy administration in emergency without particular social discomfort. It requires higher concentrations (i.e., 10 mg/ml) due to the small administrable volumes (10 ml) than licensed medicinal product. This preparation is an aqueous solution in vials free of benzyl alcohol, which is generally associated with a burning sensation during administration. The excipient composition consists in 0.9% sodium chloride, sodium citrate trisodium dihydrate and citric acid monohydrate. The preparation protocol consists in the dissolution of all drug and excipients in the sterile water under magnetic stirrer to obtain a clear solution. It is noteworthy that the availability of standardized compounded preparations of midazolam is improving the resilience of healthcare systems to the negative effects induced by the frequent shortages of Buccolam®. Indeed, between 2014 and 2015, such medicinal product resulted in a severe shortage in several EU Member States due to quality failures during the MAH manufacturing process. In this context, compounded rectal preparation of diazepam is included by AIFA among possible alternatives to overcome the unavailability of industrial medicine [68].

3.8. Propranolol

Propranolol, a non-selective beta-blocker, has been widely used in the treatment of infantile haemangiomas (IH) since Léauté-Labrèze and colleagues observed in 2008 a rapid regression of IH in a patient with a pre-existent cardiovascular disease [69]. IH are benign vascular tumours of childhood (prevalence: 3%–10% of the population) characterised by rapid growth (proliferation) of the endothelial cells followed by a stabilisation period and a slow spontaneous involution. IH are extremely heterogeneous in terms of size, location, risk of complication, rate of proliferation and involution, and results after involution. The clinical efficacy of propranolol seems related to multiple effects, such as the vasoconstriction of IH vessels (early), the blocking of proangiogenic signals that induce a growth arrest (intermediate) and the induction of apoptosis in proliferating endothelial cells, resulting in tumour regression (long-term) [69]. Although the use of propranolol has revolutionized the therapeutic approach of IH, manipulation of industrial medicinal products (e.g., capsules, tablets) [70] and compounding of extemporaneous preparations [71] have been for years the unique possibility to treat patients following the recommended dose regimen. In 2014, an oral solution containing 3.75 mg/ml propranolol hydrochloride (Hemangiol®) was authorized by the EMA following a MA application for paediatric use (Table 1) [72]. Unlike the oral solution marketed in the UK since 2000, the authorized formulation was specifically designed for paediatric patients. The medicinal product was authorized for the treatment of infants aged 5 weeks to 5 months. Considering the extensive literature supporting the label and off-label uses of propranolol, the pharmacological and toxicological data were mainly bibliographic (Table 2). However, the toxicological part was integrated by an additional study on the drug's effect on reproducibility and development. Instead, several clinical trials were included in the dossier to demonstrate the bioequivalence of the proposed formulation to those mainly used off-label (i.e., manipulated immediate-release tablets). Moreover, due to the features of infants' pharmacology and toxicology, the applicant performed clinical trials to support the positive benefit/risk balance of the treatment in infants. At the presentation of the dossier, up to 500 children were enrolled. At present Hemangiol® oral formulation 3.75 mg/ml is currently commercially available in 120 ml bottles. The extemporaneous preparation made at the IRCCS Burlo Garofolo hospital pharmacy is an aqueous solution composed of sterile water, sodium citrate trisodium dihydrate, citric acid monohydrate, sucrose. All solid components were dissolved in the sterile water under magnetic stirrer to obtain a clear solution. The propranolol was added to the formulation to obtain a final concentration of 2 mg/ml.

4. Treatment costs in Italy: licenced drugs versus magistral preparations

Cost analysis of the eight medicinal products authorized in other European countries (i.e., Denmark, France, Germany, Italy, Holland, Portugal, Sweden, United Kingdom) shows that, if commercially available, the costs are substantially in line with those in Italy; except in the UK where they are significantly higher. (Fig. 1, Table S1).

For all eight analysed drugs, the compounding of extemporaneous preparations by the community and hospital pharmacists is cheaper (Fig. 2) and feasible due to the absence of criticisms of either active principle or oral dosage forms in terms of physicochemical stability or preparation process. For most of them, the extemporaneous preparations made by the hospital pharmacy of IRCCS Burlo Garofolo were pharmaceutically equivalent to the industrial medicinal product in terms of the dosage form. It is the case of caffeine, CDCA, glycopyrronium, idebenone, and propranolol. Three are liquid dosage forms, while two are oral solid dosage forms for immediate release (i.e., capsules).

For caffeine, a multi-dose oral solution (150 ml) containing 20 mg/ml is routinely prepared by the hospital pharmacy, with a cost per milligram equal to € 0.007 (Table 4). It corresponds to a −99.6% of the price per mg of the industrial oral solution (i.e., € 1.62; Table S2). In the case of glycopyrronium, the extemporaneous syrup (50 ml), containing 0.5 mg/ml [73], resulted in a cost of € 1.122/mg, which was 10-times lower (Table S2) than the Sialanar® oral solution (10.862/mg; Table 3). A comparable situation was observable for propranolol: the cost per mg of Hemangiol® is equal to € 0.40 (Table 3), which is significantly higher than extemporaneous ones (i.e., € 0.07/mg; Table 4).

This trend was confirmed also in the case of solid preparations. In the case of CDCA and idebenone capsules, the costs of extemporaneous preparations resulted significantly lower (– 99%), than the corresponding industrial capsule (Table S2). For CDCA, such evidence agreed with the literature. Indeed, the orphan medicine (i.e., Chenodeoxycholic acid Leadiant) has been marketed at a much higher price than off-label

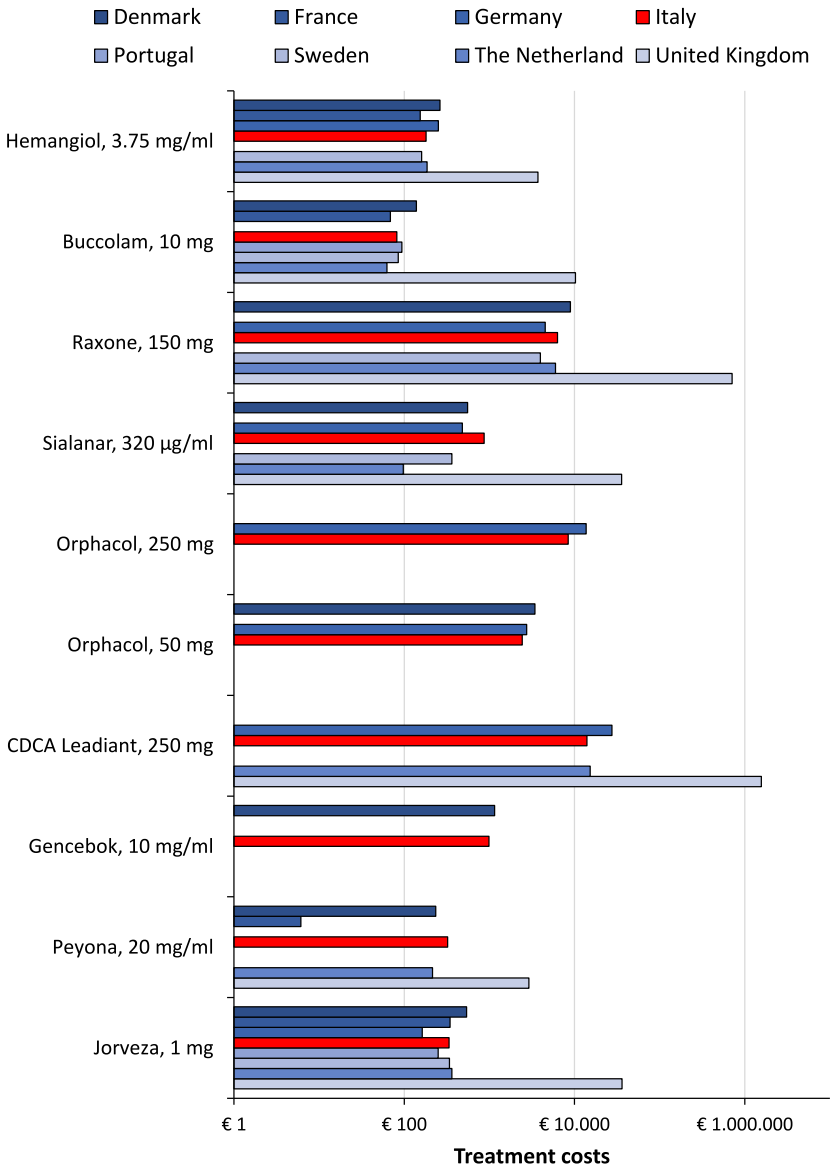

Fig. 1. - Comparative cost analysis among Italy and other European countries. Data are reported in Table S1.

treatments, which led to the medicine not being reimbursed in several EU countries [74]. For instance, in the Netherlands, authorized CDCA-containing medicine (price € 0.28 per capsule) has been used as an off-label drug for CTX since 1999. The cost for a patient is € 308 per year [8]. On the contrary, the orphan commercial product increased the price from € 30,000 to € 170,000 per patient per year. Because of the high price of the raw material, the magistral preparation is still 100 times (€ 20,000–25,000 per patient per year) higher than the original off-label medicine price [8,10].

In other cases, formulative changes have been introduced in extemporaneous preparations in comparison to industrial medicinal products based on specific clinical needs [75]. It is the case of the extemporaneous preparations containing budesonide, cholic acid and midazolam. The cost per milligram of extemporaneous preparation containing budesonide is equal to € 0.40 (Table 4), which corresponds to −89% of the equivalent costs of industrial orodispersible tablet (i.e., € 3.73/mg; Table S2). The cholic acid is formulated as a powder for an oral suspension in comparison to the industrial capsule [46]. Indeed, the Orphacol®, which has been sold in France and Italy at the maximum price of €78.00 and € 81.00 per 50-mg tablet, respectively (Table 3). Regardless the formulative changes, the cost per milligram of the extemporaneous preparation (€ 0.007; Table 4) remains significantly lower (– 99.6%) than the licenced product (i.e., € 1.62; Table S2). It is noteworthy that such costs were determined based on amount of active ingredient in a pack: e.g., a pack of 30 tablets (50 mg) contains a total of 1.5 g of cholic acid, which corresponds to 30 ml of oral suspension; the pack of 30 tablets of 250 mg contains a total of 7.5 g of active ingredient, which corresponds to 150 ml of oral suspension. Finally, this trend was also confirmed in the case of midazolam: the cost of the intranasal solution (€ 0.04/mg, Table 4) turns out to be 50-times lower than the industrial product (€ 2.04/mg; Table S2).

5. Discussion and conclusion

All analysed medicines were authorized by EMA following a centralized procedure, in consideration of their status of orphan drugs as stated by EC regulation No. 726/2004. This agrees with previous scientific analyses which identify such procedures as the most relevant for

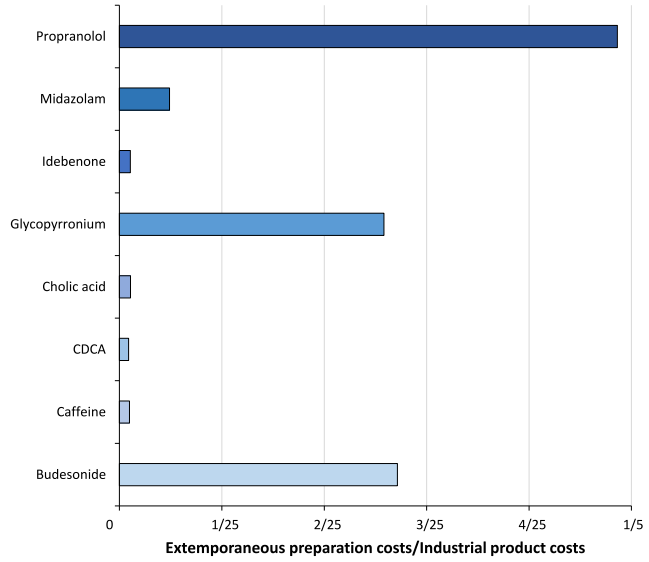

Fig. 2. Ratio of costs (€/mg/unit) of extemporaneous preparation and industrial products. Data are reported in Table S2.

repurposed drugs approval, whereas reformulated products can be also authorized by a national application [76]. To receive an orphan drug designation, the drug substance must meet three criteria.

1) Drug must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating.
2) Disease prevalence in the EU must not be more than 5 in 10,000, or it must be unlikely that marketing of the drug would generate sufficient returns to justify the investment needed for its development.
3) No satisfactory method of treatment, prevention or diagnosis of the condition concerned can be authorized, or, if such a method exists, the drug must possess a significant benefit to those affected by the condition [8].

Moreover, for repurposed or well-established use drugs with a designated orphan indication, the current regulatory framework states a market exclusivity of 10 years in the EU to protect the applicant from the market competition with similar medicines with similar indications and additional 2 years if they complied with an agreed paediatric investigation plan (PIP). On the contrary, applications for adding new indications of well-established substances submitted under article 10(5) may be granted 1 year of data exclusivity [77].

The critical analysis of the scientific and regulatory information on the eight tested medicinal products highlighted that the MA was obtained after a repurposed drug has been used for years in clinical practice as off-label use or compounding extemporaneous preparations (e.g., cholic acid). In some cases (e.g., cholic acid, glycopyrronium), the drugs are so well-known or commonly used in clinical practice that the applicant asked for MA by using the well-established use pathway. It permitted the applicant to waive ex-Novo safety and efficacy data since they are supported by extensive and continued use in the EU over at least 10 years. The usage of such a regulatory pathway is relatively frequent in repositioned old products. For example, mitotane (Lysodren®), a well-established drug that has been used in the treatment of adrenal cortical carcinoma in Europe since 1969, was authorized in 2004 based on the results of 220 published studies [78]. Currently, the use of real-world data in lieu of clinical trials has been proposed to support the placing on the market of repositioned drugs [79]. In this context, the efforts sustained by the applicant for putting the product on the market are relatively low and limited to quality aspects or bioequivalence studies to compare the test formulation versus those reported in the literature. In the case of cholic acid, such additional data have even not been provided since the marketed formulation derived from that had been compounded in the French hospitals for years. In other cases, a hybrid (called also abridged) procedure was followed by the applicant since the benefit/risk balance of the product cannot be assessed based on a full cross-reference to existing data. In these cases, new pre-clinical and clinical data were performed by the applicant to support the new use [80]. This scenario is relevant for products that change their clinical indication/designation from non-orphan to orphan or for paediatric use [77]. Indeed, due to the peculiarity of the patient population, the available data from adults cannot be transposed to children and infants, requiring additional data for understanding the pharmacological and toxicological profiles of the test drug, other than its clinical efficacy. For example, although propranolol has a well-established and known pharmacological and toxicological pattern, its use in young patients affected by IH pushed the Regulatory authority to require more detailed clinical investigations to assess its safety and efficacy profile.

As reported above, the regulatory framework on orphan drug products focused on industrial authorized medicinal products to define incentive to manufactures, without evaluating if the same drug can be obtained as extemporaneous preparation or as off-label use of already available industrial medicines, or other interventions [76]. As an example, for most analysed cases, off-label use is feasible since generic products, containing the same drug substance, are available on the market [77]. In parallel, for several rare diseases, compounding has been commonly done in hospital pharmacies before the MA of equivalent industrial orphan drugs [76]. In this context, the cost-effectiveness of a new treatment may be difficult to establish, especially when the ex-factory price is significantly higher than the price of the original medicine and its well-established use is supported by literature. This is the case of eight medicinal products discussed above; the treatment costs of authorized medicinal products in Italy resulted remarkably higher than those of equivalent magistral preparations ($\Delta > -80\%$; Fig. 2, Table S2). The obtained costs' delta seems consistent also comparing Italian costs of extemporaneous preparations versus the estimated costs of industrial products in other European Countries (Fig. 1, Table S1). In this context, it is noteworthy that costs for extemporaneous preparations in other European Countries may vary from the Italian ones due to differences in the existing national regulations and in prices of raw materials. However, unlike industrial products, there are not publicly available national database containing information to support a proper costs' quantification and comparison for extemporaneous preparations in European Countries.

The highlighted costs' deltas are also consisted with literature evidence on same or medicinal products [8,10]. It is the case of mexiletine, which was developed 40 years ago for the treatment of arrhythmias. Recently, it granted MA after being designated an orphan drug for non-dystrophic myotonia. Its price used to be € 4000 per patient per year increased up to € 80,000 per patient per year [8].

Such evidence and overall results suggested reflections about the effectiveness of current regulatory incentives to support orphan and paediatric drugs. Indeed, although incentives are higher in the EU versus the USA [77], no significant differences in the limited number of approved orphan drugs are observable. Moreover, it is noteworthy that the number of authorized orphan medicinal products is relatively low in comparison to the orphan designations, suggesting that economic and regulatory barriers may limit the success rate of products, affecting the patient access to therapy [81]. This finding pushed in 2019, the Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP) presented a proposal for establishing a framework to support not-for-profit organizations in drug repositioning [82]. The pilot project was definitively launched in 2021 [83]. However, such provisions may not be enough effective if the economic sustainability of MAH or the patient access to therapy remains not certain. Indeed, after the MA, the economic sustainability of the medicinal products can be affected by multifactorial causes, such as the limited number of patients

to be treated or reimbursement limitations adopted by National competent authorities. The scenario can be so worsened that MAH has to withdraw the medicine from the market (e.g., Hemoprostol H–W-2652 [84]) or reduce the production with a consequent substantial risk of shortages (e.g., Buccolam®). In this context, the use of magistral preparations following harmonized monographs could be a feasible and more efficient alternative to meet clinical needs. Extemporaneous preparations should be compounded on the small scale for the needs of specific patients [85]. However, in the case of rare diseases, ranging on a small scale can be difficult. For example, in the Netherland, about 50 patients are affected by CTX and are treated with CDCA; in this context, if the extemporaneous preparations for 50 patients may be considered a small scale in many situations, for CDCA, it meets the needs of the whole patient population of a country [86].

Compounding can be a valid and economical approach to overcome the unavailability of treatments. However, it is noteworthy that compounding is not a panacea for all repositioned products, since some formulations are too complex in terms of manufacturing process or technological attributes to be prepared in a compounding laboratory without expecting biopharmaceutical alteration [87]. Therefore, an "alliance" between compounding and industrial manufacturing is needed to rationalize the available resources to guarantee a worth access to therapies for patients affected by rare diseases and for children. In this context, a full assessment of therapeutic alternatives available in the market, which including off-label use and standardized procedures for extemporaneous preparations, during Health Technology Assessment (HTA) analysis is essential for healthcare authorities to rationalize pricing and reimbursement status of a product. It is needed to avoid unethical scenarios jeopardizing the patient access to therapies. These aspects are particularly relevant in the case of products potentially affected by shortage. As reported in the latest EMA/HMA guidance [88], extemporaneous preparations are a feasibility strategy to guarantee patients access to essential treatment (e.g., in the case of midazolam).

In conclusion, it is evident how critical is the assessment of proper prices of authorized medicines by healthcare authorities, to ensure economic sustainability of manufacturers and to avoid unaffordable prices for the patient or the healthcare system. If the price of the repositioned drug is too high, a patient can get the needed pharmacological treatment only where/when extemporaneous preparations can be routinely compounded by pharmacies, otherwise, the therapies cannot take place. However, this approach cannot be acceptable from a regulatory and a socioeconomic point of view: when a licenced drug is available on the market, it should be preferred to extemporaneous ones. The compounding of extemporaneous preparation should remain the last hope to ensure patient access to needed treatments. It means that the pharmaceutical community should improve its efforts as much as possible to promote the scientific research of novel pharmaceutical treatments, to increase the success rate to place them on the market, and to adopt policies able to enhance the patients' access to innovative treatments and to ensure the economic sustainability of the healthcare systems. Consequently, the price of repositioned drugs, especially those for rare diseases or other life-threatening indications, should be carefully determined to reward the manufacturer investments during pharmaceutical development and pre-authorisation clinical investigation, but should also take into consideration other aspects, such as the feasibility of magistral preparations and/or the availability of medicinal products that can be used off-label.

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Author contributions

DZ: Conceptualization, Writing - review & editing, Supervision; UMM: Conceptualization; Investigation; Roles/Writing - original draft; Writing - review & editing; MC: Investigation, Data curation, Formal analysis, Writing - review & editing; GB: Investigation, Data curation, Formal analysis, Writing - review & editing; AC: Writing - review & editing; NM: Data curation, Formal analysis, Writing - review & editing; EB: Data curation, Formal analysis, Writing - review & editing; PM: Conceptualization, Writing - review & editing Supervision.

Declaration of competing interest

The authors have no conflict of interest to declare.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

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References

[1] S. Pushpakom, F. Iorio, P.A. Eyers, K.J. Escott, S. Hopper, A. Wells, A. Doig, T. Guilliams, J. Latimer, C. McNamee, A. Norris, P. Sanseau, D. Cavalla, M. Pirmohamed, Drug repurposing: progress, challenges and recommendations, Nat. Rev. Drug Discov. 18 (2018) 41–58, https://doi.org/10.1038/nrd.2018.168.
[2] H.I. Roessler, N.V.A.M. Knoers, M.M. van Haelst, G. van Haaften, Drug repurposing for rare diseases, Trends Pharmacol. Sci. 42 (2021) 255–267, https://doi.org/10.1016/j.tips.2021.01.003.
[3] B.M. Arman, N.K. Binder, N. de Alwis, T.J. Kaitu'u-Lino, N.J. Hannan, Repurposing existing drugs as a therapeutic approach for the prevention of preterm birth, Reproduction 165 (1) (2023) R9–R23.
[4] European Medicines Agency (EMA), Veklury. https://www.ema.europa.eu/en/medicines/human/EPAR/veklury, 2019. (Accessed 7 February 2023).
[5] J. Sultana, S. Crisafulli, F. Gabbay, E. Lynn, S. Shakir, G. Trifirò, Challenges for drug repurposing in the COVID-19 pandemic era, Front. Pharmacol. 11 (2020) 1–13, https://doi.org/10.3389/fphar.2020.588654.
[6] M. Hanisch, B. Rake, Repurposing without Purpose? Early Innovation Responses to the COVID-19 Crisis: Evidence from Clinical Trials, R and D Management, 2021, https://doi.org/10.1111/radm.12461.
[7] P. Pantziarka, C. Verbaanderd, I. Huys, G. Bouche, L. Meheus, Repurposing drugs in oncology: from candidate selection to clinical adoption, Semin. Cancer Biol. 68 (2021) 186–191, https://doi.org/10.1016/j.semcancer.2020.01.008.
[8] A.B. Bayoumy, N.K.H. de Boer, A.R. Ansari, F. Crouwel, C.J.J. Mulder, Unrealized potential of drug repositioning in europe during COVID-19 and beyond: a physcian's perspective, J Pharm Policy Pract 13 (2020) 1–9, https://doi.org/10.1186/s40545-020-00249-9.
[9] C. Verbaanderd, I. Rooman, L. Meheus, I. Huys, On-label or off-label? overcoming regulatory and financial barriers to bring repurposed medicines to cancer patients, Front. Pharmacol. 10 (2020) 1–11, https://doi.org/10.3389/fphar.2019.01664.
[10] T. Sheldon, Dutch hospital makes own drug for rare condition after manufacturer hikes price to €170 000, BMJ 361 (2018), k2103, https://doi.org/10.1136/bmj.k2103.
[11] European Medicines Agency (n.d.), https://www.ema.europa.eu/en. (Accessed 7 February 2023).
[12] Orphanet, n.d. https://www.orpha.net/consor/cgi-bin/index.php?lng=EN. (Accessed 7 February 2023).
[13] EDRA S.p.A., Banca dati CODIFA. https://www.codifa.it/. (Accessed 7 February 2023).
[14] Tariffa Nazionale per la vendita al pubblico dei medicinali (i.e., National rate list of Medicines), Decree of Italian Minister of Health of March 23rd 2017, as emended by Decrees of September 22th 2017 and of December 13th 2017, https://www.gazzettaufficiale.it/home. (Accessed 7 February 2023).
[15] MEDICINPRISER.DK. https://www.medicinpriser.dk/Default.aspx. (Accessed 7 February 2023).
[16] Base de Donnees publique des medicaments. https://base-donnees-publique.medicaments.gouv.fr/index.php#result. (Accessed 7 February 2023).
[17] Juvalis. https://www.juvalis.de/. (Accessed 7 February 2023).
[18] Medicijnkosten.nl.. https://www.medicijnkosten.nl/. (Accessed 7 February 2023).
[19] Informed. Base de dados de medicamentos de uso humano. https://extranet.infarmed.pt/INFOMED-fo/. (Accessed 7 February 2023).
[20] Tandvårds- och läkemedelsförmånsverket (TLV). https://www.tlv.se/beslut/sok/lakemedel/. (Accessed 7 February 2023).
[21] NHS electronic drug tariff. https://www.drugtariff.nhsbsa.nhs.uk/#/00834576-DD_1/DD00834178/Part%20VIIIA%20products%20B. (Accessed 7 February 2023).

[22] S. Koletzko Papadopoulou, R. Heuschkel, J.A. Dias, K.J. Allen, S.H. Murch, S. Chong, F. Gottrand, S. Husby, P. Lionetti, M.L. Mearin, F.M. Ruemmele, M. G. Schäppi, A. Staiano, M. Wilschanski, Y. Vandenplas, Management guidelines of eosinophilic esophagitis in childhood, J. Pediatr. Gastroenterol. Nutr. 58 (2014) 107–118, https://doi.org/10.1097/MPG.0b013e3182a80be1.

[23] A.J. Lucendo, J. Molina-Infante, Á. Arias, U. von Arnim, A.J. Bredenoord, C. Bussmann, J. Amil Dias, M. Bove, J. González-Cervera, H. Larsson, S. Miehlke, A. Papadopoulou, J. Rodríguez-Sánchez, A. Ravelli, J. Ronkainen, C. Santander, A. M. Schoepfer, M.A. Storr, I. Terreehorst, A. Straumann, S.E. Attwood, Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults, United European Gastroenterol J 5 (2017) 335–358, https://doi.org/10.1177/2050640616689525.

[24] D. Ashat Reddy, A.R. Murali, Recent insights on the use of topical steroids in eosinophilic esophagitis, Expet Rev. Gastroenterol. Hepatol. 14 (2020) 953–963.

[25] E.S. Dellon, A. Sheikh, O. Speck, K. Woodward, A.B. Whitlow, J.M. Hores, M. Ivanovic, A. Chau, J.T. Woosley, R.D. Madanick, R.C. Orlando, N.J. Shaheen, Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis, Gastroenterology 143 (2012) 321–324.e1, https://doi.org/10.1053/j.gastro.2012.04.049.

[26] S.K. Gupta, J.M. Vitanza, M.H. Collins, Efficacy and safety of oral budesonide suspension in pediatric patients with eosinophilic esophagitis, Clin. Gastroenterol. Hepatol. 13 (2015) 66–76.e3, https://doi.org/10.1016/j.cgh.2014.05.021.

[27] J.N. Hefner, R.S. Howard, R. Massey, M. Valencia, D.J. Stocker, K.Q. Philla, M. D. Goldman, C.M. Nylund, S.B. Min, A randomized controlled comparison of esophageal clearance times of oral budesonide preparations, Dig. Dis. Sci. 61 (2016) 1582–1590, https://doi.org/10.1007/s10620-015-3990-4.

[28] S. Miehlke, P. Hruz, M. Vieth, C. Bussmann, U. Von Arnim, M. Bajbouj, C. Schlag, A. Madisch, C. Fibbe, H. Wittenburg, H.D. Allescher, M. Reinshagen, S. Schubert, J. Tack, M. Müller, P. Krummenerl, J. Arts, R. Mueller, K. Dilger, R. Greinwald, A. Straumann, A randomised, double-blind trial comparing budesonide formulations and dosages for short-term treatment of eosinophilic oesophagitis, Gut 65 (2016) 390–399, https://doi.org/10.1136/gutjnl-2014-308815.

[29] European medicines agency (EMA), jorveza, assessment report. https://www.ema.europa.eu/en/medicines/human/EPAR/jorveza. (Accessed 7 February 2023).

[30] Casiraghi, C.G. Gennari, U.M. Musazzi, M.A. Ortenzi, S. Bordignon, P. Minghetti, Mucoadhesive budesonide formulation for the treatment of eosinophilic esophagitis, Pharmaceutics 12 (2020), https://doi.org/10.3390/pharmaceutics12030211.

[31] J. Lee, M. Shuker, T. Brown-Whitehorn, A. Cianferoni, L. Gober, A. Muir, R. Verma, C. Liacouras, J.M. Spergel, Oral viscous budesonide can be successfully delivered through a variety of vehicles to treat eosinophilic esophagitis in children, J. Allergy Clin. Immunol. Pract. 4 (2016) 767–768, https://doi.org/10.1016/j.jaip.2016.02.005.

[32] E. Menditto, V. Orlando, G. De Rosa, P. Minghetti, U.M. Musazzi, C. Cahir, M. Kurczewska-Michalak, P. Kardas, E. Costa, J.M.S. Lobo, I.F. Almeida, Patient centric pharmaceutical drug product design—the impact on medication adherence, Pharmaceutics 12 (2020), https://doi.org/10.3390/pharmaceutics12010044.

[33] Casiraghi, C.G. Gennari, U.M. Musazzi, M.A. Ortenzi, S. Bordignon, P. Minghetti, Mucoadhesive budesonide formulation for the treatment of eosinophilic esophagitis, Pharmaceutics 12 (2020) 1–12, https://doi.org/10.3390/pharmaceutics12030211.

[34] European Medicines Agency (EMA), Nymusa, Assessment Report, EMEA/H/C/001014), 2009.

[35] K.S. Beam, S. Aliaga, S.K. Ahlfeld, M. Cohen-Wolkowiez, P.B. Smith, M.M. Lauhon, A systematic review of randomized controlled trials for the prevention of bronchopulmonary dysplasia in infants, J. Perinatol. 34 (2014) 705–710.

[36] European medicines agency (EMA), Gencebok, assessment report. https://www.ema.europa.eu/en/medicines/human/EPAR/gencebok. (Accessed 7 February 2023).

[37] (EMA/372967/2020), European Medicines Agency (EMA), Gencebok, Assessment Report, 2020.

[38] A.E. DeBarber, P.B. Duell, Update on cerebrotendinous xanthomatosis, Curr. Opin. Lipidol. 32 (2021) 123–131.

[39] Orphanet: cerebrotendinous xanthomatosis (n.d.), https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=en&Expert=909. (Accessed 7 February 2023).

[40] F. Ginanneschi, A. Mignarri, M. Mondelli, G.N. Gallus, M. Del Puppo, S. Giorgi, A. Federico, A. Rossi, M.T. Dotti, Polyneuropathy in cerebrotendinous xanthomatosis and response to treatment with chenodeoxycholic acid, J. Neurol. 260 (2013) 268–274, https://doi.org/10.1007/s00415-012-6630-3.

[41] G. Yahalom, R. Tsabari, N. Molshatzki, L. Ephraty, H. Cohen, S. Hassin-Baer, Neurological outcome in cerebrotendinous xanthomatosis treated with chenodeoxycholic acid: early versus late diagnosis, Clin. Neuropharmacol. 36 (2013) 78–83, https://doi.org/10.1097/WNF.0b013e318288076a.

[42] European Medicines Agency (EMA), Chenodeoxycholic Acid Leadiant, Assessment Report, 2016. EMA/650359/2016), https://www.ema.europa.eu/en/medicines/human/EPAR/chenodeoxycholic-acid-leadiant. (Accessed 7 February 2023).

[43] J.E. Heubi, K.D.R. Setchell, K.E. Bove, Inborn errors of bile acid metabolism, Clin. Liver Dis. 22 (2018) 671–687.

[44] E. Gonzales, M.F. Gerhardt, M. Fabre, K.D.R. Setchell, A. Davit-Spraul, I. Vincent, J. E. Heubi, O. Bernard, E. Jacquemin, Oral cholic acid for hereditary defects of primary bile acid synthesis: a safe and effective long-term therapy, Gastroenterology 137 (2009) 1310–1320.e3, https://doi.org/10.1053/j.gastro.2009.07.043.

[45] EMA/596651/2013), European Medicines Agency (EMA), Orphacol, Assessment Report, 2011.

[46] D. Zanon, F. Burlo, G. Scaramuzza, N. Maximova, L. Matarazzo, G. Maggiore, E. Barbi, Safety and effectiveness of compounded galenic cholic acid for bile acid synthesis disorder: a case report, Endocr., Metab. Immune Disord.: Drug Targets 22 (2022) 1047–1052, https://doi.org/10.2174/1871530322666220407114607.

[47] P. You, J. Strychowsky, K. Gandi, B.A. Chen, Anticholinergic treatment for sialorrhea in children: a systematic review, Paediatr. Child Health 28 (2022) 82–87.

[48] K.T. Blissit, E. Tillery, C. Latham, J. Pacheco-Perez, Glycopyrrolate for treatment of clozapine-induced sialorrhea in adults, Am. J. Health Syst. Pharm. 71 (2014) 1282–1287, https://doi.org/10.2146/ajhp130636.

[49] C.B.R. Fairhurst, H. Cockerill, Management of drooling in children, Arch Dis Child Educ Pract Ed 96 (2011) 25–30, https://doi.org/10.1136/adc.2007.129478.

[50] J. Tahmassebi, Prevalence of drooling in children with cerebral palsy attending special schools, Dev. Med. Child Neurol. 45 (2007) 613–617, https://doi.org/10.1111/j.1469-8749.2003.tb00965.x.

[51] K.P. Garnock-Jones, Glycopyrrolate oral solution: for chronic, severe drooling in pediatric patients with neurologic conditions, Pediatr. Drugs 14 (2012) 263–269, https://doi.org/10.2165/11208120-000000000-00000.

[52] (EMA/555265/2016), European Medicines Agency (EMA), Sialanar, Assessment Report, 2016.

[53] T.T. Nguyen, T.T.D. Nguyen, T.K.O. Nguyen, T.K. Vo, V.G. Vo, Advances in developing therapeutic strategies for Alzheimer's disease, Biomed. Pharmacother. 139 (2021), 111623, https://doi.org/10.1016/j.biopha.2021.111623.

[54] L.J. Thal, M. Grundman, J. Berg, K. Ernstrom, R. Margolin, E. Pfeiffer, M.F. Weiner, E. Zamrini, R.G. Thomas, Idebenone treatment fails to slow cognitive decline in Alzheimer's disease, Neurology 61 (2003) 1498–1502, https://doi.org/10.1212/01.WNL.0000096376.03678.C1.

[55] Orphanet: Friedreich ataxia (n.d.), https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=45&Disease_Disease_Search_diseaseGroup=Friedreich-s-ataxia&Disease_Disease_Search_diseaseType=Pat&Disease(s)/group of diseases=Friedreich-ataxia&title=Friedreich ataxia&search=Disease_. (Accessed 7 February 2023).

[56] European Medicines Agency (EMA), Raxone, Assessment Report, 2015.

[57] European Commission, Union Register of medicinal products. https://ec.europa.eu/health/documents/community-register/html/reg_od_act.htm?sort=a. (Accessed 7 February 2023).

[58] European Medicines Agency (EMA), Questions and Answers on Recommendation for the Refusal of the Marketing Authorisation for Sovrima, 2008.

[59] EMEA/387246/2009, European Medicines Agency (EMA), Sovrima, Assessment Report, 2008.

[60] G.M. Buyse, T. Voit, U. Schara, C.S.M. Straathof, M.G. D'Angelo, G. Bernert, J. M. Cuisset, R.S. Finkel, N. Goemans, C.M. McDonald, C. Rummey, T. Meier, Efficacy of idebenone on respiratory function in patients with Duchenne muscular dystrophy not using glucocorticoids (DELOS): a double-blind randomised placebo-controlled phase 3 trial, Lancet 385 (2015) 1748–1757, https://doi.org/10.1016/S0140-6736(15)60025-3.

[61] G.M. Buyse, N. Goemans, M. van den Hauwe, D. Thijs, I.J.M. de Groot, U. Schara, B. Ceulemans, T. Meier, L. Mertens, Idebenone as a novel, therapeutic approach for Duchenne muscular dystrophy: results from a 12 month, double-blind, randomized placebo-controlled trial, Neuromuscul. Disord. 21 (2011) 396–405, https://doi.org/10.1016/j.nmd.2011.02.016.

[62] G.M. Buyse, N. Goemans, M. Van Den Hauwe, T. Meier, Effects of glucocorticoids and idebenone on respiratory function in patients with duchenne muscular dystrophy, Pediatr. Pulmonol. 48 (2013) 912–920, https://doi.org/10.1002/ppul.22688.

[63] T. Meier, T. Voit, U. Schara, C.S.M. Straathof, M.G. D'Angelo, G. Bernert, J. M. Cuisset, R.S. Finkel, N. Goemans, C. Rummey, M. Leinonen, P. Spagnolo, G. M. Buyse, F. Knipp, M. van den Hauwe, V. Doppler, T. Gidaro, S. Coopman, S. Lutz, J. Kirschner, S. Borell, E. Brighina, S. Gandossini, K. Gorni, E. Falcier, L. Politano, P. D'Ambrosio, A. Taglia, J.J.G.M. Verschuuren, J.J. Vílchez Padilla, N. Muelas Gómez, T. Sejersen, M. Hovmöller, P.Y. Jeannet, C. Bloetzer, S. Iannaccone, D. Castro, G. Tennekoon, R. Finkel, C. Bönnemann, C. McDonald, E. Henricson, N. Joyce, C.M. McDonald, S. Apkon, R.C. Richardson, Idebenone reduces respiratory complications in patients with Duchenne muscular dystrophy, Neuromuscul. Disord. 26 (2016) 473–480, https://doi.org/10.1016/j.nmd.2016.05.008.

[64] B.J. Anderson, J. Lermann, C.J. Cotè, Pharmacokinetics and pharmacology of drugs used in children, in: A Practice of Anesthesia for Infants and Children, sixth ed., Elsevier, 2019, pp. 100–176, https://doi.org/10.1016/B978-0-323-42974-0.00007-0.

[65] L. Lourenco-Matharu, P.F. Ashley, S. Furness, Sedation of children undergoing dental treatment, Cochrane Database Syst. Rev. (2012), https://doi.org/10.1002/14651858.CD003877.pub4.

[66] B.D. Glass, A. Haywood, Stability considerations in liquid dosage forms extemporaneously prepared from commercially available products, J. Pharm. Pharmaceut. Sci. 9 (2006) 398–426.

[67] European medicines agency (EMA), Buccolam, assessment report. https://www.ema.europa.eu/en/medicines/human/EPAR/buccolam. (Accessed 7 February 2023).

[68] AIFA, Informazioni sulla carenza dei medicinali Buccolam® e Micropam®. https://www.aifa.gov.it/documents/20142/847339/2021.05.21_comunicazione_carenza_buccolam_micropam.pdf, 2021. (Accessed 7 February 2023).

[69] M. Kowalska, W. Debek, E. Matuszczak, Infantile hemangiomas: an update on pathogenesis and treatment, J. Clin. Med. 10 (2021) 4631, https://doi.org/10.3390/jcm10204631.

[70] Casiraghi, U.M. Musazzi, I. Franceschini, I. Berti, V. Paragò, L. Cardosi, P. Minghetti, Is propranolol compounding from tablet safe for pediatric use? Results from an experimental test, Minerva Pediatr. 66 (2014) 355–362.
[71] Casiraghi, U.M. Musazzi, P. Rocco, S. Franzè, P. Minghetti, Topical treatment of infantile haemangiomas: a comparative study on the selection of a semi-solid vehicle, Skin Pharmacol. Physiol. 29 (2016) 210–219, https://doi.org/10.1159/000447672.
[72] European medicines agency (EMA), Hemangiol, assessment report. https://www.ema.europa.eu/en/medicines/human/EPAR/hemangiol. (Accessed 7 February 2023).
[73] D. Zanon, C. Tumminelli, A.M.C. Galimberti, L. Torelli, A. Maestro, E. Barbi, N. Maximova, Compounded glycopyrrolate is a compelling choice for drooling children: five years of facility experience, Ital. J. Pediatr. 47 (2021) 1–8, https://doi.org/10.1186/S13052-021-01173-7/FIGURES/5.
[74] I. Rooman, L. Meheus, I. Huys, Verbaanderd, On-label or off-label? overcoming regulatory and financial barriers to bring repurposed medicines to cancer patients, Front. Pharmacol. 10 (2020) 1–11, https://doi.org/10.3389/fphar.2019.01664.
[75] P. Minghetti, D. Pantano, C.G.M. Gennari, A. Casiraghi, Regulatory framework of pharmaceutical compounding and actual developments of legislation in Europe, Health Pol. 117 (2014) 328–333, https://doi.org/10.1016/j.healthpol.2014.07.010.
[76] M. Dooms, H. Pincé, S. Simoens, Do we need authorized orphan drugs when compounded medications are available? J. Clin. Pharm. Therapeut. 38 (2013) 1–2, https://doi.org/10.1111/jcpt.12006.
[77] S. Murteira, A. Millier, Z. Ghezaiel, M. Lamure, Drug reformulations and repositioning in the pharmaceutical industry and their impact on market access: regulatory implications, J Mark Access Health Policy 2 (2014), 22813, https://doi.org/10.3402/jmahp.v2.22813.
[78] European medicines agency (EMA), lysodren (n.d.), https://www.ema.europa.eu/en/medicines/human/EPAR/lysodren. (Accessed 1 July 2021).
[79] G.S.Q. Tan, E.K. Sloan, P. Lambert, C.M.J. Kirkpatrick, J. Ilomäki, Drug repurposing using real-world data, Drug Discov. Today 28 (2023), 103422.
[80] P. Minghetti, U.M. Musazzi, A. Casiraghi, P. Rocco, Old active ingredients in new medicinal products: is the regulatory path coherent with patients' expectations? Drug Discov. Today (2020) https://doi.org/10.1016/j.drudis.2020.05.013.
[81] STAMP Commission Expert Group, Repurposing of Established Medicines/active Substances Agenda Item 3, 2016.
[82] STAMP Commission Expert Group, Draft - Proposal for a Framework to Support Not-For-Profit Organisations in Drug Repurposing, 2019.
[83] European Medicines Agency (EMA), Repurposing of authorised medicines: pilot to support not-for-profit organisations and academia | European Medicines Agency (n.d.), https://www.ema.europa.eu/en/news/repurposing-authorised-medicines-pilot-support-not-profit-organisations-academia. (Accessed 7 February 2023).
[84] European Medicines Agency (EMA), Hemoprostol H-W-2652. https://www.ema.europa.eu/en/hemoprostol-h-w-2652, 2017. (Accessed 7 February 2023).
[85] F. Selmin, A. Casiraghi, U.M. Musazzi, M. Fortini, P. Minghetti, An outlook on the European and Italian rules to guarantee magistral formulas, Int. J. Pharm. Compd. 23 (2019) 6–12.
[86] S. Kalkman, M. Arentshorst, J. Hoekman, W. Boon, E. Uijtendaal, G. van Thiel, E. Moors, In-hospital production of medicines: preparing for disruption, Trends Biotechnol. 38 (2020) 1045–1047, https://doi.org/10.1016/j.tibtech.2019.09.011.
[87] U.M. Musazzi, G.M. Khalid, F. Selmin, P. Minghetti, F. Cilurzo, Trends in the production methods of orodispersible films, Int. J. Pharm. 576 (2020), https://doi.org/10.1016/j.ijpharm.2019.118963.
[88] Good practice guidance for patient and healthcare professional organisations on the prevention of shortages of medicines for human use. https://www.ema.europa.eu/en/documents/other/good-practice-guidance-patient-healthcare-professional-organisations-prevention-shortages-medicines_en.pdf, 2022. (Accessed 7 February 2023).