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## ORIGINALS

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## Development of a carbocysteine 10% + urea 5% cream for the topical treatment of congenital ichthyosis

## Desarrollo de una crema de carbocisteína 10% + urea 5% para el tratamiento tópico de las ictiosis congénitas

Lara González-Freire<sup>1,2</sup>, María Carmen Dávila-Pousa<sup>1</sup>, Ana Batalla-Cebey<sup>3</sup>, Carlos Crespo-Diz<sup>1,2</sup><sup>1</sup>Servicio de Farmacia, Complejo Hospitalario Universitario de Pontevedra, Pontevedra. Spain. <sup>2</sup>Instituto de Investigación Sanitaria Galicia Sur, Fundación Biomédica Galicia Sur, Pontevedra. Spain. <sup>3</sup>Servicio de Dermatología, Complejo Hospitalario Universitario de Pontevedra, Pontevedra. Spain.

## Author of correspondence

Lara González Freire  
Avda. Mourente, s/n  
36071 Pontevedra. Spain.Email:  
lara.gonzalez.freire@sergas.esReceived 20 December 2020;  
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## Abstract

**Objective:** Optimization of a topical formula of N-acetylcysteine and urea for the topical treatment of ichthyosis.**Method:** We reviewed the chemical structure of the N-acetylcysteine molecule and its metabolic processes. A search was conducted of possible alternative molecules with a chemical structure similar to that of N-acetylcysteine that could have improved organoleptic properties. The following databases were used: PubChem®, Botplus®, the Drug Information Centre of the Spanish Agency of Medicines and Medical Devices. The molecule selection criteria were as follows: structural similarity, same therapeutic group, same mechanism of action, same authorized indication, absence of unpleasant smell, and being marketed as raw material in Spain. To complete the pharmaceutical development and validation of the compound, several tests and controls were conducted following the emulsion production procedure of the National Formulary. In order to establish the validity period, we followed the recommendations of the "Guide to Good Drug Preparation Practices in Hospital Pharmacy Services".**Results:** N-acetylcysteine has a free sulfhydryl group, which is responsible for its smell, and undergoes deacetylation. Its main metabolites are cystine and cysteamine. The following molecules were assessed: cystine, cysteamine, carbocysteine, cysteine and methionine. Carbocysteine

## Resumen

**Objetivo:** Optimización de una fórmula magistral tópica de N-acetilcisteína y urea para el tratamiento tópico de la ictiosis.**Método:** Se revisó la estructura química de la molécula de N-acetilcisteína y sus procesos metabólicos. Se realizó una búsqueda de posibles moléculas alternativas con una estructura química similar a la N-acetilcisteína que pudiesen mejorar sus propiedades organolépticas. Bases de datos: PubChem®, Botplus®, Centro de Información de Medicamentos de la Agencia Española de Medicamentos y Productos Sanitarios. Criterios de selección de la molécula: similitud estructural, mismo grupo terapéutico, mismo mecanismo de acción, misma indicación autorizada, ausencia de olor desagradable y estar comercializada como materia prima en España. Para el desarrollo galénico y validación de la fórmula se realizaron varios ensayos y controles siguiendo el procedimiento de elaboración de emulsiones del Formulario Nacional. Para establecer el periodo de validez se siguieron las recomendaciones de la "Guía de buenas prácticas de preparación de medicamentos en los servicios de farmacia hospitalaria".**Resultados:** La N-acetilcisteína presenta grupo sulfhidrido libre, responsable del olor, sufre desacetilación y sus principales metabolitos son cistina y cisteamina. Las moléculas evaluadas fueron: cistina, cisteamina, carbocisteína, cisteína y metionina. Se seleccionó la carbocisteína por

## KEYWORDS

Congenital ichthyosis; Rare diseases; Drug compounding; Therapy; Acetylcysteine; Carbocysteine; Effectiveness; Tolerance.

## PALABRAS CLAVE

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was selected because it met all the selection criteria. Carbocisteine is practically insoluble in water and soluble in mineral acids and alkaline hydroxides solutions. Unlike N-acetylcysteine, it does not have a fetid smell. It reaches its maximum stability at pH 5.5 to 7.5. The composition of the compound (100 g) was as follows: carbocisteine (10 g), urea (5 g), glycerine (15 g), water (44 mL), sodium hydroxide (1 g), and Neo PCL® Oil/Water (O/W) (25 g). It has an expiration period of 30 days. The organoleptic characteristics, emulsion type, and pH remained stable within the established expiration period. The carbocisteine compound has been incorporated into the group of topical treatments available for the treatment of patients with ichthyosis in our hospital.

**Conclusions:** The carbocisteine molecule is a good therapeutic alternative that lacks the unpleasant smell of N-acetylcysteine. The carbocisteine compound developed has been included as topical treatment for ichthyosis due to its tolerability, acceptability, and effectiveness in the treatment of patients affected by this genodermatosis.

## Introduction

Congenital ichthyoses comprise a heterogeneous group of genodermatoses characterized by keratinization defects leading to dry skin, desquamation, hyperkeratosis, and erythema. They often also involve itching, abnormal sweating and thermoregulation, and heat intolerance<sup>1,3</sup>.

Most congenital ichthyoses are included among the rare diseases. Their prevalence has been estimated at approximately 1/100,000 to 1/1,000,000,000 individuals<sup>1,3</sup>.

The common clinical feature of hereditary ichthyosis is skin peeling, usually generalized, which is present from birth or from the first months of life. The disease has a strong impact on quality of life, due to changes in physical appearance and associated symptoms<sup>1,3</sup>.

There is currently no curative treatment for this disease, and so the therapeutic objective is symptomatic control. It is mainly managed by hydration and keratolysis of the affected areas. For this purpose, emollients and lubricants are used, such as urea, glycerol, kerosene, or propylene glycol, as well as topical keratolytics, such as lactic acid, ammonium lactate, salicylic acid, and N-acetylcysteine (NAC). In the most severe forms, oral retinoids are used<sup>1,5</sup>.

Treatment should be optimized and individualized in each case, because of great variability in skin tolerance to different topical products and in the response to each therapy. Short- and long-term side effects also guide the choice of the different therapeutic alternatives. In addition, patients with ichthyosis have reduced skin barrier function with increased transepidermal water loss. Such increased skin permeability may favour intoxication secondary to the absorption of topically applied substances<sup>6,7</sup>.

Urea is a small organic molecule that retains water in the stratum corneum, reduces epidermal proliferation, has regenerative and antimicrobial effects, and facilitates the penetration of other active ingredients. It acts as a moisturizer at concentrations of less than 5% and has keratolytic action at higher concentrations<sup>1</sup>.

N-acetylcysteine is a hypoallergenic and non-toxic amino acid derivative with an anti-proliferative effect on keratinocytes<sup>1</sup>.

Although current data are based on case series or isolated cases, formulations that combine NAC 10% and urea 5% have been shown to be effective, safe, and well tolerated in patients with ichthyosis, who show a marked response after several weeks of use<sup>1</sup>.

The magistral formula (MF) of NAC and urea has the disadvantage of an unpleasant sulphurous smell that in routine clinical practice causes a significant lack of adherence and even rejection of treatment. The NAC molecule has a free sulfhydryl (SH) group, which is responsible for this unpleasant smell. This aspect has led to the search for similar molecules and the development of new therapeutic alternatives that minimize this effect and improve treatment adherence.

Objective: Optimization of a MF of NAC and urea with improved organoleptic properties for the topical treatment of ichthyosis.

## Methods

Firstly, we used PubChem to review the chemical structure of the NAC molecule and its metabolic processes<sup>8</sup>, because our aim was to search for

cumplir todos los criterios de selección. La carbocisteína es prácticamente insoluble en agua y soluble en disoluciones de ácidos minerales e hidróxidos alcalinos. A diferencia de la N-acetilcisteína, carece de olor fétido. Presenta su máxima estabilidad a pH 5,5-7,5. La composición de la fórmula magistral (100 g): carbocisteína (10 g), urea (5 g), glicerina (15 g), agua (44 mL), hidróxido sódico (1 g) y Neo PCL® Oil/Water (O/W) (25 g). Periodo de caducidad: 30 días. Los caracteres organolépticos, signo de la emulsión y pH permanecieron estables durante el periodo de caducidad establecido. La fórmula magistral de carbocisteína elaborada se ha incorporado al arsenal de tratamientos tópicos disponibles para los pacientes con ictiosis de nuestro centro.

**Conclusiones:** La molécula de carbocisteína resultó ser una buena alternativa terapéutica que subsana el olor desagradable de la N-acetilcisteína. La fórmula magistral de carbocisteína desarrollada fue incluida como tratamiento tópico de la ictiosis gracias a su tolerabilidad, aceptabilidad y efectividad en el tratamiento de pacientes afectados de esta genodermatosis.

an alternative with similar therapeutic effects. Next, we searched for possible alternative molecules with a chemical structure similar to NAC that could improve its organoleptic properties. The following databases were used: PubChem<sup>8</sup>, BoiPlus<sup>9</sup>, and the Medicines Information Centre of the Spanish Agency of Medicines and Health Products (AEMPS)<sup>10</sup>.

The molecule for this indication was selected according to the following criteria: having structural similarity, belonging to the same therapeutic group, and having the same mechanism of action, the same authorized indication, and an absence of unpleasant smell. A key requirement was that any potential alternative molecule was available as raw material marketed in Spain by an AEMPS authorized laboratory. We assessed the characteristics of the different molecules using the information in the Summary of Product Characteristics of the laboratory (Acofarma, Spain) that distributes the raw material.

To design the possible formulation, we followed the same criteria that were applied regarding the MF with NAC plus urea. For the pharmaceutical development and validation of the formula, we conducted several tests and controls following the emulsion preparation procedure of the National Formulary (PN/L/002/00)<sup>11</sup>. To establish the period of validity of the MF, we followed the recommendations of the Guide to Good Drug Preparation Practices in Hospital Pharmacy Services (GBBP) for non-sterile preparations<sup>12</sup>.

In order to be able to use the new MF, authorization as an "off-label" drug was requested from the Pharmacy and Therapeutics Committee and the management of the hospital, after signed informed consent was given by patients or their legal guardians in the case of minors.

## Results

### Review of the N-acetylcysteine molecule

N-acetylcysteine is a white crystalline powder that is readily soluble in water and 96% ethanol. It is a thiol derivative, which is commonly used as a mucolytic, antioxidant, nephroprotectant, and antidote for acetaminophen poisoning<sup>8</sup>.

In addition to being a keratolytic agent, NAC modulates keratinocyte proliferation and differentiation. When NAC enters cells it is rapidly hydrolysed to cysteine, a precursor of glutathione, which is a well-studied antioxidant that maintains the cellular redox state. By decreasing free radicals and increasing cysteine levels, NAC increases glutathione levels, which inhibit inflammatory factors and promotes epidermal proliferation. Applied topically, NAC prevents irritation caused by radiotherapy and protects against solar erythema<sup>2,6,13,14</sup>.

N-acetylcysteine is an amino acid derivative with multiple therapeutic uses and rare adverse effects, which include pruritus, irritation, or burning sensations. Its dermal bioavailability is less than 3%, with hepatic metabolism and renal excretion, and so adverse effects such as nausea, vomiting, urticaria, or anaphylactic reactions are more common when NAC is administered orally or intravenously<sup>9</sup>.

## Search for possible alternatives and their characteristics

The NAC molecule has a free SH group, which is responsible for the foul smell. This group undergoes deacetylation and its main metabolites are cystine and cysteamine. Thus, these two molecules were initially selected as possible alternatives. Carbocysteine is in the same therapeutic group (ATC classification: R05CB) and has a similar chemical structure to NAC<sup>9</sup>.

In addition, we searched PubChem<sup>®</sup> for other different molecules with a similar structure to NAC that could be used as possible therapeutic alternatives. The molecules assessed were cystine, cysteamine, carbocysteine, cysteine, and methionine.

Cystine is a white crystalline powder that is almost insoluble in water and 96% ethanol. It dissolves in dilute solutions of alkaline hydroxides. Cystine is a sulphur-containing aliphatic amino acid biosynthesized from cysteine, and is present in many foods. It is involved in the metabolism of the skin and adnexa, and is a constituent of keratin. It is used as a dietary supplement and in the treatment of congenital homocystinuria. In addition, it is indicated in cases of diffuse alopecia, alopecia areata, acne, seborrheic eczema, nail diseases, psoriasis, and skin disorders with sulphur deficiency<sup>15</sup>.

Cysteamine is a white powder that is soluble in water and ethanol. It has an unpleasant smell due to the presence of free SH groups. Furthermore, it is not marketed as a raw material in Spain<sup>8</sup>.

Carbocysteine is a white crystalline powder that is soluble in dilute solutions of mineral acids and alkaline hydroxides, and is almost insoluble in water and 96% ethanol. It is a mucolytic agent that reduces the viscosity of bronchial secretions. Carbocysteine is used in respiratory tract disorders associated with excessive mucus such as bronchiectasis, asthmatic bronchitis, pulmonary emphysema, pneumonia, tuberculosis, cystic fibrosis, and in all conditions in which mucolytics and expectorants are required. It attains maximum stability at pH 5.5 to 7.5. It can sometimes cause nausea, headache, gastric discomfort, diarrhoea, and skin eruptions when administered orally<sup>16</sup>. Unlike NAC, the carbocysteine molecule lacks a free SH group that cannot be released during the oxidation process. This means that the carbocysteine molecule lacks a foul smell<sup>17</sup>.

Cysteine is a bright white crystalline powder. Because of its antibiotic properties, it is used in topical preparations for the treatment of various skin conditions. However, due to the presence of the free SH group, it has a certain acidic smell<sup>18</sup>.

Methionine is an almost white crystalline powder, fairly soluble in water and very slightly soluble in 96% ethanol. It dissolves in dilute acids and in dilute solutions of alkaline hydroxides. Methionine increases glutathione synthesis. It is used as an alternative to NAC in the treatment of paracetamol overdose to prevent liver damage. It also has lipotropic action and is used as an adjuvant in the treatment of liver diseases, pancreatitis, schizophrenia, and urinary incontinence. It can be administered to treat alopecia and intervenes in keratinization processes. It can cause nausea, vomiting, drowsiness, and irritability when administered orally<sup>19</sup>.

## Selection of the molecule

Cysteine and cysteamine, despite being metabolites of NAC, have the free SH group in their molecule, which gives them the same unpleasant smell as NAC. Furthermore, cysteamine is not marketed as a raw material in Spain. For these reasons, they were rejected as therapeutic alternatives in the preparation of the MF (Table 1).

Among the three remaining molecules, carbocysteine was selected as a possible therapeutic alternative because it met all the selection criteria: structural similarity to NAC, belonging to the same therapeutic group, having the same mechanism of action and same authorized indication as a mucolytic, lacking a free SH group, and being available as a raw material in Spain.

Both cystine and methionine were considered as a second choice in case the MF of carbocysteine could not be developed or was not effective for the indication sought (i.e. a keratolytic in the topical treatment of ichthyosis). However, although raw material is available, there is no marketed drug containing either of these molecules as a monocomponent, which implies a lack of information on their safety (Table 1).

## Pharmaceutical development and formulation validation

The raw carbocysteine material was acquired from the Acofarma laboratory, which is authorized by the AEMPS for the distribution of raw materials<sup>20</sup>.

To determine the concentration of carbocysteine to be used in the MF, we took as a reference the concentration of NAC (10%) plus urea (5%). This mixture is synergistic, because urea, which is also a keratolytic agent, offers an optimal pharmacological effect and also seems to provide the most effective transcutaneous penetration of the active ingredients<sup>6,21</sup>.

We selected the same excipients as those used in the standard NAC MF, due to the good tolerance demonstrated with their use in our hospital<sup>22</sup>. In addition, by using the same excipients, effectiveness could also be compared by making minimal variations in the MF.

Given the characteristics of the patients and the disease, in which these MFs should be applied over large areas of the body, we kept the nonionic self-emulsifying O/W absorption base. This base makes application easier, achieves better homogenization without residue or an oily sensation, and is easily absorbable and dermatologically innocuous<sup>1,5,22</sup>.

Glycerine is an osmotic dehydrating agent with hygroscopic and lubricating properties. It also has local and topical anti-inflammatory activity, and is an emollient which protects and softens the skin<sup>1,5</sup>.

Rosemary essence had already been incorporated into the initial NAC and urea MF to reduce its smell to acceptable levels<sup>5</sup>. By substituting the NAC for carbocysteine, the sulphurous smell was eliminated and it was no longer necessary to add the rosemary essence.

The first step in the development and preparation of the MF was to try to solubilize the carbocysteine with sodium hydroxide (NaOH) in the water phase. However, this was only achieved when the formula had a pH of at least 8. This pH level was not appropriate because it was outside the range of maximum stability of the active principle (AP), neither was it appropriate for chronic use over the entire body surface.

**Table 1.** Molecules and selection criteria

Molecule	Structural similarity	Same therapeutic group	Same mechanism of action	Same indication	Free sulphhydryl group	Availability of raw material
Cystine	Yes	No	No	No	No	Yes
Cysteamine	Yes	No	No	No	Yes	No
Carbocysteine	Yes	Yes	Yes	Yes	No	Yes
Cysteine	Yes	No	No	No	Yes	Yes
Methionine	Yes	No	No	No	No	Yes

**Table 2.** Composition of the N-acetylcysteine magistral formula and the new carbocisteine plus urea magistral formula

NAC 10% + Urea 5% O/W (100 g)	Carbocisteine 10% + Urea 5% O/W (100 g)
NAC 10 g	Carbocisteine 10 g
Urea 5 g	Urea 5 g
Glycerine 5 g	Glycerine 15 g
Water 44 mL	Water 44 mL
NaOH 1 g	NaOH 1 g
Neo-PCL O/W 25 g	Neo-PCL O/W 25 g
Argan oil 5 g	
Rosemary essence 1.5 mL	

NAC: N-acetylcysteine; NaOH: sodium hydroxide; Neo PCL O/W: nonionic self-emulsifying oil/water absorption base.

The next step was to pulverize the powder in a mortar and moisten it with glycerine. A paste was obtained which was added into the cooling phase once the emulsion was created. However, the particle size was inadequate because it was noticeable to the touch after application. To eliminate this effect, the particle size was reduced by pulverizing it using an electric grinder. The resulting powder was then moistened with glycerine and incorporated into the water phase under constant stirring.

We used NaOH to adjust the pH level to between 5 and 6, which is appropriate for application over the entire body surface and is within the maximum stability range of the AP.

Table 2 shows the composition of the original NAC MF and the new carbocisteine and urea MF.

We established a validity period of 30 days, which is line with the criteria described in the GBBP's risk matrix for nonsterile and nonoral water-containing preparations<sup>12</sup>.

In accordance with the emulsion preparation procedure described in the National Formulary (PN/L/FF/002/00), we conducted the following controls<sup>11</sup>:

- Organoleptic characteristics: white, uniform, homogeneous, and odourless O/W cream over its established shelf life.
- Type of the emulsion according to the PN/L/CP/002/00 procedure: stable over its established shelf life.
- pH control according to PN/L/CP/001/00 procedure as a O/W emulsion: within the pH of maximum stability of the AP over its shelf life. Table 3 shows the pH values.

Figure 1 shows the standard operating procedure for the new carbocisteine plus urea MF.

## Use in clinical practice

Initial authorization was obtained for the carbocisteine-urea MF developed for patients with lamellar ichthyosis who were previously receiving the NAC MF. After obtaining the relevant authorizations, the new MF was applied to small specific areas of the body to assess tolerance, the absence of adverse effects, and effectiveness<sup>17</sup>.

The carbocisteine and urea MF was incorporated into the arsenal of topical treatments available to treat patients with ichthyosis in our hospital, given that there were no side effects, tolerance was good, effectiveness was at least similar to that of the NAC MF, and there was the added benefit of greater acceptance due to the absence of a bad smell<sup>17</sup>.

**Table 3.** pH determination values

pH determination time	pH values (mean $\pm$ SD)
Day 0	5.5 $\pm$ 0.4
Day +30	5.5 $\pm$ 0.5

SD: standard deviation.

## Discussion

Ichthyoses comprise a heterogeneous group of genetic diseases characterized by abnormal keratinization of the skin. Early symptoms are characterized by thickening of the stratum corneum, skin peeling, and dry skin. In addition, the skin's ability to perspire may be impaired leading to hyperthermia and even circulatory collapse<sup>1</sup>.

As these are rare diseases, few high-quality studies have assessed the available treatments. Most of the published literature is based on expert opinion and small case series. The development of new treatment options is hampered by the low number of patients, which makes it difficult to conduct controlled studies and clinical trials<sup>23</sup>.

The search for molecules with a similar chemical structure is one of the strategies used to develop new drugs or treatments for a given disease that have better efficacy or fewer adverse effects than existing drugs. In our study, this was the fundamental criterion followed in the search for an alternative to NAC with improved organoleptic properties and analogous efficacy.

From the pharmaceutical point of view, a determining factor is the availability of raw material to prepare the formula. It is also relevant that the raw material is marketed as a monocomponent and is authorized for human use—which means that safety data are available—although the administration route may differ. In any case, since the drug is used in the topical treatment of ichthyosis, it would be reasonable to assume that any potential adverse effects would be milder than those derived from its systemic administration.

It has been shown that the NAC 10% plus urea 5% MF is an effective and safe therapeutic alternative in the treatment of ichthyosis within a few weeks of use<sup>6</sup>. Despite the advantages initially presented by topical treatment with NAC, the foul smell of the emulsion due to the presence of free SH groups makes it difficult for many patients to continue treatment<sup>17</sup>.

Among all the alternatives studied, carbocisteine has a similar chemical structure to that of NAC, belongs to the same therapeutic group, has the same indications and mechanism of action, is available as raw material in Spain, and does not carry the free SH radical. These aspects led to its selection as an alternative AP to NAC.

The same concentration of carbocisteine was selected as that used in the NAC (10%) MF and it was combined with urea 5%. Several authors have reported that this association not only has a synergistic effect, because urea is another keratolytic agent, but also seems to improve the transcutaneous absorption of NAC<sup>6,21</sup>. We hypothesized that this effect obtained with NAC would also be obtained with carbocisteine.

The development of the carbocisteine plus urea MF was hampered by its low solubility and high concentration (10%), which necessitated a reduction in particle size to make it easier to spread. Particle size was reduced by pulverising it in an electric grinder.

The key advantage of the new carbocisteine and urea MF was that, unlike NAC, it did not have a foul smell. The replacement of NAC by carbocisteine improved the organoleptic characteristics of the MF, making its use possible as a therapeutic alternative to NAC treatment.

Batalla *et al.* conducted a study in our hospital of 4 patients diagnosed with ichthyosis who received treatment with a carbocisteine plus urea MF. All but one patient reported that the effectiveness of the carbocisteine and urea MF was at least similar to that of the initial NAC MF. Acceptability of the MF was higher because of the absence of a foul smell. All patients reported good tolerance and an absence of adverse effects<sup>17</sup>.

However, it was harder to spread the MF. This obstacle was overcome by reducing particle size and moistening with glycerine during the manufacturing process<sup>17</sup>.

Treatment should be individualized according to the patients' degree of tolerance to different topical products<sup>6,7</sup>. If needed, the NAC and urea concentrations can be modified. This possibility is maintained with the new carbocisteine plus urea MF.

The carbocisteine molecule proved to be a good therapeutic alternative that eliminates the foul smell of NAC. The carbocisteine and urea MF developed has been included as a topical treatment for ichthyosis due to its tolerability, acceptability, and effectiveness in the treatment of patients with this genodermatosis.

Figure 1. Standard Operating Procedure for the new carbocysteine magistral formula.

CARBOCISTEINE 10% + UREA 5% O/W II			Code: 377	
Pharm. form: Cream	Shelf life: 30 days	Acronym: CARBOCIS-C6		
Adm. route: Topical	Protect from light: No	Validated: 07/19/2017		
To be prepared by: Technician	Storage: Room temperature	Dispensable: Yes		
Indications: symptomatic treatment of ichthyosis and lamellar ichthyosis.		Risk level: <b>MEDIUM</b> Preparation: <b>Nonsterile</b>		
Composition				
I	F	Comp quantity	Ingredient	Amount prepared
		5 g	Urea Acofarma	5 g
		44 mL	Versylene Fresenius sterile water 1L Fresenius Kabi	44 mL
		25 g	Neo PCL® O/W Acofarma	25 g
		10 g	Carbocisteine Acofarma	10 g
		15 g	Glycerin Acofarma	15 g
		1 g	Sodium hydroxide (NaOH) pellets Acofarma	1 g
Equipment		Preparation		
1 - Glass rod		Weigh and measure all the components.		
1 - Sartorius analytical balance		Finely pulverise the carbocisteine in the glass blender. Once pulverised, add the glycerine and homogenize again in the blender until a fine paste is formed. Set aside.		
1 - Precipitation beaker		Dissolve the sodium hydroxide in 10-20% of the water.		
1 - Magnetic stirrer and stirring rod		Put the remaining water in a precipitation beaker and heat to between 50°C and 60°C.		
1 - Test tube		Add the urea and shake until completely dissolved.		
1 - Blender		Once the urea is dissolved, add the aqueous phase to the paste formed by the glycerine and carbocisteine and homogenize again in the blender. Slowly add the sodium hydroxide solution and homogenize.		
		Put the Neo PCL® in the precipitation beaker and melt at the same temperature as the aqueous phase.		
		When the two phases reach the same temperature (50-60°C) gradually pour the aqueous phase (which is in the beaker) over the oily phase (Neo PCL®) while stirring.		
		Continuously and progressively emulsify with the blender.		
		Finally, stabilize the emulsion by stirring moderately during the entire cooling phase.		
		Pack and label.		
Packaging: Quantity to be prepared, 100 g distributed in one 125-mL plastic bottle with 100 g each.				
Quality Controls				
Control	Requirement	To be performed by	Sampling	
Organoleptic characteristics				
	Thick whitish cream.	Technician	No	
pH control				
	5-6	Technician	No	

Adm. route: administration route; O/W: Oil/Water; Pharm. form: pharmaceutical form.

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## Funding

No funding.

## Conflict of interests

No conflict of interests.

## Contribution to the scientific literature

Congenital ichthyoses are a group of genodermatoses included among the rare diseases. Currently, there is no curative treatment, but the therapeutic objective is to palliate the symptoms. Lubricants, emol-

lients, and keratolytics are used for this purpose. Moreover, because these are rare diseases, few studies have assessed the available treatments. Several case series have shown that N-acetylcysteine and urea formulations are effective; however, their unpleasant smell makes continuity of treatment difficult.

This study presents the development of a new magistral formula for the topical treatment of congenital ichthyosis using an alternative molecule to N-acetylcysteine that lacks an unpleasant smell, meets the requirements established by the Guide to Good Drug Preparation Practices in Hospital Pharmacy Services and the National Formulary, and, in addition to being effective, is accepted and tolerated by patients diagnosed with ichthyosis.



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