Joana Rafaela Sousa Barbosa

Relatórios de Estágio e Monografia intitulada "Simultaneous Administration of Insulin and GLP-1 Agonists. Technologically Possible?" referentes à Unidade Curricular "Estágio", sob a orientação, respetivamente, do Dr. Hélder Mesquita, da Dra. Marta Queiroz, e do Professor Doutor António José Ribeiro e apresentados à Faculdade de Farmácia da Universidade de Coimbra, para apreciação na prestação de provas públicas de Mestrado Integrado em Ciências Farmacêuticas

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Universidade de Coimbra

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UNIVERSIDADE DE COIMBRA

Eu, Joana Rafaela Sousa Barbosa, estudante do Mestrado Integrado em Ciências Farmacêuticas, com o nº 2012114341, declaro assumir toda a responsabilidade pelo conteúdo do Documento Relatórios de Estágio e Monografia intitulada "Simultaneous administration of insulin and GLP-1 agonists. Technologically possible?" apresentados à Faculdade de Farmácia da Universidade de Coimbra, no âmbito da unidade de Estágio Curricular.

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Coimbra, 17 de julho de 2017.

Joana Rafaela Sousa Barbosa

(Joana Rafaela Sousa Barbosa)

AGRADECIMENTOS

Aos meus pais, que me proporcionaram a oportunidade de crescer e me apoiaram incondicionalmente durante todo o percurso.

Às minhas irmãs, pelos momentos caricatos e descontraídos.

Aos meus amigos, por terem sido a minha segunda família durante os últimos cinco anos.

Ao Petico, pela ajuda a vários níveis nos meus distintos momentos críticos.

À Faculdade de Farmácia da Universidade de Coimbra, pela incrível formação prestada.

À Farmácia da Estação e ao Hospital CUF Porto, pela oportunidade de estágio.

Aos meus orientadores de monografia e de estágio.

A Coimbra, que me vê partir de coração cheio.

E por fim...

A mim, porque fui capaz.

A TODOS OBRIGADA.

"We must never forget that we may also find meaning in life even when confronted with a hopeless situation, when facing a fate that cannot be changed.
When we are no longer able to change situation, we are challenged to change ourselves...
...to turn one's predicament into a human achievement"

Viktor E. Frankl

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Faculty of Pharmacy of the University of Coimbra

I. INTERNSHIP REPORT
IN COMMUNITY PHARMACY

Farmácia da Estação

Orientation:
Dr. Hélder Mesquita

LIST OF ABBREVIATIONS

BMI	Body mass index
BP	Blood pressure
ICD	International common denomination
NCP	National code of product
SWOT	Strengths, Weaknesses, Opportunities, Threats

LIST OF TABLES

1. INTRODUCTION

The pharmacist as an agent involved in the education and provision of public health care has an intervention at different levels, both preventive and therapeutic.

Nowadays, the pharmaceutical class is seen as an accessible way to contact, obtain information and solution for different problems, consequently the community pharmacy must be capable to provide a set of differentiated and specialized health services. Society has evolved, and the pharmacist must have the ability to adapt, change and respond effectively to the patients' needs. Within the pharmaceutical activities focused on the patient, there is the dispense of medication, where the pharmacist has a central role in the provision of information that can improve the correct use of drugs.

After five years of academic formation, the internship in community pharmacy allowed me to apply and consolidate all the knowledge acquired and additionally, to develop the social and human component, associated with the exercise of the pharmaceutical profession, being essential for my future entry into the labor market.

The Farmácia da Estação presents itself as a united team with a strong sense of social and professional responsibility. My internship took place between the months of January and May. This report has the purpose to describe the acquired abilities and activities developed, in the community pharmacy, with which I had the opportunity to contact, addressing the aspects related to their operation and with the practice of the pharmaceutical profession.

2. SWOT ANALYSIS

A SWOT analysis was performed in order to make a critical analysis, intending a personal reflection on my performance and on the activities and practices considered important and experienced during the internship. An innovated analysis strategy that critically evaluates strengths, weaknesses, opportunities, and threats, intended to demonstrate the adequacy of the theoretical knowledge obtained, with the reality of the practice within the labor market. (1)

Table I represents, the following strengths, weaknesses, opportunities, and threats of this experience.

Table I. *SWOT analysis of the internship at Farmácia da Estação*

STRENGTHS	WEAKNESSES	OPPORTUNITIES	THREATS
-Team integration and work environment - Internship planning and functions performed - Learning and the continuous follow-up - Heterogeneity of pharmacy patients and costumers - Sifarma2000® and support technologies -Provided services at the pharmacy	- Internship duration - Difficulties in specific areas - Active principle and the commercial name - Lack of Information on external formations - Adaptation to the pace of work	- Psychological and social improvement - Manipulated drugs - Paperless electronic recipes - Kaizen philosophy - The new Sifarma, "Novo Atendimento"	- Request of prescription drugs without prescription - The trainee from costumer's perspective

2.1 STRENGTHS

2.1.1 Team integration and work environment

The integration in the Farmácia da Estação, was very simple because I was truthfully embraced by all the elements of the team, which allowed me to have a continuous learning through all its orientations and shared knowledge.

The work environment was remarkable and distinct, giving me the perception of the necessity to be a competent, focused professional and of the need to have a good relationship with co-workers. This experience gave me not only a sense of precision and demand but a means of teaching and social, which made me develop components of relationship and responsibility. There was no monotony in work, I felt that every day was an opportunity, with challenges to overcome, making me able to provide health care effectively, always with the support of the team, to whom I owe only gratitude.

2.1.2 Internship planning and functions performed

The first day of internship began with the presentation of the facilities and of the team members, followed by the explanation of the structuring and planning of my curricular internship, which consisted essentially on three phases: the backoffice; the economic and regulatory affairs component; and the balcony attendance.

The first phase allowed me to know the procedure of organization and disposal of a pharmacy, and the cycle of backoffice. I started to assume various tasks, from the daily, weekly and instantaneous execution of orders, to the verification, by confirming the number of baths received that should be accompanied by an invoice with a duplicate or delivery note. The reception of the same orders involved the entrance of all products into the computer system through their NCP, the expiration date, pharmacy and costumer prices, discounts and the total value of the invoice. Invoices were after properly filed and finally the drugs were storage in the appropriate place.

All this was essential to identify and familiarize myself with all the existing products and to establish a first contact with the commercial names while making the distinction of the generics, simultaneously allowed me to learn the therapeutic indications and mechanisms of some active principles. The accomplishment of all these tasks implies the manipulation and gain of experience in the secondary tools of the software Sifarma2000®.

The second phase, the economic and regulatory affairs component, raised my perception on the management of financial resources, acquiring sense of rigor and responsibility by the possibility to execute the regularization of returns and credit notes, the analysis and management of stock for request of medications orders, and the management of invoices and lots to be invoiced with different regimens of co-participation. This last task involved verification of the recipes conformity, where it was essential to check their organism, the doctor's signature and the expiration date. After this, at the end of each month, the billing is closed and the receipts are organized in batches of 30, which in turn are grouped by agency, with the respective batch identification entry, batch summary and monthly invoice, so that the pharmacy is reimbursed with the amount of the co-participations. All a set of tasks that I never had access before, developing bases with great utility for future application in a professional and a personal level.

Finally, the balcony attendance phase, which started with supervision until I fully demonstrated the autonomy to correctly execute it, individually. My first contact with the public started with some insecurity, however, the support given by the team and with the emerging of a diversity of situations, I became more confident, independent acquiring high responsibility and demand. It was the most important phase of my internship allowing me to more deeply applying, perfecting and consolidating all the knowledge, passing through a huge professional breakthrough.

2.1.3 Learning and the continuous follow-up

One of the most important pillars of my internship was the knowledge acquired, due to the continuous support by the team, allowing me a permanent evolution and gradual transition from an education state to the labor market, which is of the utmost importance. I received guidance that allowed the development of my attitude as a professional. The daily contact and the practical resolution of various situations with different themes, regarding medical devices, custom medication, simple pathologies and services provided by the pharmacy, taught me the need to constantly update knowledge, improving my performance, by focusing on people, trying to better assist in the delivery of health care.

2.1.4 Heterogeneity of pharmacy patients and costumers

Given its location, close to several medical services and to the train station, the Farmácia da Estação, is much requested as a place of health care, either by the neighboring population as by tourists. In addition, the extended office hours and the opening on Sunday mornings, attracts a heterogeneous variety of patients, regarding the socioeconomic class and age. This required a constant adaptation to counseling situations for various pathologies and ages, which, in some cases, I did not know how to respond, such as drugs and dosages of pediatrics. However, each case became a lesson, perfecting my abilities, noted at the end of the internship, where I already had greater sensitivity and confidence for the recommendation and orientation of the patient.

The possibility of working over the weekend gave me a completely different notion of patterns of work, essentially because of the greater number of clients, with a fast need to perform the tasks, without leaving aside accuracy and competence. It was a challenging opportunity giving me team spirit by helping both, the patient and the whole team, even when all the balconies were occupied, the responsibility for the reception and for making orders, facilitated the drug dispensing by the team, being more timely effective.

2.1.5 Sifarma2000® and support technologies

To assist the pharmaceutical activity, there was a computer system designated Sifarma2000®. In addition to its primary function, this program has variable secondary functions such as order management and returns, consultation of products and their scientific information. This last point made it possible to perform every care with higher quality and safety, since it provides all the information needed such as precautions, mechanism of action, adverse reactions and drug interactions. In addition, the access of the client personal file, with their consumption history, was very useful since several patients did not remember the commercial name or laboratory of their habitual medication.

The attendance component of the software, allows the dispensing of suspended, prescript and non-prescript drugs, to create reservations, credits and the return of products. An instrument of great importance with the ability to strictly control the dispensing of drugs by the requirement of prior validation, which allowed me to detect misconceptions in the selection of look-alike and sound-alike drugs. The same applies to the psychotropic and narcotic drugs, with a required registration of specific data of the prescribing physician, of

the patient and customer responsible for receiving the medication. All this requirement of the software led me to develop work routines, such as double checking, acquiring the ability to counsel by constantly consulting information in the program.

Regarding the request of instantaneous orders of drugs, the existence of the Cooprofar Gadget made it possible to perform this task more quickly, also to verify existences and prices. The existence of a cash-guard system lead to a great minimization of mistakes in terms of change and time management, providing greater attention to the patients.

2.1.6 Provided services by the pharmacy

The Farmácia da Estação has at its disposal a determination service of several physiological and biochemical parameters, such as: measurement of blood pressure (BP), body weight, body mass index (BMI), total cholesterol level, triglycerides, capillary blood glucose measurement and pregnancy tests. Performing most of these services lead to the improvement of communication and therapeutic counsel, being a private moment, where many times the patients feel comfortable to expose the help they need, underlying the importance of professional secrecy. These services thought me to monitor patients who were medicated, to detect situations of non-adherence to therapy and possible pathologies, namely hypertension and diabetes. I felt a strong obligation to recommend non-pharmacological measures, depending on the situation, fluid intake, physical exercise, weight control, reduction in salt and caffeine, and avoidance of stress were often suggested.

The pharmacy also participates in the Valormed initiative, which made me contribute to the patient education on the treatment of drug residues. Many of them did not know this existence. In addition, there was a continuous promotion of additional activities and services, such as nutritional screening, evaluation of asthma control and allergic rhinitis, pregnancy counseling with 3D and 4D ultrasound, creating a better comprehension of the associated products and the contexts of their use.

2.2 WEAKNESSES

2.2.1 Internship duration

The conclusion of the internship was essentially differentiated by a greater self-sufficiency and independence to overcome the challenges that initially caused me insecurity. With an extended duration, my abilities could be further improved, with the opportunity to increase the range of learning and consolidate the acquired routines. Nonetheless, completing a four-month internship in a community pharmacy resulted in a very enriching experience, in which I thrive on knowledge, taking advantage of every moment until the end.

2.2.2 Difficulties in specific areas

During the internship, I faced some difficulties in specific areas such as pediatric, veterinary and dermocosmetics. In the pediatrics field, I was asked about products for specific conditions several times. These were conditions such as cramps, skin irritations, lactic crust, congestion and colds for instance. Initially, it was very challenging to proper counsel, since there were young children and babies involved however, the guidance and support given by the orientation team were crucial to develop my skills.

The veterinary area was particularly unsettling. Despite my academic formation in this subject, the topics learnt were not enough and not applicable in the day-to-day life of a pharmacy, lacking on the agility to indicate this type of products in real context. The help from the professional team was essential.

Dermocosmetics was also a troubling area. There is a wide range of brands with similar products to different pathologies. Patients usually asked the best product to treat a specific condition and I was not able to give them a straight answer. Here enters the learning to correctly distinguish these products and therefore present the patients a better solution. Acquiring this knowledge progressively increased my confidence while solving this daily demands. The products exposure by the trademark delegates was also very important.

Lastly the medical devices, an area that I gained experience by contacting with the products in the pharmacy and with the various situations that came up alongside the patients' needs. In my opinion, the theoretical unit of the course should be obligatory and not optional, given the importance of this knowledge in the practice of community pharmacy.

2.2.3 Active principle and the commercial name

Another difficulty in the beginning of providing services to the public was the association of the active principle with the commercial name, considering that most patients refer their medication by the commercial name and often not correctly or without a good pronounce. With daily contact, whether in the attendance or in the backoffice, a strong evolution occurred in this aspect. In addition, Sifarma2000® has very good potentialities that were helpful.

Prescription by international common denomination (ICD) was a great measure allowing the user to have a decision regarding the cost of their treatment and helping us, health care providers, by having an easier work on identifying drugs. (2)

2.2.4 Lack of Information on external trainings

The existing formations for health professionals, especially for pharmacists, are a great way to be constantly updated and simultaneously to review some knowledge. I was not able to participate in external formations, due to the lack of information in distant locations from the big cities, and in my perspective, it could have been a way to fill knowledge gaps about the specific areas already mentioned. However, I obtained some internal training through delegates by promoting their products, mainly in the areas of supplements, such as the several products of the Absorvit® range and of Silfarmaplus industry.

2.2.5 Adaptation to the pace of work

Adaptation to the daily work routine was progressively acquired over time, with an initial period of adjustment. The pace of work was entirely different from what I used to experience during my academic formation. The many standing hours, having to constantly deal with many different personalities, without breaks between meals, initially left me exhausted. However, I manage to adapt and to deal with such situations, by reinforcing breakfast and including more hours of sleep every night, for instance.

2.3 OPPORTUNITIES

2.3.1 Psychological and social improvement

Interaction with the public has improved my social skills, dealing with multiple personalities happened on a daily basis, and this grow made me a better health professional. The pressure set by people, even if unintentional, was a huge psychological challenge, to which it had never been exposed. Initially I considered this as a threat, however, over time I started to see it as a strengthening that will be necessary and tested in several future moments of my life.

Communication and empathy are an extremely necessary link in the pharmaceutical-patient relationship and for the quality of the provided services, having the need to obtain understanding from the perspective of the patient, always placing it as a priority focus. Dealing with many users with weaknesses and limitations, as users without hearing, blind, taciturn or illiterate, hindered the necessary communication, forced me the adoption of other forms of action, adjusting the style of relation to the specific situation. Observing of the posture and the response to different situations by part of the team, served as an example, showing the importance of previous experience and that some aspects are achieved with time and dedication.

2.3.2 Manipulated drugs

There were some requests for manipulated drugs during my stay in the Farmácia da Estação, an opportunity I had access to, completing my formation. Preparing manipulated drugs includes a set of procedures: registration of the several raw-materials and the quantities used of each, checking and recording of all intermediate and final quality control parameters and calculation of fees. These procedures must be respected to ensure patient safety. Some of the manipulated preparations were: 10% acetylsalicylic acid ointment, 1% trimethoprim oral suspension, and an alcoholic solution of boric acid at saturation.

2.3.3 Paperless electronic recipes

Paperless electronic recipe became mandatory in April 2016, and includes an "access and dispensing code" and a "right of option code" for drug dispensing validation. This is an innovation in which the patients can receive the mentioned codes through the cellphone number or even by email, and may choose to take only part of the drugs, prescript and non-prescript, with the possibility of raising the rest in different dates and establishments. The prescriptions are also accessible by inserting the citizen card in the smart card system. Eliminating paper support, increasing the safety of prescribing and reducing bureaucracy in relation to the conformity of the prescription, are some of the main advantages. (3)

In my internship, I was able to experience patients' disappointment, with a preference for electronic prescription with paper, especially the elderly with less skill to handle the cellphone. However, as a trainee, I had the possibility of working with the several types of recipes and considered this one as an easier way to work, allowing greater time management in the balcony attendance, essentially when compared to the manuals recipes.

2.3.4 Kaizen philosophy

During the internship, the Kaizen philosophy was introduced in the pharmacy, a concept that includes five aspects: organization, productivity, continuous improvement, operational efficiency, and algorithms. Created in Japan after World War II, to rebuild economic and industrial activity. I had access to the explanation of the concept, verifying its gradual but not total application due to the high flow of users. However, I realized that it would be one of the future steps of the pharmacy. In my opinion it's an added value, an innovative methodology that allows greater organization of space and of teamwork, as it forces the changes of habits and routines with future results in productivity. An unknown concept, which I consider to be very useful, demonstrating the clearly necessity for evolution by the constant changes in society, having the pharmacies the obligation to accompanied.

2.3.5 The new Sifarma, "Novo Atendimento"

My internship at Farmácia da Estação, gave me access to all the potentialities of Sifarma2000® and of the new software Sifarma "Novo Atendimento". This new software has been applied to three pilot pharmacies across the country, in order to verify its adaptation to the daily work of a pharmacy, its possible failures and if whether it will, in fact, be more advantageous than the previous version.

It is a tool with an innovative aspect, functioning as a web browser with easier access. It is able to identify the user by any available data, name, address, phone contact and even taxpayer number. The existing products are presented in a more user-friendly way, with simplified form to consult all the information of the product. Additionally, allows a greater pharmacotherapeutic monitoring, with the distinction of the patient to whom the medicines are destined and the client to whom the ones are dispensed, if they are not the same person. One of the great distinctions, regarding the previous Sifarma2000® is the non-existence of suspended sales, so the patient will pay or put the total amount in credit, receiving the co-participated amount after with the recipe.

Development is still in ongoing, with emerging tools based on the previous version and also new ones. I was able to see improvements in response to the pharmacies feedback, such as changing the color of the letters to make it easier to view or add options for multiple drug selection, details that are only found on day-a-day and usual work routines. I also participated in the attribution of opinions and ideas for the continuous improvement of the program, leaving me extremely honored by helping a potential tool to be used by all pharmacies in the country.

Working with this new software provided me adaptability since several times I had to use with both programs at the attendance balcony, because the new Sifarma does not have all the features active yet, such as the reservations and orders. All this required concentration, agility, never leaving aside the attention and demand to the patients. A distinctive opportunity to which I had access, and may have a great impact in my profession as a future pharmaceutical. Some images of the new Sifarma model can be noted in the attachments.

2.4 THREATHS

2.4.1 Request of prescription drugs without prescription

Passing through all the duration of my internship, there were always patients requesting prescription drugs without the medical prescription for this purpose. Justification included, habitual routine medication or by previous experience to solve a punctual situation. This happened essentially applied to antibiotics or benzodiazepines. I was able to understand the impact of the pharmacist on education and information of the population, explaining the reason why it is not possible to give in this type of medication. The patients did not always react in the best way, so it is necessary to maintain the professional ethics, dealing with this type of situations in the calmest way possible.

2.4.2 The trainee from customer's perspective

For all students recently graduated in any area, there is always a transition phase from the college to the labor market, part of this transition occurs at the internship, passing through learning and adaptation to the place where we are going to work or to form. Many people accept or begin to accept the reality that there will be trainees everywhere, and that only practice makes them professionals capable of satisfying all their needs with the efficiency they want. Still, there are many exceptions. As I started to be more exposed to the pharmacy public attendance, I experienced some difficulties inherent to this process. In some situations, I realized the low receptivity or patience of some patients when they were or were going to be attended by me, with the refusal of some of them. I had to learn how to deal with these situations, always with the proper professionalism, respecting the desire of the patients and costumers. However, the initial shock and the all-similar situations made me grow, not letting me affect or discourage, trying to accept everything as an experience and improvement.

3. CONCLUSION

The end of the internship in the Farmácia da Estação represents for me a whole process of learning, evolution, and development, both professional and personal. With some days of extreme exhaustion, others with a contagious energy and several times questioning my abilities. However, now I realize that was a pleasing experience, with very kind people that will always be a part of my life and memory.

Contacting the professional reality and feeling the patients' confidence in the pharmacist, always expecting a complete advice, is a great incentive for those who are at the beginning of the activity. Listening is as important as communicating, and now more than ever, I understand and value the pharmacist in society as well as community pharmacies.

The five years of academic formation and the months of internship, prepared me for the entry into my future professional career, committing myself to a constant professional development and a constant personal evolution, not leaving aside the high standards of exigency always required.

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CLINICAL CASES

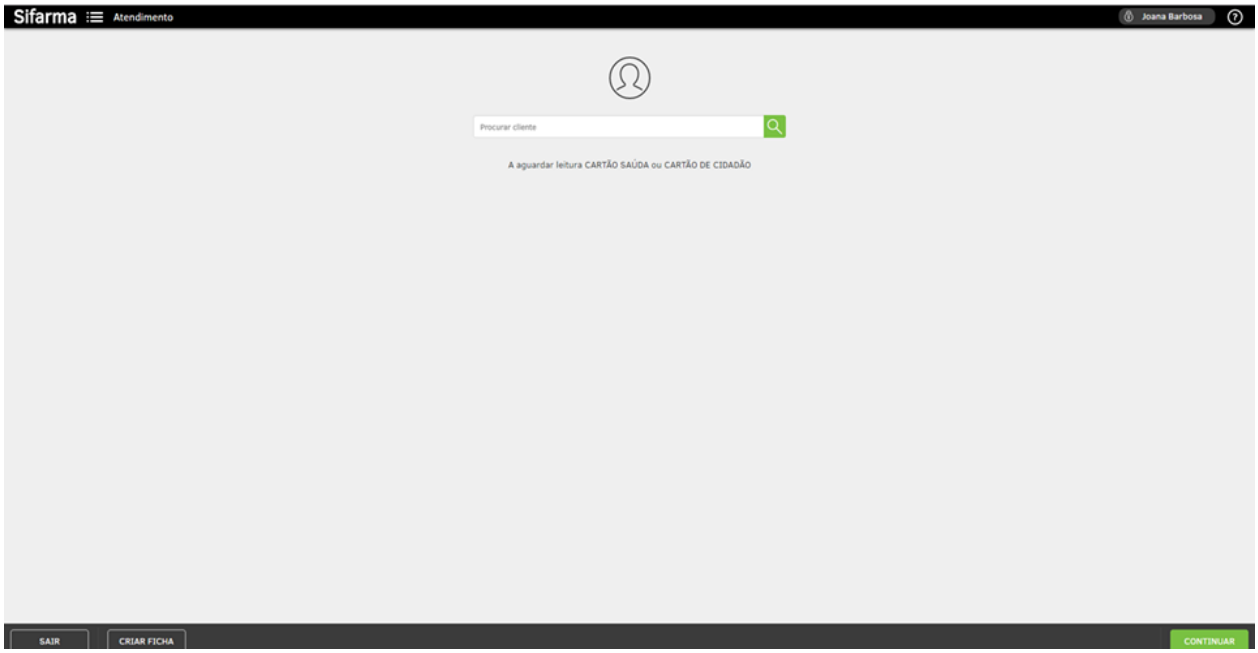
Case I

An adult man went to the pharmacy complaining of a lot of cough. After some questions, the patient indicated that it was a dry cough. However, when I was almost advising him to take Bisoltussin® (dextromethorphan hydrobromide) the patient coughed, and I realized it was an expectorant cough. Therefore, I suggested taking Fluimucil® (acetylcysteine) in effervescent tablets, to release the expectoration. The recommended dose is 1 tablet per day, preferably at night. Along with pharmacological therapy, the user was advised to drink many fluids, being hydration very important, acting as natural mucolytic. The importance of distinguishing between types of cough was also emphasized, by explaining that dry cough drugs avoid mucus expulsion what may result in pneumonia.

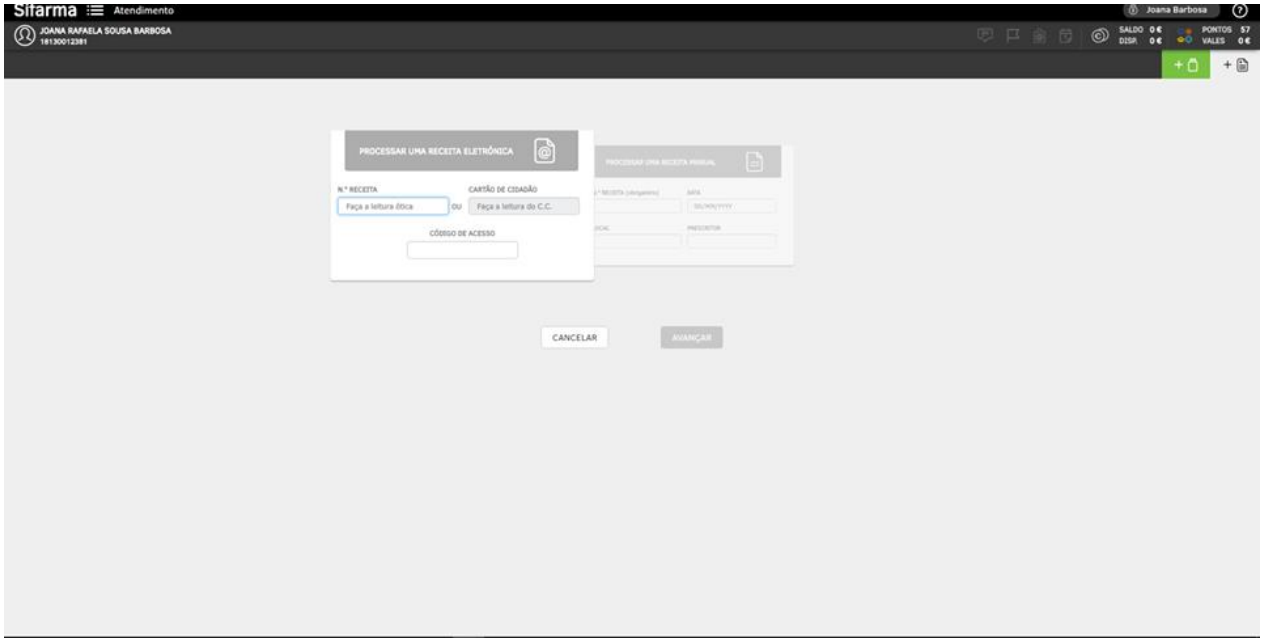
Case II

A mother of a 1-year-old girl went to the pharmacy indicating that her daughter has allergic symptoms and nasal congestion, which avoids her from breathing properly. She did not want syrups, so I recommended an antihistamine, Fenistil® drops, for use 3 to 10 drops three times daily, because of its anticholinergic properties, helping to dry the mucous and thus to decongest the upper airways.

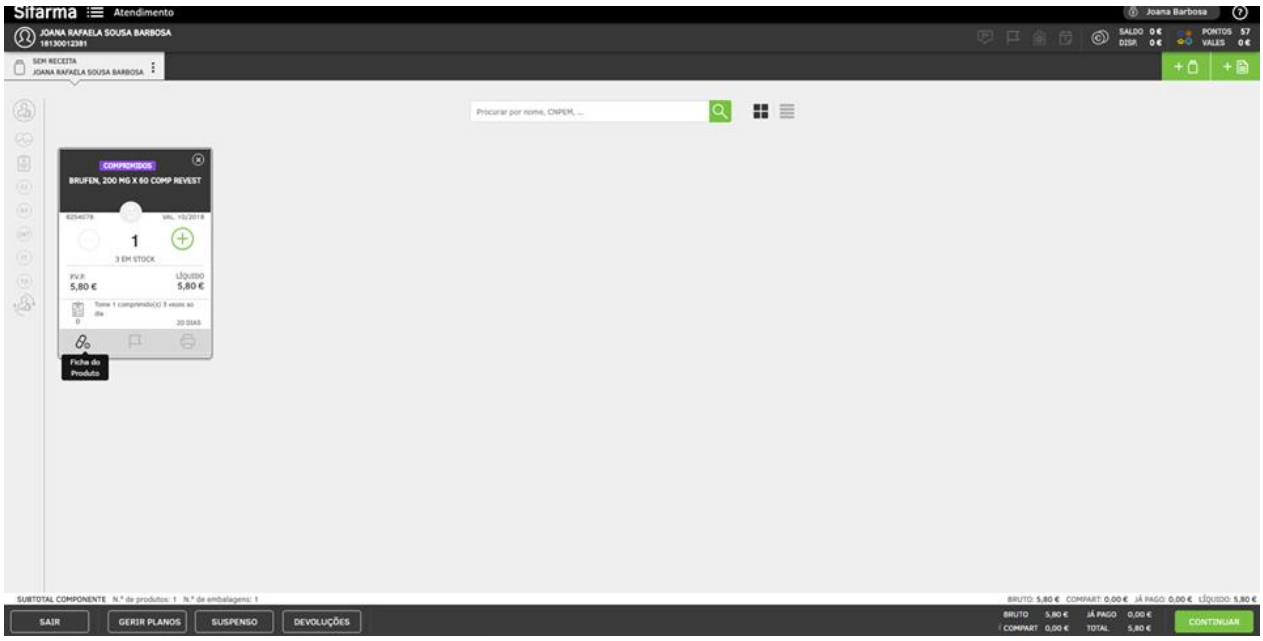
ATTACHMENT I. Sifarma "Novo Atendimento"



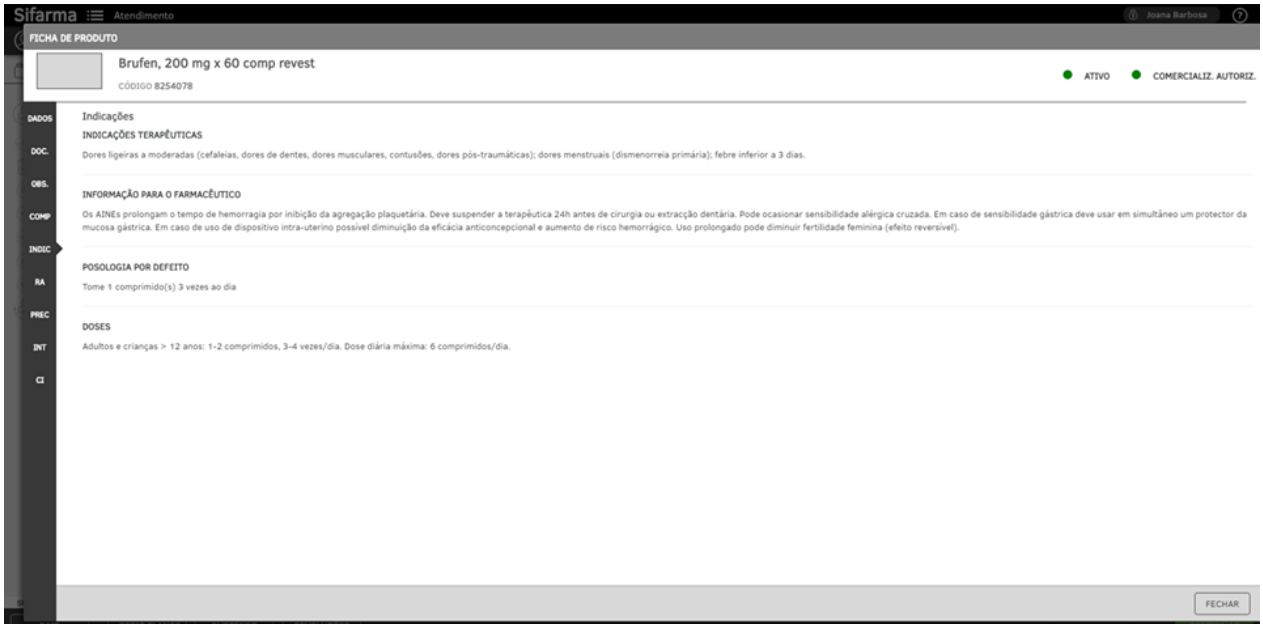
i. Main menu.



ii. Recipes menu.



iii. Attendance menu, open on customer personal file.



iv. Product data sheet, with pharmacological information of the drug.

Faculty of Pharmacy of the University of Coimbra

II. INTERNSHIP REPORT
IN HOSPITAL PHARMACY

CUF Porto Hospital

Orientation:
Dra. Marta Queiroz

LIST OF ABBREVIATIONS

CPH	CUF Porto Hospital
IV	Intravenous
LASA	Look-Alike, Sound-Alike
NICU	Neonatal intensive care unit
PICU	Prolonged intensive care unit
PS	Pharmaceutical services
SWOT	Strengths, Weaknesses, Opportunities, Threats

LIST OF TABLES

1. INTRODUCTION

The pharmacist by performing functions in counseling and monitoring, and through dispensing drugs or providing health care, has an active role in society. The area of hospital pharmacy is an area of great curiosity and expectation, which by not providing a direct contact with the public is not very recognized, but has an extreme importance in the proper treatment of the patients and in the functioning of a hospital.

Since the academic formation is the initial basis of all pharmacists, it is essential to perform a curricular internship to consolidate all the knowledge acquired. So, to enrich my experience in the pharmaceutical area, I decided to do part of the curricular internship in hospital pharmacy, to understand the circuit of the medicines in a hospital level as well the importance of the pharmaceutical services and health care provided by the hospital pharmacist.

My internship took place between May and July, and the purpose of this report is to describe it with a critical analysis. The activities developed, as a trainee, will be addressed, as well the operation of each sector of the pharmaceutical services that I had the opportunity to experience.

2. SWOT ANALYSIS

A SWOT analysis was performed in order to make a critical analysis, intending a personal reflection on my performance and on the activities and practices considered important and experienced during the internship. An innovated analysis strategy that critically evaluates strengths, weaknesses, opportunities, and threats, intended to demonstrate the adequacy of the theoretical knowledge obtained, with the reality of the practice within the labor market. (1)

Table I represents, the following strengths, weaknesses, opportunities, and threats of this experience.

Table I. *SWOT analysis of the internship at CUF Porto Hospital*

STRENGTHS	WEAKNESSES	OPPORTUNITIES	THREATS
- Internship planning - Oncology - Distribution, Reception and Storage - Psychotropic, narcotic drugs and blood products - Outpatient drug distribution - Non-sterile galenic preparations - Professional experience	- Internship duration - Observational internship - External and internal trainings - Adaptation to the pace of work	- Passage through all interconnected sectors - Kaizen philosophy - JCI accreditation - UptoDate® and Neofax®	- Lack of the Hospital Pharmacists recognition - A sector of difficult access

2.1 STRENGTHS

2.1.1 Internship planning

On the first day of the internship at the CUF Porto Hospital (CPH), a plan was assigned to all trainees in order to distribute into the different areas, offering the opportunity to learn and have a perception of what is done in the various sectors. The two-month internship was divided essentially into two distinct parts: Oncology and the Distribution, Reception and Storage. Underlying, there was a pharmacotherapeutic validation component, included in each of these areas. The execution of non-sterile galenic preparations and the component involving psychotropic, narcotic drugs and blood products, were other areas explored.

The pharmaceutical services (PS) are responsible for the internship of countless trainees, so some training routines already existed, and at the first day of internship we were advised to read the operating manual of each sector, to understand the working standards and legislation before performing any kind of functions. This organization and orientation of the internship, in my opinion, is a great advantage, allowing us, trainees, a great learning and global perspective of the function of hospital pharmacist, applied into the practice, something that is easier to learn by experiencing, and also to assist them in the best way without causing disturbance in the work developed by all professionals.

2.1.2 Oncology

My first month started with oncology, an area I was not very knowledgeable about, so I had a lot of curiosity and desire to know more. The preparation of cytotoxic drugs is done in a separate division, consisting of a wardrobe room, an antechamber and the chamber room, where the preparation of the medicines takes place. Between these two last divisions, there is a double door window with a transfer, through which the product transfers are made. In the antechamber, all operations carried out are before and after the preparation of the cytotoxic agents such as the preparation of all the material and final repackaging. All contents are placed in a tray, then sprayed with 70% alcohol and transferred to the preparation room, where the pharmacist properly equipped, collects the tray and over disinfects all the material received, proceeding to the preparation of the medication in a

vertical laminar flow chamber. Once finalized, the cytotoxic drugs are properly labeled and packaged according to their stability characteristics.

However, prior to preparation, there is a validation of the prescription of the cytotoxic drug by a hospital pharmacist. For this purpose, the dilution volumes (if necessary for the procedure), the dosages, and the doses (by body surface and/or weight) are calculated and analyzed. During my internship, sometimes the prescript doses did not correspond to the values obtained, so the pharmacist did an evaluation and contacted the prescriber physician when the difference in values was greater than 5%. When everything was accordingly, the production map was created and printed. This document contains all patient therapeutics, with the premedication included, which I prepared and consisted essentially of anti-emetics or corticosteroids. The batches and the expiration date of cytotoxic drugs were registered. After the preparation of the drugs, one of the labels was placed on the production map, signed by two pharmacists and archived on computer and on paper. I had the opportunity to perform this procedure daily, contacting with new therapeutics and protocols for different types of cancer and with the resulting secondary effects, a constant learning by integrating the prevention, problem and solution of the instituted therapies.

In the last week of the internship, I had the opportunity to help in the preparation of trays with all the drugs and necessary material, to observe, inside the camera room, the preparation, and the packaging of cytotoxic drugs in the antechamber. For the hospital pharmacist, it is extremely important to know the safety and cytotoxic manipulation standards, such as room characteristics, equipment operation, storage temperatures and the existing protocols/guidelines, and also to have a systematic and organized routine to prevent medication errors. I realized the existence of a constant need for continuous learning since oncology is an area in constant development. It was a very interesting area that allowed me to understand the specific role of the pharmacist and to gain perspective on the therapeutic situation point in this field.

2.1.3 Distribution, Reception and Storage

My last month of the internship was in medication reception and storage. I noticed how drugs are organized in the pharmaceutical services and, as oncology, I handled drugs and drug formulations for the first time, resulting in a need to investigate and learn, for to better understand their uses and differences. The distribution component, in the CPH, is

carried out in four different ways: unit dose distribution, distribution of psychotropic, narcotic drugs and blood products, outpatient drug distribution and by stock replenishment.

The unit dose distribution provides medication for 24 hours from 16 o'clock each day, being prepared around 14 o'clock by the printing of the validated prescriptions, and by the identification of all the patients in medication cassettes. There were also morning and afternoon changes, consisting of the medication withdrawal or addition regarding the previous unit dose distribution. Offering me the perspective that the treatment and patient entry is a dynamic and constantly changing process. The morning changes also covered different periods of time for the distinct hospital units: for pediatrics, UCIP and UCIN, supply was between 10 to 15 o'clock; to internal medicine, palliative and surgical care, supply was between 11 to 16 o'clock. So, despite the continuous validation needed, a complete validation of the instituted therapeutics happened on these three points during the day, and the main analyzed information was: patient data, prescription drugs, dose, pharmaceutical form, units, route of administration and duration of therapy. It is also important, prior to any validation, to consult the patient's medical history in the computer system, so that it is possible to understand the reason for all the prescript therapies.

I had the opportunity to execute the unit dose and the morning changes, contacting with different therapeutics to different pathologies, and the constant change in the patients' diet required an analysis of the best formulation type to be sent for some drugs. In surgeries, regarding some drugs, acetaminophen for instance, the first prescribed doses up to 7 o'clock from the following day, were IV. The observation and participation in this vast circuit gave me a completely different vision of the one acquired in the academic formation, not in content but by the practice itself, consolidating knowledge and creating new ones.

2.1.4 Psychotropic, narcotic drugs and blood products

Concerning blood products, psychotropic and narcotic drugs, I was allowed to perceive their circuit inside the hospital and the legislation to which they are subject. In CPH, to have strict control of the movements of these substances, as they are stored in closed cabinets and refrigerators, it is mandatory to register their entry and exit in a specific document upon their dispensation to hospital services, a service requisition where the designation and units of the demanded drugs were described. This requisition accompanies these special regimen drugs until the destination, so the administration date and the patient

identity, are also registered. Subsequently this document is signed by the medical director of the service, returned to the PS, to replace stock, and filed.

The dispensing of blood products has a similar circuit, also requiring an own requisition document, which I also had the opportunity to fill. When returned to the PS, all data is checked and both versions, the service and the pharmacy one, are archived and the stock is replenished. Because of their variability, as products with a biological origin, each product must have a CAUL (batch use authorization certificate) also filed in the PS. In addition to these medications, there are others off-label use drugs, which obligate the filling of an informed consent document by the patient. Thus, knowing the circuit of this type of medication was interesting since most of them are medicines of exclusive hospital character, with a rigorous use control and registration.

An example of the requisitions model can be found in the attachments for each class of drugs.

2.1.5 Outpatient drug distribution

The outpatient distribution is managed by a legislation that specifies which drugs can be delivered, the exclusive hospital dispense drugs, many of them with a very narrow therapeutic window, requiring monitoring. (1) I was able to attend this type of distribution and the procedure was similar to the attendance on community pharmacy, based on collecting prescription from patients and on medication dispense, carried in single dose (only the blister) with a respective label filled with patients' data and with the posology and remarks of the drugs, all under the pharmacist supervision, further validation and signature. The necessary information was provided for the correct use of the medicines upon the dispense. The medication can only be provided for a one month and seven days treatment, after a consultation and surgical intervention, respectively.

Medicines not covered by the legislation can be dispensed under certain conditions, as in the case of rupture, by presenting a prescription stamped and signed by three pharmacists of three different pharmacies, proving the situation. (1) This enabled me to conciliate and apply the acquired knowledge of both internships, using the obtained attendance skills from community pharmacy, in the hospital practice with new drugs and therapies.

2.1.6 Non-sterile galenic preparations

Non-sterile galenic preparations allowed the manipulation of drugs according to the needs of the patient, in a specific room. During the internship, in addition to completing the preparation sheets, I could practice some of the acquired knowledge from the academic formation, through the preparation of medicated papers and some liquid formulations. The weighings and measurements were always doubly validated by pharmacists, reducing preparation errors. A preparation sheet of an oral suspension of composed nystatin mouthwashes, often prescribed because of the secondary effects of chemotherapy and/or radiotherapy treatments, can be noted in the attachments.

2.1.7 Professional experience

This internship provided me practical and technical abilities in an area of my great interest and curiosity. All the experienced activities can have a great impact on my future labor market entrance. Work in a hospital context involves the occurrence of several activities simultaneously, a very organized system. At the CPH this work systematics are enforced on the daily routines of the PS team, forcing my capabilities for organization, agility, and adaptation, establishing competencies in the field of interprofessional relations, the so-called soft-skills, important at various levels.

2.2 WEAKNESSES

2.2.1 Internship duration

The two months of the internship are insufficient to exploit all its potentialities, allowing only a superficial insight of the sectors passed. The complexity of the operations associated with the hospital pharmacy require more adaptation time, being a reality with which we do not have much contact, unfortunately, even by the patient perspective. Every week I came across new activities in the sectors, making the acquirement of knowledge a difficult task, as it turns to be a lot of information to assimilate in a short period of time.

However, I got a more complete and global perception of the PS functioning, and over the hospital itself.

2.2.2 Observational internship

The hospital pharmacist has a high responsibility in the performance of all the activities. However, having already experienced an earlier internship in a community pharmacy with professionals equally responsible, that enabled the performance of all functions that took place in, I consider the hospital pharmacy internship essentially observational.

Despite the high workload, relatively simple tasks such as fill out requisitions forms for prescribed special regimen drugs were assigned only once. The preparation of cytotoxic drugs and sterile galenic formulations are examples of activities where I was only allowed to observe, assisting the pharmacist when necessary. However, I tried to intervene, taking the initiative to execute tasks without being asked for, as the elaboration of bags for ambulatory distribution, and the organization and scheduling of the oncological patients' therapeutic, while the pharmacist performed the preparation of the drugs in the camera room. As well the preparation of the clinical meetings, involving validation of patient therapy and the confirmation of its applicability, verification of the medical analyzes values and of drug Interactions. Pharmacists do not always have time for these performed tasks, so receiving the feedback from being one of the first trainees to do so, made me proud beyond all the extra enrichment provided to my internship.

2.2.3 External and internal trainings

CPH health professionals have the opportunity, during the year, to participate in external and internal trainings on a wide range of topics. Over the course of my internship, the possibility to participate has not been granted. In my point view, these qualifications are a plus for any health professional even for us trainees, and could somehow expand our help capacity and improvement PS gaps. It could have been an important opportunity for me, about to enter the extremely competitive and constantly recruiting new skills world of work.

2.2.4 Adaptation to the pace of work

The physical adaptation to the work routines had to be strengthened since every day I made a total 4 hours trip, through various public transports, to the internship place. I consider that different periods of time should exist for the internship and for the monograph preparation. By not always being capable of managing time to investigate and consolidate everything learned and for simultaneously carry out the monograph, the advantages of my internship were not completely taken. So, I considered a negative point.

2.3 OPPORTUNITIES

2.3.1 Passage through all interconnected sectors

One of the most interesting opportunities was experiencing the different interconnected hospital sectors, participating in the several pharmaceutical and non-pharmaceutical activities of overall sectors. During this stage at CPH, I attend clinical sessions of the various hospital units, composed of physicians, pharmacists, and nurses. The updated clinical situation of all hospitalized patients was discussed as the best acting strategy, so that everyone could intervene with the provision of health care, having the pharmacist an active role in all concerning medicines.

Besides, I followed nurses in the drug administration to general hospitalization patients and in the hospital-day, in which the direct patient interaction required a greater psychological and human component. A meeting with the hospital nutritionist, scheduled by us trainees, covered subjects regarding enteric and parenteral nutrition, under what conditions should be used, the different existing diets, their professional role in the evaluation of hydro-electrolyte balance and on the individualized care according to the nutritional needs of the patient. I also had the opportunity visit the OR (operating room), and their advanced warehouse where all the medication, medical equipment, and devices are located. Later I attended a surgery removal of the lumbar disc hernia, where the physicians and nurses have sequentially explained the steps, giving emphasis when they included drugs. It was important to understand in practice, the need to have a good relationship among different professionals, all working in proving health care.

2.3.2 Kaizen philosophy

A concept that had been briefly introduced in the first internship, was fully applied to this one, where kaizen philosophy was already implemented, allowing the consolidation of the previously acquired theoretical basis with the practical application. The organization provided by this method is admirable, acting in the most varied small things, allowing a great time management. Medications are stored in different places by type of formulation and in alphabetical order. (3) In addition, there is a region with the highest turnover drugs, near to where the unit dose is done. The replenishment and management of stock is carried out with *kanbans,* consisting in a plastic card containing the code, designation, location, ordering point and the necessary order quantity of each product. The products are removed (always from the front to the back and from the right to the left) until reaching the *kanban*, underlying the necessity to do order the specific product. (3) Examples of the kaizen philosophy application in the organization and storage of drugs can be noted in the attachments.

2.3.3 JCI accreditation

Joint Commission International (JCI), is a worldwide organization involved in improving health services and safety through the provision of education, publications, consultation, and evaluation services. My internship marked the beginning of a JCI accreditation plan to the hospital quality management system. (2) In the PF, safe practices have been implemented regarding drug identification. New labels were made with new signs, symbols, and colors and with inserting capital letters in the middle of the drugs denominations, avoiding errors in the reception, storage and selection of medications known as LASA (Look-Alike, Sound-Alike). These measures were applied to all the emergency suitcases and cars, and simultaneously a periodic review was made, registering the expiration date and batch number of all medications. By assisting the whole process, I realized that there is a record of all the times the emergency bag or car was used as a safety measure ensuring the integrity of its contents. This enabled me to know the mandatory medication of emergency cars and suitcases, to understand their organization and the need of a twice-yearly review.

A very important point of this accreditation is the requiring of the drug interactions registration by all the physicians, informed by the pharmacist, an earned victory. There were also audits to evaluate the correct implementation of these measures, so I could experience the work environment under pressure. Not being aware of how this type of accreditation and quality control is usually processed, a global perception of its function and role was acquired, another point of learning. An example of a label and of an emergency car organization, according with the measures implemented by JCI, can noted at the attachments.

2.3.4 UpToDate® and Neofax®

UpToDate® and Neofax® are online platforms for medical information, with the first containing information on the most diverse areas of health and the last one only providing information directed to pediatrics and neonatal drugs. In the CPH it is possible to have unlimited access to this database through an internal network. A very useful tool that I used on the clinical meetings preparation, to validate pharmacological therapeutics, confirmation of doses, interactions and to allow a research based on constantly updated and credible scientific information. (4)

2.4 THREATHS

2.4.1 Lack of the Hospital Pharmacists recognition

In current society, the hospital pharmacist is not entirely recognized as a health professional with several responsibilities, starting with the management of the drug circuit within the hospital, promoting the rational use of medication and monitoring all the instituted therapy to the hospitalized patient. Throughout my entire internship, the need for the existence of pharmaceutical services at the hospital was devalued. In the clinical meetings, many physicians clearly highlighted our presence as unnecessary. For some health professionals, the pharmacist is nothing more than a medication guardian. Therefore, in my opinion, it is the responsibility of the hospital pharmacist to change this dogma, actively bet on the pharmaceutical intervention and taking part of the multidisciplinary team that operates the hospital services, imposing our central role in the provision of health care.

2.4.2 A sector of difficult access

In the current job market, the hospital pharmacy area is very difficult to access, with very scarce hiring of pharmaceutical professionals, because of the tight management of financial resources. The emerging of health professionals, instructed to work in areas of the pharmacist responsibility, is considered a threat to our profession, leading to increased competition. Most of the non-computer practical tasks are taken over by pharmacy technicians. This situation is valid not only in this sector but also in the community pharmacy and pharmaceutical industry. Inducing concern to my future position in the labor market.

3. CONCLUSION

My internship at CPH, despite the short duration, gave me the opportunity to familiarize myself with the activity of the pharmacist in the hospital sector, learning the multiplicity of the procedures and all the demanding responsibilities of this profession. The pharmaceutical activity in the hospital environment, passes not only through the distribution of medication but also by including the production of manipulated drugs, promotion of drugs rational use, validation of medical prescriptions and the pharmacotherapeutic monitoring of the hospitalized patients.

Although the pharmacist is already a reality in hospitals, it is still necessary to daily affirm our position in the clinical services, demonstrating the benefits of our presence, reducing medication errors and improving therapeutic decisions.

This internship provided me a large range of new knowledge that will certainly be of great use to start my professional life as pharmaceutic. So, I end my academic formation with a different perspective of what it is to be a pharmacist, of what it is our role in the society, and with different ideas concerning my future.

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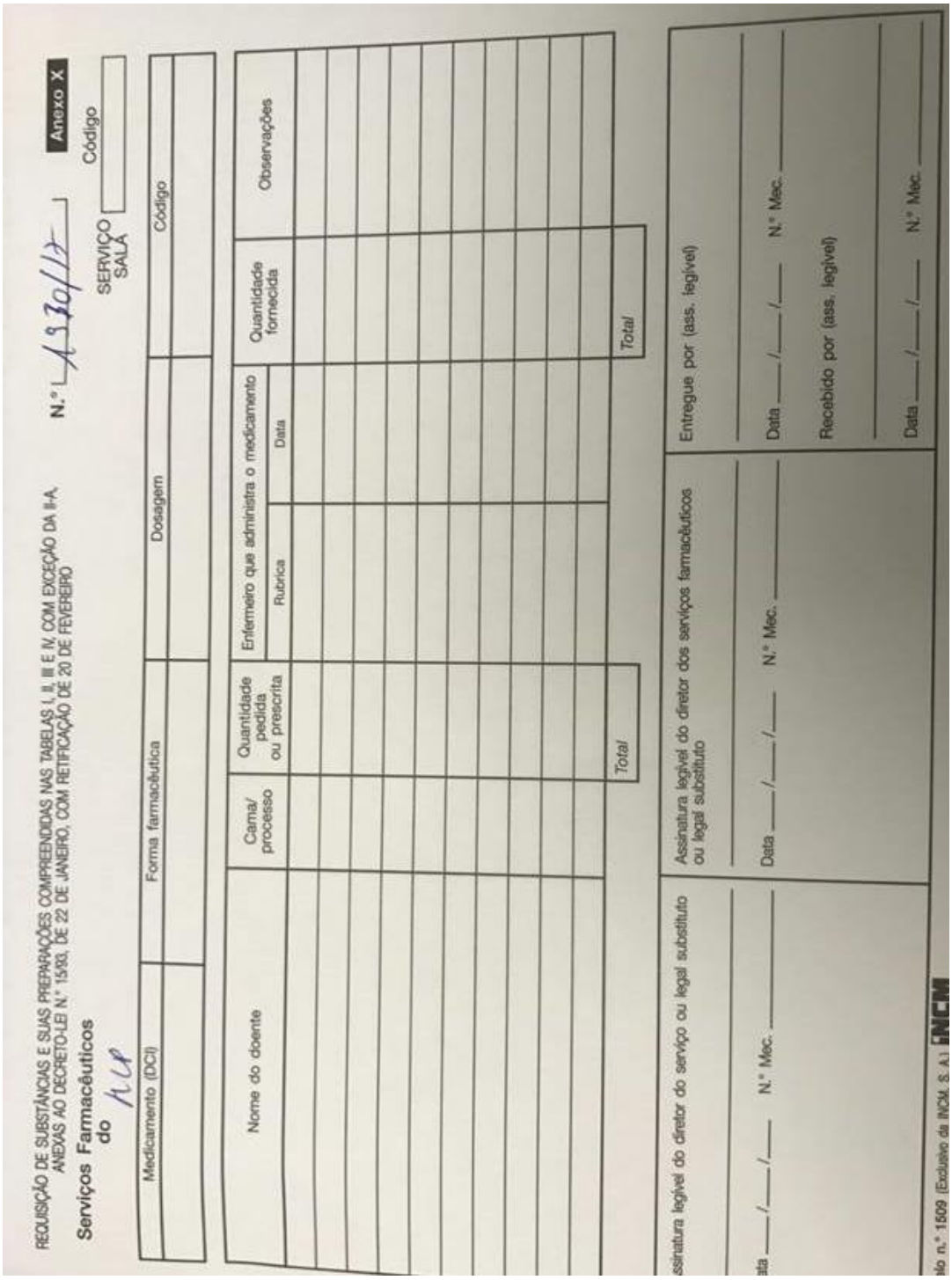
2. Joint Commision International. - About JCI. JCI. [Accessed 3 july 2017]. Available from: http://www.jointcommissioninternational.org/about/

3. *Kaizen Institute*® - Quem Somos [Accessed 6 july de 2016]. Available from: https://pt.kaizen.com/quem-somos/kaizen-institute.html

4. *UpToDate*® - Especialidades. [Accessed 6 july 2017]. Available from: http://www.uptodate.com/pt/home/content

ATTACHMENTS

ATTACHMENT I. Requisition sheet for psychotropic and narcotic drugs.



REQUISIÇÃO DE SUBSTÂNCIAS E SUAS PREPARAÇÕES COMPREENDIDAS NAS TABELAS I, II, III E IV, COM EXCEPÇÃO DA II-A, ANEXAS AO DECRETO-LEI N.º 15/93, DE 22 DE JANEIRO, COM RETIFICAÇÃO DE 20 DE FEVEREIRO

Anexo X

N.º 1930/12

Serviços Farmacêuticos do H.U.P.

SERVIÇO SALA

Código

Medicamento (DCI)	Forma farmacêutica	Dosagem	Código

Nome do doente	Cama/ processo	Quantidade pedida ou prescrita	Enfermeiro que administra o medicamento		Quantidade fornecida	Observações
			Rubrica	Data		
		Total			Total	

Assinatura legível do diretor do serviço ou legal substituto

Data ___/___/___ N.º Mec. _____

Assinatura legível do diretor dos serviços farmacêuticos ou legal substituto

Data ___/___/___ N.º Mec. _____

Entregue por (ass. legível)

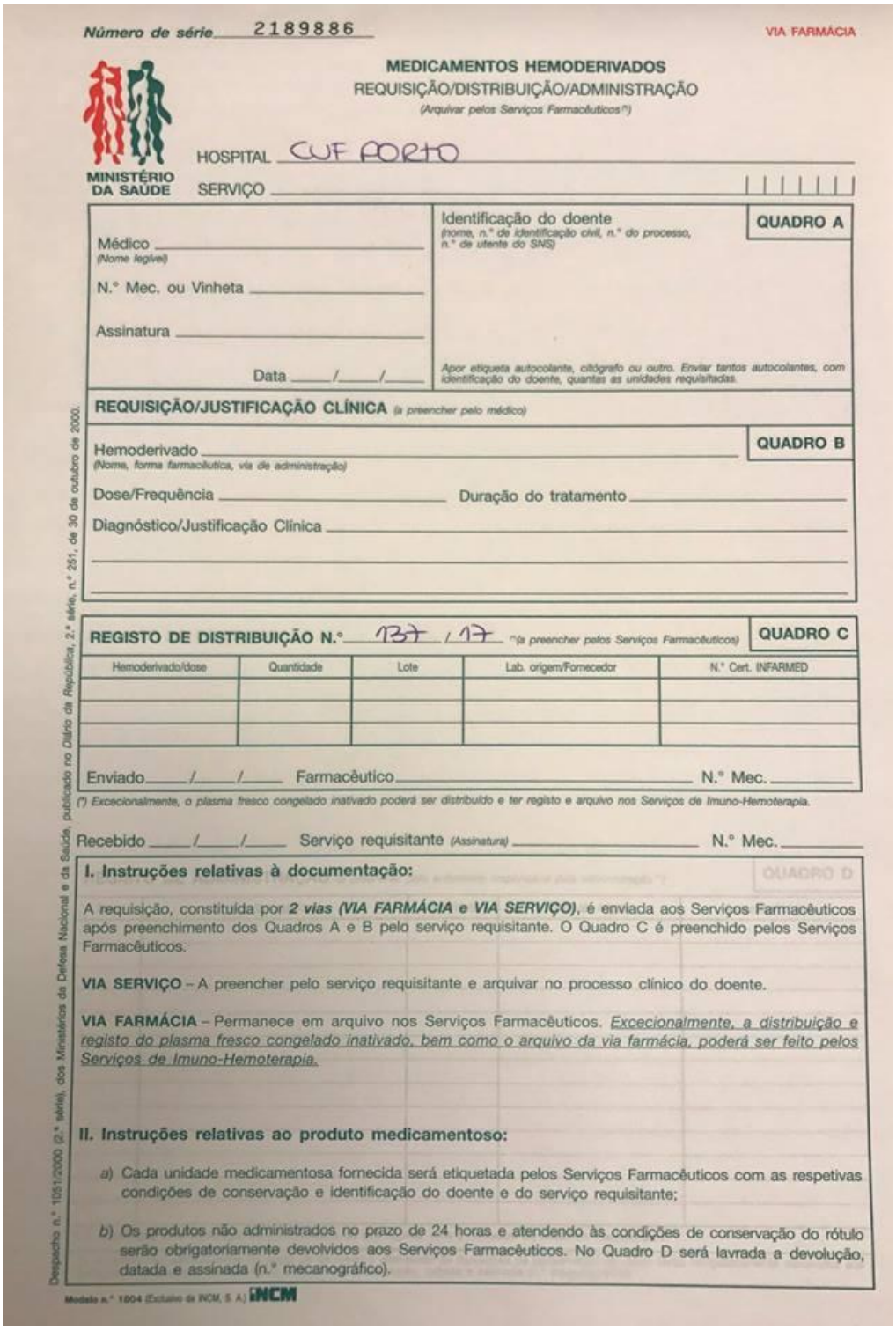
Data ___/___/___ N.º Mec. _____

Recebido por (ass. legível)

Data ___/___/___ N.º Mec. _____

...ão n.º 1509 (Exclusivo da INCM, S. A.) INCM

ATTACHMENT II. Requisition sheet for blood products.



Número de série 2189886 — VIA FARMÁCIA

MINISTÉRIO DA SAÚDE

MEDICAMENTOS HEMODERIVADOS
REQUISIÇÃO/DISTRIBUIÇÃO/ADMINISTRAÇÃO
(Arquivar pelos Serviços Farmacêuticos (*))

HOSPITAL CUF PORTO

SERVIÇO

Médico *(Nome legível)*

N.º Mec. ou Vinheta

Assinatura

Data ___/___/___

Identificação do doente *(nome, n.º de identificação civil, n.º do processo, n.º de utente do SNS)* — **QUADRO A**

Apor etiqueta autocolante, citógrafo ou outro. Enviar tantos autocolantes, com identificação do doente, quantas as unidades requisitadas.

REQUISIÇÃO/JUSTIFICAÇÃO CLÍNICA *(a preencher pelo médico)*

Hemoderivado *(Nome, forma farmacêutica, via de administração)* — **QUADRO B**

Dose/Frequência — Duração do tratamento

Diagnóstico/Justificação Clínica

REGISTO DE DISTRIBUIÇÃO N.º 137/17 *(a preencher pelos Serviços Farmacêuticos)* — **QUADRO C**

Hemoderivado/dose	Quantidade	Lote	Lab. origem/Fornecedor	N.º Cert. INFARMED

Enviado ___/___/___ Farmacêutico N.º Mec.

(*) *Excecionalmente, o plasma fresco congelado inativado poderá ser distribuído e ter registo e arquivo nos Serviços de Imuno-Hemoterapia.*

Recebido ___/___/___ Serviço requisitante *(Assinatura)* N.º Mec.

I. Instruções relativas à documentação: — QUADRO D

A requisição, constituída por ***2 vias (VIA FARMÁCIA e VIA SERVIÇO)***, é enviada aos Serviços Farmacêuticos após preenchimento dos Quadros A e B pelo serviço requisitante. O Quadro C é preenchido pelos Serviços Farmacêuticos.

VIA SERVIÇO – A preencher pelo serviço requisitante e arquivar no processo clínico do doente.

VIA FARMÁCIA – Permanece em arquivo nos Serviços Farmacêuticos. *Excecionalmente, a distribuição e registo do plasma fresco congelado inativado, bem como o arquivo da via farmácia, poderá ser feito pelos Serviços de Imuno-Hemoterapia.*

II. Instruções relativas ao produto medicamentoso:

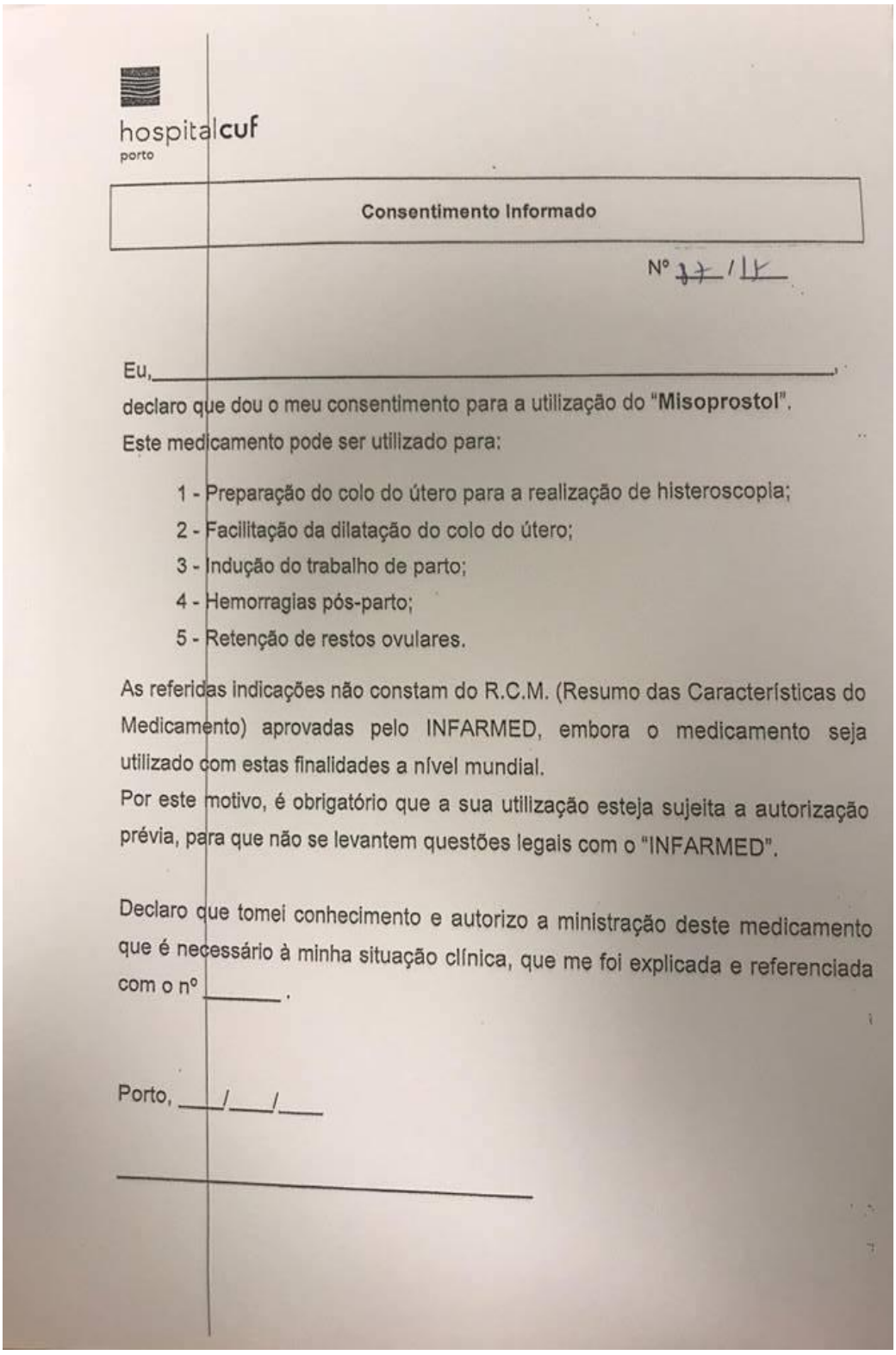
a) Cada unidade medicamentosa fornecida será etiquetada pelos Serviços Farmacêuticos com as respetivas condições de conservação e identificação do doente e do serviço requisitante;

b) Os produtos não administrados no prazo de 24 horas e atendendo às condições de conservação do rótulo serão obrigatoriamente devolvidos aos Serviços Farmacêuticos. No Quadro D será lavrada a devolução, datada e assinada (n.º mecanográfico).

Despacho n.º 10512/2000 (2.ª série), dos Ministérios da Defesa Nacional e da Saúde, publicado no *Diário da República*, 2.ª série, n.º 251, de 30 de outubro de 2000.

Modelo n.º 1004 (Exclusivo da INCM, S. A.) INCM

ATTACHMENT III. Informed Consent for Misoprostol drug administration.



hospitalcuf
porto

Consentimento Informado

Nº 37 / 17

Eu, _____,
declaro que dou o meu consentimento para a utilização do "**Misoprostol**".
Este medicamento pode ser utilizado para:

1 - Preparação do colo do útero para a realização de histeroscopia;
2 - Facilitação da dilatação do colo do útero;
3 - Indução do trabalho de parto;
4 - Hemorragias pós-parto;
5 - Retenção de restos ovulares.

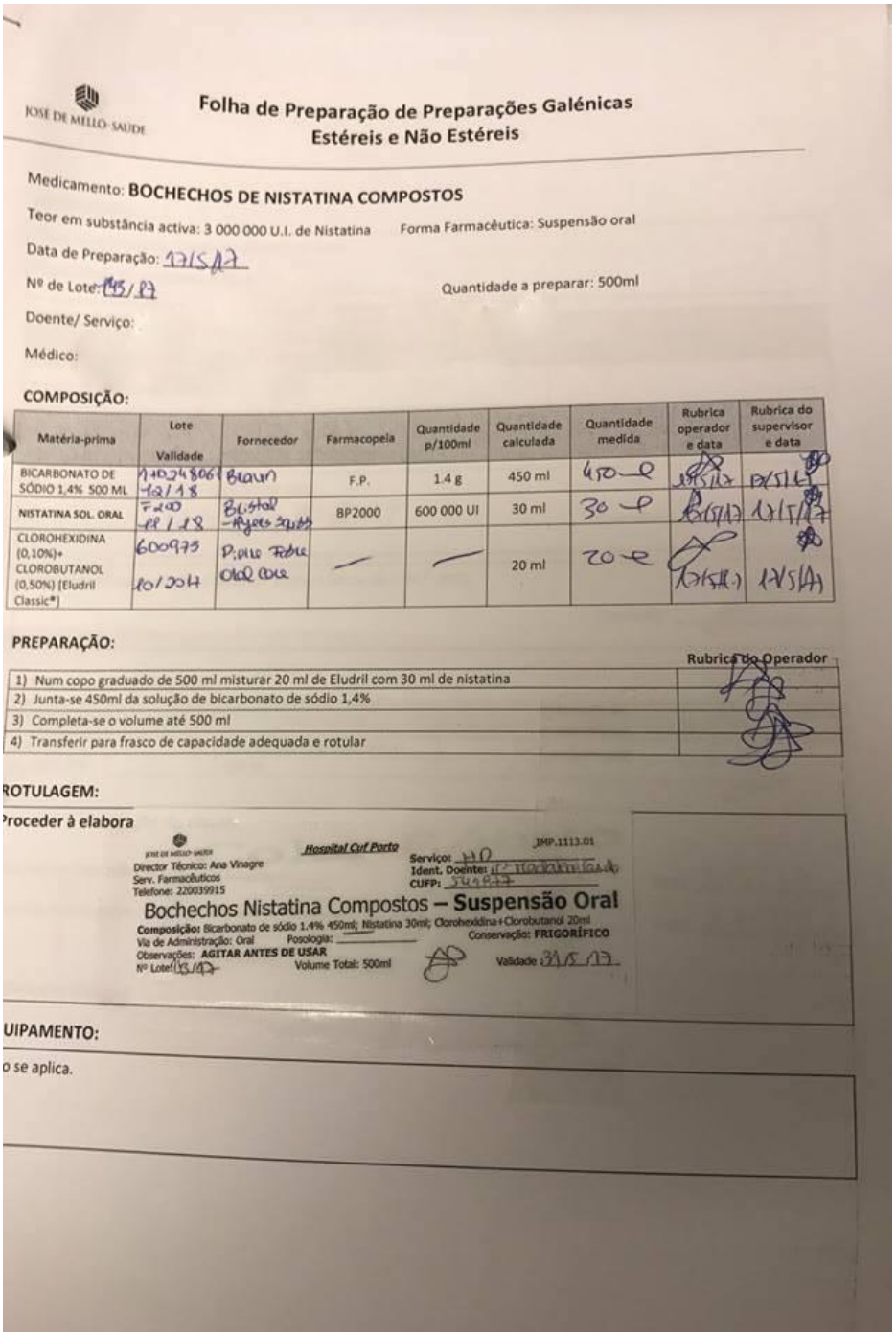
As referidas indicações não constam do R.C.M. (Resumo das Características do Medicamento) aprovadas pelo INFARMED, embora o medicamento seja utilizado com estas finalidades a nível mundial.
Por este motivo, é obrigatório que a sua utilização esteja sujeita a autorização prévia, para que não se levantem questões legais com o "INFARMED".

Declaro que tomei conhecimento e autorizo a ministração deste medicamento que é necessário à minha situação clínica, que me foi explicada e referenciada com o nº _____.

Porto, ___/___/___

_____

ATTACHMENT IV. Preparation sheet of the oral suspension of composed nystatin mouthwashes.



JOSÉ DE MELLO SAÚDE

Folha de Preparação de Preparações Galénicas Estéreis e Não Estéreis

Medicamento: **BOCHECHOS DE NISTATINA COMPOSTOS**

Teor em substância activa: 3 000 000 U.I. de Nistatina Forma Farmacêutica: Suspensão oral

Data de Preparação: 17/5/17

Nº de Lote: 195/17 Quantidade a preparar: 500ml

Doente/ Serviço:

Médico:

COMPOSIÇÃO:

Matéria-prima	Lote / Validade	Fornecedor	Farmacopeia	Quantidade p/100ml	Quantidade calculada	Quantidade medida	Rubrica operador e data	Rubrica do supervisor e data
BICARBONATO DE SÓDIO 1,4% 500 ML	14D24806 / 12/18	Braun	F.P.	1.4 g	450 ml	450 g	17/5/17	17/5/17
NISTATINA SOL. ORAL	F200 / 08/18	Bristol	BP2000	600 000 UI	30 ml	30 g	17/5/17	17/5/17
CLOROHEXIDINA (0,10%)+ CLOROBUTANOL (0,50%) [Eludril Classic®]	600975 / 10/2017	Pierre Fabre	—	—	20 ml	20 g	17/5/17	17/5/17

PREPARAÇÃO:

	Rubrica do Operador
1) Num copo graduado de 500 ml misturar 20 ml de Eludril com 30 ml de nistatina	
2) Junta-se 450ml da solução de bicarbonato de sódio 1,4%	
3) Completa-se o volume até 500 ml	
4) Transferir para frasco de capacidade adequada e rotular	

ROTULAGEM:

Proceder à elabora

JMP.1113.01

Hospital Cuf Porto

Director Técnico: Ana Vinagre
Serv. Farmacêuticos
Telefone: 220039915

Serviço: HD
Ident. Doente:
CUFP:

Bochechos Nistatina Compostos – **Suspensão Oral**

Composição: Bicarbonato de sódio 1.4% 450ml; Nistatina 30ml; Clorohexidina+Clorobutanol 20ml
Via de Administração: Oral Posologia: Conservação: **FRIGORÍFICO**
Observações: **AGITAR ANTES DE USAR**
Nº Lote: 195/17 Volume Total: 500ml Validade 31/5/17

EQUIPAMENTO:

Não se aplica.

ATTACHMENT V. Application of the Kaizen philosophy in the organization and storage of drugs.

ATTACHMENT VI. Kaizen philosophy: region with the highest turnover drugs.

ATTACHMENT VII. Label example according to the measures implemented by JCI.

ATTACHMENT VIII. Emergency car according to the measures implemented by JCI.

Organization is made by type of drug formulation. The red highlighted separation is where the electrolytic concentrates are.

"Silence is a source of great strength"

"Great acts are made up of small deeds"

Lao Tzu

Faculty of Pharmacy of the University of Coimbra

III. MONOGRAPH

Simultaneous administration of insulin and GLP-1 agonists. Technologically possible?

Orientation:
Prof. Dr. António Ribeiro

LIST OF ABBREVIATIONS

BID	*"Bis in die"* Twice a day
BMI	Body mass index
BPG	Blood plasma glucose
CA	Citric acid
CCP	Comprehensive Care Plan
CV	Cardiovascular
DM	Diabetes *Mellitus*
DPP-4	Dipeptidyl peptidase-4
EC	Ethyl cellulose
EMA	*European Medicines Agency*
EQW	Exenatide once weekly
ExBID	Exenatide twice daily
FDA	*Food and Drug Administration*
FITC	Fluorescein isothiocyanate
FPG	Fasting plasma glucose
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic polypeptide
GIPR	Glucose-dependent insulinotropic polypeptide receptor
GLP-1	Glucagon-like peptide 1
GLP-1R	Glucagon-like peptide 1 receptor
GLP-1RAs	Glucagon-like peptide 1 receptor agonists
HbA_1c	Glycated hemoglobin
HDL	High-density lipoprotein
IDeg	Insulin Deglutec
IDegLira	Insulin Deglutec/Liraglutide
IGlar	Insulin Glargine
IGlarLixi	Insulin Glargine/Lixinatide
IV	Intravenous
LAR	Long-acting release

LDL	Low-density lipoprotein
LEAD	Liraglutide Effect and Action in Diabetes
ODA	Oral antidiabetic agents
OGTT	Oral glucose tolerance test
PLGA	Poly lactic-co-glycolic acid
PPG	Postprandial glucose
PPS	Dimethyl palmitotyl ammonio propanesulfonate
PYE	Patient year exposure
QD	*"Quaque die"* Once a day
Sc	Subcutaneous
SCMC	Sodium carboxymethyl cellulose
SNAC	Sodium N-[8-(2-hydroxybenzoyl) amino]caprylate
TEER	Transendothelial electrical resistance
T2DM	Type 2 Diabetes *Mellitus*

LIST OF IMAGES AND TABLES

ABSTRACT

The regular practice of physical exercise together with a balanced diet, are nowadays, essential for the implementation of a healthy lifestyle, which is indispensable for both, prevention and control, of various diseases.

Diabetes *mellitus*, whose prevalence has increased dramatically, also obeys to this set of non-pharmacological measures, as the first step of action. However, this approach, in most cases is not enough, and it is necessary to implement a pharmacological treatment that has presented a great challenge in glycemic control due to the limitations of existing therapies, such as weight gain, hypoglycemia and repeated reliance on injectable therapies, contributing to patient non-adherence.

This monograph presents new classes and pharmaceutical forms, which have been overcoming some of these obstacles and also help in the treatment of the disease. In addition to insulin, therapies based on incretins effects such as exenatide and liraglutide, increasingly have co-formulations with clear advantages over monotherapy.

Incretins, endogenous hormones of our body, as a result of several studies, have been shown to play a central role in glucose homeostasis, drawing attention in the scientific world. The mimicking and enhancement of the action of incretins and of the endogenous insulin secretory pathway, together in combination therapy, are likely to present physiologically more relevant means for the metabolic control of type 2 diabetes.

The development of modified release systems in oral, mucoadhesive and single injection formulations, minimize the inconvenience of successive parenteral administrations. Further research, studies and clinical practice will be essential to understand the true implications of these new options, their safety profiles, advantages and disadvantages, concisely, their added value in diabetes therapy.

Keywords: Diabetes *Mellitus*; Incretins; GLP-1; Insulin; Combination therapy; New formulations; Clinical trials.

RESUMO

A prática regular de exercício físico juntamente com uma alimentação equilibrada são, nos dias de hoje, fundamentais para a implementação de um estilo de vida saudável, sendo este indispensável quer para a prevenção como para o controlo de várias doenças.

A diabetes *mellitus*, cuja prevalência tem aumentado drasticamente, também obedece a este conjunto de ditas medidas não farmacológicas, como primeiro passo de atuação. No entanto, esta abordagem na maior parte dos casos não é suficiente, sendo necessário um tratamento farmacológico que tem lançado um grande desafio no controlo glicémico devido às limitações das terapêuticas atuais existentes, nomeadamente, o aumento de peso, hipoglicemias e a repetida dependência em injetáveis, contribuindo para a não adesão do paciente.

Esta monografia apresenta novas classes e formas farmacêuticas, que têm vindo a ultrapassar alguns destes obstáculos e a coadjuvar no tratamento da doença. Adicionalmente à insulina, terapias baseadas no efeito das incretinas, como por exemplo, o exenatido e liraglutido, dispõem cada vez mais de co-formulações com claras vantagens relativamente à monoterapia.

As incretinas, hormonas endógenas do nosso organismo, como resultado de várias pesquisas, demonstraram ter um papel fulcral na homeostase da glucose, chamando a atenção no mundo científico. A mimetização e intensificação da ação das incretinas e da via endógena de secreção da insulina, em terapia combinada, são suscetíveis a apresentar meios fisiologicamente mais relevantes para o controlo metabólico da diabetes tipo 2.

O desenvolvimento de sistemas de libertação modificada em formulações orais, mucoadesivas e injeções únicas, minimizam o inconveniente das administrações parentéricas sucessivas. Mais investigações, estudos e práticas clínicas, serão imprescindíveis para compreender as verdadeiras implicações existentes nestas novas opções, os seus perfis de segurança, vantagens e desvantagens, em suma, a sua mais valia na terapia da diabetes.

Palavras-chave: Diabetes *Mellitus*; Incretinas; GLP-1; Insulina; Terapia combinada; Novas formulações; Ensaios clínicos.

1. INTRODUCTION

Diabetes *mellitus* (DM) is the term used to describe a chronic disease that results from our body's lack of ability to conceive or use the produced insulin, consequently, blood glucose levels increase developing hyperglycemia. (1)(2)

In 2014, there were an estimated 422 million people with DM compared to 108 million in 1980, an increase from 4.7% to 8.5% of the world's population. (1) In Portugal, a prevalence of 11.7% and 13.3% was estimated in 2009 and in 2015 respectively, though there was a decrease in the number of years of life lost (-32%), and also with the number of hospitalizations (-27.9%) with diabetes as the main cause. (3) Drastic changes in the population's lifestyle and the expansion of the associated risk factors, reflects this concerning increase. (3)

Insulin is a hormone produced by the ß cells of the pancreas, responsible for the balance of blood sugar levels, by flushing glucose from the bloodstream into the cells and turning it into energy or storing it for future use. (1) The primary structure of insulin is proinsulin that, with a succession of proteolytic cleavages, generates mature insulin and a residual C-peptide. (4) Mature insulin is composed by two chains, with two disulfide bridges between them, which creates a quaternary structure, having a self-assembly property. (5) Circulating insulin is stored in intracellular granules and released by the pancreas in a hexameric form, dissociating to dimeric and lastly to monomeric granules once released to the bloodstream, being this last one the active form. (5) So insulin has a tendency to associate by the interaction between its structural components, a very explored property in marketed insulins. (5)

1.1 Type 2 Diabetes *Mellitus*

Compared to a healthy person, in type 2 diabetes *mellitus* (T2DM), the increase of insulinemia upon physiological request is much less pronounced, and the extent of circulating hormone is not adequate, decreasing glucose uptake. So glucagon is released to increase lipolysis and stimulate the liver to produce glucose, further aggravating hyperglycemia. (4)

This condition may be asymptomatic for a long period of time making it difficult to diagnose, and often it only happens upon secondary effects appearance. The diagnosis of DM is made through glycaemia levels, with standard reference values. Glycated hemoglobin

(HbA_1c), evaluates the patient's exposure to glucose in the last three months, used to diagnose and to monitor adhesion to therapeutics. (6)(7)

1.2 Treatments

Every patient with T2DM should have a comprehensive care plan (CCP), to reduce the risk of diabetes complications without exposing patient safety. (8) A very solid relationship between body mass index (BMI) and DM exists, so CCP should start by including lifestyle changes. (3) Oral antidiabetic agents (ODA), the next point of the CCP, are required when diet and regular exercise are not effective. Glycemic goals and the selection of agents should be based on patient characteristics. T2DM is not dependent on exogenous insulin, but when not responding to ODA, many patients end up with insulin replacement therapy. There are two main types if insulins: rapid acting/prandial, and long acting/basal. The first is involved in controlling postprandial glucose (PPG) levels specifically taken after meals, instead of the last one, basal insulin, that controls glucose levels between meals and during fasting periods. Therefore, another point of the CCP is the education of the patient. (8)(9)

Pharmacological agents for the treatment of T2DM are effective, although there are limitations to their action due to the high frequency of adverse effects and to the difficulty in maintaining a long term glycemic control. (8)(9) Also the progressive loss of ß cells functions makes extremely difficult to control the disease, even with an early treatment the levels of glucose and HbA_1c increase with time. (4)

Combination therapy of insulin and incretin receptor agonists, is an approach to delay ß cell deterioration and to better and faster achieve glycemic targets, decreasing adverse effects. (8)(9)

2. INCRETIN-BASED THERAPIES

An oral administration of the same amount of glucose, produce a greater insulin secretion and response, when compared to intravenous (IV) administration in humans, the "incretin effect". This effect is caused by the release from the gastrointestinal tract, as a result of nutrient ingestion, of hormones called incretins that have the ability not only to potentiate insulin secretion, an insulinotropic effect, but also to regulate physiological

functions within and outside the pancreas. Incretins are produced and secreted by intestinal L and K cells. (10)

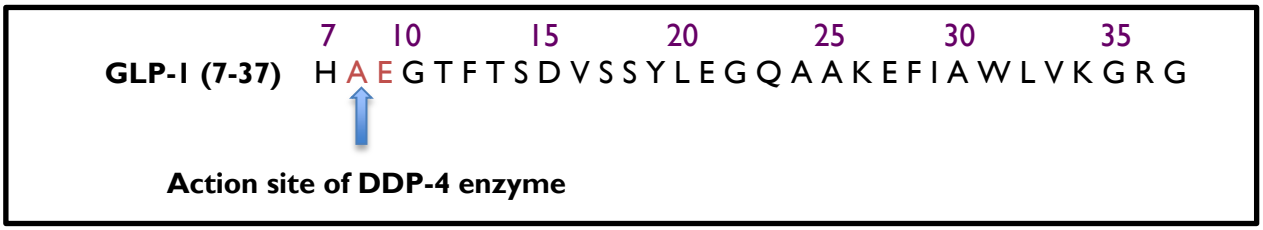
Concentrations of these hormones are low at fasting, proving high dependence in a meal and since stimulation of insulin production is higher after oral glucose administration, direct contact between the luminal contents and intestinal L and K cells, is needed as a major form of stimulation of GLP-1 and GIP, respectively. Hereafter, the secretion patterns of these hormones are related to gastric emptying, intestinal transit, digestion and nutrient absorption. (10)

2.1 GLP-1 and GIP

At 1970 the first incretin hormone was isolated, the glucose-dependent insulinotropic polypeptide (GIP), followed by glucagon-like peptide 1 (GLP-1) in 1985. GIP is mostly produced in the gastrointestinal (GI) tract through K cells, located in the duodenum and in the jejunum. GLP-1 is one of the proglucagon gene products, having homology with glucagon in its 30 amino acid sequence. Mostly produced by L cells located in the ileum and colon. (11) After secretion, both hormones are rapidly metabolized by enzyme dipeptidyl peptidase-4 (DPP-4), found on the surface of endothelial cells, proximal to the intestinal L and K cells, resulting in the inactive metabolites of incretins. Therefore, both peptides have extremely short half-life, ranging from 5 to 7 minutes for GIP and less than 2 minutes for GLP-1. (10)(11)

About 50% to 70% of insulin secreted in response to oral glucose is due to the incretins through their connection to specific receptors on ß cells, GLP-1R and GIPR. But a significant amount of GLP-1 has already been inactivated by DPP-4 before entering the systemic circulation (Image 1). (10)(12) This enzymatic reaction is already possible to balance by emerged drugs with a slightly different structure of GLP-1 endogenous hormone, increasing their half-life. (10)(11)

Image 1. *Structure of endogenous GLP-1 hormone and action site of DPP-4 enzyme* (12)



2.2 The Incretin effect

Incretins became a target of great interest due to their pleiotropic potential with numerous extra-glycemic biological functions, associated with various tissues and organs in which their specific receptors exist (Table1).

Table 1. *Locations of action and main physiological functions performed by GLP-1 and GIP* (10)(11)

	GLP-1	**GIP**
Glycemic effects	Exerts actions through an endocrine and neurocrine pathway	Exerts actions mainly through an endocrine pathway
Pancreas	Stimulates biosynthesis, secretion and growth of insulin inhibiting apoptosis	
	Increases insulin gene transcription and enhances the glucose-sensing system	
	Inhibits glucagon secretion	Enhances glucagon secretion in response to hypoglycemia
Central and peripheral nervous system	Suppresses appetite and food intake	No known effect on appetite or food intake is known
Gastrointestinal tract	Decreased rate of gastric emptying mediated by specific receptors in the brain, promoting vagal stimulation	No effect on gastric emptying is known
	Decreases the motility of intestinal transit as well as glucose uptake	Inhibits acid secretion in stomach at supraphysiological doses
Extra-glycemic effects	Extra-glycemic effects have been interrelated	Extra-glycemic effects on specific tissues
Adipose tissue	Involved in the lipolysis control of white adipose tissue	Regulates lipid metabolism, with the incorporation of fatty acids in triglycerides
Bones	Implicated in bone formation, the underlying mechanism is still unclear	Increases bone formation by stimulation of osteoblast and inhibition of osteoclasts
Cardiovascular system	Involved in the regulation of heart rate and blood pressure and myocardial and endothelial function	No clear clinical evidence on cardiovascular system is known
Liver	Reduce gluconeogenesis and hepatic steatosis	Increases hepatic glucose production in hypoglycemia

3. GLP-1 AGONISTS

The discovery of incretins came with several investigations that have been carried out to improve our knowledge of their impact on the body. Since then, considering the influence of these hormones, with substantial relevance to GLP-1, the incretin hormone that seems to have greater therapeutic potential, new oriented strategies have emerged: the incretinomimetics, analogues and agonists of GLP-1. (12) They work through mimicking the endogenous incretin hormones functions, extending their half-life by being resistant to DPP-4 degradation, which is possible through some structural modifications based on the structure of these endogenous incretins. (12)

3.1 Type 2 DM and the role of GLP-1RAs

In patients with type 2 diabetes *mellitus*, the incretin effect is severely compromised, not controlling hyperglycemia after glucose ingestion. (10) Based on the detection of C-peptide concentrations, a marker of insulin secretion, patients with T2DM, in contrast to healthy people, did not show significant changes in the values of this marker, after glucose intake, indicating the lack of insulin secretion and the loss of incretins action. (10) However, other types of diabetes also have a decrease in the incretin effect, and the secretion and action of GIP and GLP-1 is unaltered in people with normal glucose tolerance but with high risk for the disease, suggesting the loss of effect as a consequence and not a cause of the disease. (10)

The secretion of GIP in T2DM is preserved, contrary to the insulinotropic action, severely engaged. GLP-1 maintains insulinotropic capacity despite its poor secretion, having low endogenous plasma levels. So unlike GIP, GLP-1 exogenous administration produces insulin secretion and glycemic regularization. (10) As justification, studies point to a glucotoxicity-induced suppression leading to a down regulation or impairment of receptor signaling. (10)

Moreover, this disease often results in weight gain and hypoglycemia, outcomes from the intense therapies applied. By not having insulinotropic activity in the presence of low glucose concentrations, incretins do not promote hypoglycemia and by having action on gastric emptying, suppressing appetite, makes them important regarding weight loss. (10)(11) All this supports the potential use of incretin hormones in the treatment of T2DM, although, because of their short half-life, therapeutic administration of native GLP-1 is impractical, it

would be necessary continuous infusions or repeated subcutaneous (Sc) injections at several point of the day, resulting in a very expensive therapeutics, with low adherence. (10)

So the incretin defect in diabetes appears to have two causes: reduced secretion of GLP-1 and deteriorated insulinotropic effect of GIP. (10) GLP-1 receptor agonists (GLP-1RAs) emerged to overcome the dysfunction of the GLP-1 endogenous hormone. Although some differences between these drugs, most of the GLP-1RAs shown positive results in reduction of HbA_1c, fasting glycemia and weight. Additionally, some risk factors were improved by demonstrating an important action in cardiovascular (CV) complications, reducing blood pressure, triglycerides and also in low-density lipoprotein (LDL) cholesterol. On the other hand, there is a beneficial effect on high-density lipoprotein (HDL) cholesterol. (13-16)

The pancreatic function of ß cells also improved when compared to patients treated with placebo. The effects of GLP-1 on ß cells are categorized as: acute, GLP-1 increases the secretion of insulin in a glucose-dependent manner, sub-acute, GLP-1 stimulates transcription and biosynthesis of proinsulin, and chronic GLP-1 stimulates both, the proliferation and neogenesis of ß cells and decreases their apoptosis. (13-16)

3.2 Exenatide

By replicating the structure of the exendin-4 molecule, from Gila monster, Exenatide, a synthetic peptide with 39 amino acids, was developed. It has only 53% of homology with endogenous GLP-1, due to a larger number of amino acids and to a change at position 8 (Ala for Gly), making it resistant to degradation by DPP4. (13)(17)

It can be classified as short acting and long acting. Starting with the short acting, twice-daily exenatide, ExBID, was the first GLP-1RA to be approved in 2005 by FDA and 2006 by EMA, available under the name Byetta®, with an initial dose of 5µg, changed to 10µg after one month of treatment if well tolerated by the patients. It has a half-life relatively short of about 2.4hours. (13)(17)

Long-acting release exenatide (LAR) experienced some technological modifications to increase its half-life and action. Molecules were encapsulated into small biodegradable PLGA microspheres, having a sustained release of the drug, slowly metabolized through diffusion and erosion of these microspheres. This allows a weekly subcutaneous administration of 2mg at any time of the day, with or without meals. It was approved for use in 2011 by EMA and 2012 by FDA, currently available in a single injection named Bydureon®, exenatide once

weekly (EQW). Patients who are less tolerant to frequent injections can use EQW as an alternative. (13)(17)

ExBID revealed greater results in PPG levels, due to gastric emptying being slower than with EQW intake. So continuous activation of the GLP-1 receptor decelerates gastric emptying more than repeated exposure. (14) The primary amino acid sequence of ExBID does not differ from the one of EQW and by being a non-human peptide, antibody formation is observed in 40% of the patients. (17)

3.3 Liraglutide

The GLP-1 Liraglutide analogue, available as Victoza®, was the second GLP-1RA to be approved in 2009 by EMA and 2010 by FDA, for clinical use in the treatment of T2DM. (14) The amino acid sequence is 97% identical to human GLP-1 and structural changes are summarized as a substitution at position 34 (Lys for Arg) and the addition of a linear C16 fatty acid at position 26 (Lys). This allows a non-covalent binding to albumin, increasing half-life to about 13hours, making it suitable for once-daily (QD) subcutaneous administration. (13)(18) Initial dosage should be 0.6mg in the first week of treatment, to reduce and stabilize adverse gastrointestinal effects. After, the dose should be increased to 1.2mg and can be further augmented to 1.8mg to provide the desired glycemic control. (18)

3.4 Lixisenatide

Lixisenatide is a new GLP-1RA recently approved in 2013 by EMA (Lyxumia®) and in 2016 by FDA (Adlyxin®). It is structurally identical to exenatide, differing by the addition of 6 carboxyterminal lysine residues and by the deletion of the amino acid 38 (Pro), which extends the half-life of lixisenatide about 2 to 5 hours. Starting dosage is 10μg for the first 14 days after titrated to 20μg. It is available as two strengths pre-filled pens, 10μg/0.2ml and 20μg/0.2mlor both, for once-daily administration. (19) Similarly, to exenatide, many patients had a positive antibodies status (50% to 60%). Gastrointestinal events were the most common adverse events. (19)

3.5 Safety and tolerability

The main side effects of GLP1-RAs are dose-dependent and consist essentially of nausea, vomiting, and diarrhea that tend to decline over time. Small subcutaneous nodules may occur as a result of successive injections and other occurrences such as headache, constipation, dyspepsia, and asthenia, have fewer reported cases. (20)(13)

The formation of antibodies was reported for most GLP-1RAs however, glycemic action was not affected and higher values were related to the low homology with the endogenous GLP-1. (20)

The risk of thyroid cancer was associated with the use of liraglutide in rats, however, thyroid C-cell hyperplasia and tumors, after long exposure to the GLP-1RA, were found only in rats, demonstrated to have a greater expression of the GLP-1R and a higher density of C-cells when compared to monkeys and humans. In addition, calcitonin levels, an indicator of C-cell hyperplasia (>20ng/L), did not show any variation in the LEAD studies, "liraglutide effect and action in diabetes" (<1.0ng/L). There are also some concerns about the potential increased risk of pancreatitis or pancreatic cancer owing to the manifestation of some cases. The relation with the use of GLP-1-RAs has not been clinically supported. (13) Reports on acute gallstone disease may be related with slowing gallbladder motility or rapid weight loss. (13)

4. SIMULTANEOUS ADMINISTRATION: THE TECHNOLOGICAL CHALLENGE

4.1 Add-on therapies

Resulting from their beneficial and synergic effect, combinations of GLP-1RAs and insulin were developed in a single device and formulation, facilitating co-administration: iDegLira and iGlarLixi, recently approved by EMA and FDA. (12)

4.1.1 Combining GLP-1 and Insulin

A progressive disease often demands the intensifying of the treatment, and current strategies consist in the addition of prandial insulin at mealtimes, covering postprandial glucose in patients on a basal insulin background not achieving adequate results. The weight gain and the risk of hypoglycemia will be greater when associated with intensive insulin regimens. (21)

GLP-1RAs target PPG by performing in a glucose-dependent manner. (21) Since basal insulin is normally applied based on fasting plasma glucose (FPG), incretinomimetics may complement the action of these insulins, replacing the prandial ones. The GLP-1RAs associated low risk of hypoglycemia and significant loss of body weight, present a better option then basal-bolus insulin regimens. (21) Several studies have shown a reduction in insulin dose when in combination therapy, another clear advantage. Despite the benefits, gastrointestinal adverse effects often follow incretinomimetics, so it is still unclear if a dose adjustment is needed, in order to decrease these effects. (21)

Identifying potential target population is important. Obese patients (BMI>40Kg/M^2 and $HbA_1c \geq 9$) have a greater severity of the disease and high risk of obesity aggravation with intensive insulin regimens, so a not providing weight gain therapy is required. (21) Conversely, in advanced stage diseases, damaged pancreatic ß cells with low secretion capacity, limit GLP-1RAs position, due to the inability to stimulate insulin secretion. More beneficial results occur at an earlier-stage disease. The cost-effectiveness of the regimens should also be evaluated. (21)

4.1.2 Effects of individual and co-administration

A meta-analysis of 19 comparative studies between insulin and GLP-RAs was performed to assess which therapy had the best results in glycemic control (HbA_1c), weight loss, cholesterol levels, and cardiovascular benefits. In safety issues, the adverse effects and risk of hypoglycemia were evaluated. (22) Results were presented for each class of drugs separately in monotherapy, insulin versus GLP-1RAs. On the other hand, other study presented outcomes for the administration of both therapeutic classes, in combination therapy. (23)

In the first study, individual administration or monotherapy, GLP-1RAs have shown slightly better results concerning to glycemic control when compared to simple insulin regimens (-0.02%). These results were more pronounced with long-acting GLP-1RAs (-0.17%). (23)(24) Although, FPG levels decreased more with basal insulin, especially when compared to short-acting GLP-1RAs, which have greater results in PPG because their improved influence on gastric emptying, less effective overnight owed to the lower half-life. Long-acting GLP-1RAs act over both, FPG and PPG, having better results mainly in FPG levels by ensuring higher drug concentrations during the night. Over time, PPG reductions with long-acting drugs may become insignificant due to tachyphylaxis.

Weight loss was associated with GLP-1RAs treatment (-3.7kg), with greater outcomes achieved by short-acting GLP1-RAs, instead of the weight gain with insulin. (23)(24) Blood pressure, LDL cholesterol, and triglycerides levels, remained as well almost unchanged with insulin comparing with GLP-1RAs where levels lowered (-2.8mmHg; -0.23mmol/L; -0.13mmol/L, respectively). Hypoglycemia episodes appear to be linked to the use of intense therapies based on insulin and sulfonylureas as background rather than GLP-1Ras (-40%). Gastrointestinal adverse effects have higher rates with GLP-1RAs. (23)(24)

Regarding combined therapies, a real world glycemic control study was made to GLP-1RAs therapy, using liraglutide QD and exenatide QW, with and without insulin. Measuring of HbA_1c levels were the primary outcomes, followed by weight, LDL and blood pressure outcomes. Glycemic control outcomes were stratified by baseline insulin use, presented as: "insulin first prescribed with GLP-1RA on index date"; "no insulin prescribed during the baseline period", and "insulin prescribed before index date." (22) This study reflects the reality, where the imposed treatments are not monitored and patients may not

adhere to therapy and recommended lifestyles. Results are shown in Table 2. (22)

Concerning glycemic outcomes, there were increased benefic results rather than monotherapy. Significant improvements were observed when GLP-1RAs were used alone and even better results by starting both, GLP-1RAs and insulin, at the same time. (22) So HbA_1c levels had higher results in patients who were prescribed both therapies for the first and at the same time, when compared with those who GLP-1RAs were add to a prior use of insulin. (22) Weight, LDL and blood pressure reductions were also substantially using combined therapy, and there were less detected hypoglycemia episodes. (22) Patients with prior use of insulin may not achieve the desirable glycemic control due to a probable greater progression of their disease, starting with higher HbA_1c values before the study. (22)

Table 2. *Study results by baseline insulin use and HbA_1c outcomes at 1 year follow up* (22)

	Baseline insulin use			**Combined therapy outcomes**			
	HbA_1c (%)						
Overall *n=51,41	Insulin first prescribed with GLP-1RA on index date (n=1,115)	No insulin prescribed during the baseline period (n=1,822)	Insulin prescribed before index date (n=2,204)	**Weight (kg)** (n=4,804)	**LDL (mg/dL)** (n=1,734)	**Blood pressure goal (%)** (n=4,826)	
Baseline mean	8.2	8.2	8.6	108.0	90.1	<140/90 mmHg	73.2
Follow-up mean	7.6	7.7	8.2	105.8	88.0	<140/90 mmHg	76.5
Mean difference	-0.6	-0.5	-0.4	-2.2	-2.1	<140/90 mmHg	+3.3
HbA_1c goal, *n (%)							
<7%	979 (22.9)	437 (15.6)	190 (12.4)	-	-	-	
<8%	2.284 (53.5)	1.191(42.5)	513 (33.4)	-	-	-	
<9%	3.225 (75.6)	1.885(67.2)	869 (56.6)	-	-	-	

*n, number of patients entering the study.

Studies have shown that GLP-1RAs in monotherapy have higher or equivalent results than simplified insulin regimens (once daily basal insulin or twice daily premixed insulin). In combination with insulin, the results are equally good, with lower risks and further promoting a decrease in the gastrointestinal adverse effects associated with incretinomimetics. (22)(23)

4.2 Development of new formulations

4.2.1 Oral delivery systems

GLP-1 peptide is secreted from the L cells in the intact form and rapidly inactivated by DPP-4 enzyme as it enters the blood vessels, then it is released to the splanchnic and portal blood until it finally enters the systemic circulation, suffering from the same enzymatic reaction. Hereafter it acts in several organs as pancreas, where binding to its specific receptors on ß cells, initiates a signal cascade with the alteration of ion channel activity and increased Ca^{2+} levels, enhancing the exocytotic process of insulin. (10)

Therefore, in a healthy person, the liver is exposed to concentrations of GLP-1 and insulin much higher than those normally found in the systemic circulation. Current routes of administration do not mimic the physiological release of GLP-1 and insulin, not leading to this portal-systemic concentration gradient, which compromises the role of both drugs regarding hepatic glycogenolysis, gluconeogenesis and suppression of glucagon secretion in the postprandial state. (25)(26)(27) Oral delivery systems would more easily follow the physiological path of endogenous secretion. A more simplified and cheaper form of administration, with less adverse effects by better replication of the endogenous physiology, non-invasive, not involving sophisticated sterile manufacturing or health care professionals, promoting a large patient acceptability. (25)

GLP-1RAs and insulin are both protein drugs and the use of proteins and peptides as therapeutic agents present great difficulties concerning their oral administration. (25) GI tract has several barriers making the absorption of these oral drugs very difficult. Its variable pH leads to the proteins denaturation or destruction, before reaching the target site and the rapid degradation by GI lumen enzymes leads to a short biological half-life (25)(28). Another barrier are the intestinal epithelium cells that can be overcome by a transcellular route, passing through cells or by a paracellular route, across the intestinal cell junctions. Nevertheless, their high molecular weight and both, hydrophilic and hydrophobic sides, makes this entry difficult. In addition, an immune response of the organism could result in their destruction. (25)(28)

To overcome these obstacles, instead of modifying the characteristics of the GI tract, the best way of acting is through the modification of the chemical structure of the drugs, such as the addition of functional groups or through the use of different formulations, where

delivery systems protect peptides and promote the crossing of biological barriers. Two other approaches widely used in these oral formulations are: absorption enhancers, which increase permeability through a slight modification of tight junction properties, and enzymatic inhibitors that induce a conformational change in enzymes. However, the first ones may damage the membrane, leading to local inflammation and long administration of the last ones, may result in the deficiency of some enzymes. (25)

A delivery agent or carrier, sodium N-[8-(2-hydroxybenzoyl)amino]caprylate (SNAC), from Eligen® technology, facilitate the transport of peptides and proteins across biological membranes, by creating a weak noncovalent drug-carrier complex that causes an increase in lipophilicity, preserving the chemical integrity of the drug, without damage the biological barriers. Once in the general circulation, the complex spontaneously dissociates by dilution and the active therapeutic is released. (25)(29) To verify the effectiveness of this agent, a single oral dose of endogenous GLP-1 using SNAC or placebo (SNAC alone), was administered 15min prior to an oral glucose tolerance test (OGTT). Orally administered GLP-1 using SNAC result in higher concentrations of insulin when compared to the levels achieved by endogenous GLP-1, after a glucose intake. SNAC alone did not reveal any biological effects. (29)

Once-daily Semaglutide has been developed co-formulated with SNAC, an oral tablet currently in phase IIIa clinical trial known as "the peptide innovation for early diabetes treatment" (PIONEER). A significant advantage, since all other available GLP-1RAs are injectable products. (12)

4.2.2 Mucoadhesive intestinal devices

In order to overcome the limitations of oral delivering peptides and proteins, and the weaknesses from the subcutaneous route, mucoadhesive intestinal patch-based devices were developed for oral drug administration. Exogenous oral insulin and GLP-1 is delivered straight to the liver through portal circulation, the primary site involved in the regulation of glucose homeostasis. These devices allow an increasing performance of targeting drugs with a GI local action. Besides, lead to the prolongation of the drug residence time at the acting site by providing intimate contact between the formulation and the absorptive intestinal mucosa. (30)(31)

Intestinal patches can be made from several mucoadhesive polymers such as carbopol, pectin, chitosan, PLGA, ethyl cellulose (EC), and SCMC for instance, all FDA approved. (30)(31) Regarding the construction, EC is often used as a water impermeable background layer on all sides except one, to prevent leakage of the content into the lumen, to allow an unidirectional release, and further to avoid the access of proteolytic enzymes. (30)(31) The devices can additionally be coated on both sides with other polymers (Eudragit® L 100, talc, or both) called coated patches, and placed in enteric-coated gelatin capsules. This extra coating allows its subsequent release into the intestine without being degraded in the stomach. (30) Once released from the capsules, the patches adhere to the intestinal mucosa and promote a unidirectional release of drugs and continued absorption through the intestinal epithelium, due to a local reservoir with a high concentration gradient. A strong adhesion force is required to withstand its own weight, peristaltic movement and mucus flow of the intestine. (30)(31) An inhibitor of proteases and an enhancer of permeability, citric acid and PPS respectively, are often added in the formulation. (30)(31)

Considerable mucoadhesive intestinal delivery systems have been studied for the release of proteins, peptides, and small molecules through multiple non-invasive routes such as buccal, transdermal, and the desired oral route. A non-invasive drug delivery device that leads to a steady release for a long period of time, and increase life quality of patients with T2DM. (31) The potential risk of damage the biological membrane or altering the intestinal natural flora with of long term use is still unknown, more studies are needed. (30)

4.2.3 Results obtained/clinical trials

Different studies were made to prove the efficiency of a mucoadhesive patch device in the improvement of oral and intestinal absorption of therapeutics macromolecules, recombinant human insulin and exenatide. (30)(31) The drug release of both drugs, self-aggregation and mucoadhesion of the devices was tested *in vitro* and also *ex vivo* studies. Regarding *in vivo* studies, reduction on blood glucose was measured in single and multiple doses of insulin. All these tests were performed in coated and uncoated patches, to verify the influence of coating.

Starting with *in vitro* studies, to test the drug release devices were loaded with FITC-insulin and exenatide, and placed in tubes with 10 ml of PBS at pH 7.4 and on a shaker for 30 minutes, to simulate physiological conditions of the intestine. The release was after evaluated by fluorescence measurement at 488/525 nm and by Elisa kits (Table 3). In another *in vitro*

study, the devices were also loaded with insulin and exenatide, and their deliver ability was tested using a 3-day Caco-2 monolayer transport model (Table 3). The integrity of membrane was evaluated by TEER (transendothelial electrical resistance) measurements, which results did not exhibit significant changes, emphasizing the devices safety. (30)(31)

Micropatches are associated with significant drug loss because of their predisposition to adherence to each other once released from the capsule, to address this problem, directing adhesion to the intestinal mucosa, different mucoadhesive polymers can be used in the coating. Thus, to evaluate the level of self-aggregation, some devices were left uncoated while others were coated with Eudragit L100, with talc or a combination of both polymers. Followed introduced into resistant enteric capsules and placed in vials with the same previous intestinal simulated conditions (Table 3). (30)(31)

The mucoadhesion of these devices was *ex vivo* tested, using a cut section of a porcine intestine, with the exposition of the inner mucosa to coated and uncoated micropatches loaded with 10% w/w coumarin. At the end of 30minutes, the number of small yellow spots was counted to determine the number of patches mucoadded (Table 3).

Table 3. *Mucoadhesive efficacy studies and results: in vitro and ex vivo efficacy studies* (30)(31)

<table>
<tr><th colspan="3">In vitro efficacy studies</th></tr>
<tr><td colspan="3">Drug release from the patches</td></tr>
<tr><td rowspan="2">Coated L 100 and Uncoated</td><td>FITC-Insulin</td><td>90% release in $^{1}/_{2}$h and 5h</td></tr>
<tr><td>Exenatide</td><td>47% release in 5h</td></tr>
<tr><td rowspan="2">Transport across Caco-2 monolayer</td><td>Insulin</td><td>17.7μg vs 8.9μg (without patch) in 5h</td></tr>
<tr><td>Exenatide</td><td>127.3ng vs 63.8ng (without patch) in 5h</td></tr>
<tr><td colspan="3">Preventing self-Aggregation</td></tr>
<tr><td colspan="2">Uncoated</td><td>Aggregated considerably</td></tr>
<tr><td rowspan="3">Coated</td><td>L 100</td><td>Mostly individually released from the capsules</td></tr>
<tr><td>Talc</td><td>Aggregated considerably</td></tr>
<tr><td>L100 + Talc</td><td>Mostly individually released from the capsules</td></tr>
<tr><th colspan="3">Ex vivo efficacy studies</th></tr>
<tr><td colspan="3">Mucoadhesion study</td></tr>
<tr><td colspan="2">Uncoated</td><td rowspan="2">13-14 patches adhered in $^{1}/_{2}$h</td></tr>
<tr><td rowspan="2">Coated</td><td>L100</td></tr>
<tr><td>L100 + Talc</td><td>4-5 patches adhered in $^{1}/_{2}$h</td></tr>
</table>

In vivo experiments were evaluated in male rats where the efficacy of oral delivery insulin was assessed by the measure of BPG levels over time. Additionally, to evaluate the influence of the coating, and of the addition of permeation enhancers and protease inhibitors, different formulations were tested: uncoated PSS insulin versus L 100 coated insulin with and without PPS or citric acid. A control group was subcutaneously injected only with insulin (Table 4). (30)

To improve efficacy and bioavailability of insulin, an initial dose of 50U/kg, was divided in multiple administrations over time and compared to a single oral take (Table 4). However other factors were evaluated as the size of the patches, in which, through a comparative evaluation, micropatches (500μm) were more effective because of their increased contact surface area, with greater expose of intestinal epithelium to the delivery systems. Larger sized patches may lose part of the drugs to the luminal fluids. The same happens with round devices, so preferably rectangular-shaped devices are used to certify a one-way delivery without loss. (31)

Table 4. *Mucoadhesive efficacy studies and results: in vivo efficacy studies* (30)(31)

<table>
<tr><th colspan="4">In vivo efficacy studies</th></tr>
<tr><td colspan="4">Reductions on blood plasma glucose (BPG) %</td></tr>
<tr><td rowspan="4">Oral</td><td colspan="2">Uncoated PSS</td><td>9.5% after 5h</td></tr>
<tr><td rowspan="3">Coated</td><td>L 100</td><td>14.5% after 1h
27% after 5h</td></tr>
<tr><td>L100 PSS</td><td>22% after 1h
27% after 5h</td></tr>
<tr><td>L100 PSS + CA</td><td>31% after 5h</td></tr>
<tr><td colspan="3">Subcutaneous injection</td><td>54% after 1h
28% after 5h</td></tr>
<tr><td colspan="4">Oral multiple or single dosing</td></tr>
<tr><td rowspan="2">Coated
(L100 PSS + CA)</td><td>Multiple doses</td><td>41% after 8h</td></tr>
<tr><td rowspan="2">Single dose</td><td>31% after 8h</td></tr>
<tr><td>Uncoated</td><td>18% after 8h</td></tr>
</table>

4.3 Current treatment options

4.3.1 Injectable therapy

The primary mode of administration of insulin and GLP-1RAs is through subcutaneous route, as it is suitable for daily self-administration, not suffering from GI tract degradation. However, this pathway has limitations by being invasive causing local pain, allergies and may also origin lipodystrophy by successive injections, leading to patient non-compliance, many of them having needle phobia. (32) Also, subcutaneous injections are unable to mimic endogenous secretion, resulting in a lack of insulin in the portal circulation, where only 20% reaches the liver. Increasing insulin doses as a solution, can lead to peripheral hyperinsulinemia, predisposing to hypoglycemia and weight gain. (5)(33)

New drug delivery systems have been developed based on the release mechanism, divided into open loop system and closed loop system. (5) All systems currently marketed are based on open loop systems, acting by mimicking the endogenous release of insulin by the pancreas. So insulin is released at a constant rate over a long period of time. (5) At this type of systems, insulins just like GLP-1RAs are classified according to the duration of action into short acting, long acting and combination insulins, for instance. (5)(33)

By modulating the capacity of aggregation of endogenous insulin, different release patterns are created. The aggregation reduces the release and solubility of insulin. This modeling can be done through chemical reformations, using zinc and chelating ions, such as EDTA or citrate, or by a biotechnological pathway, the attachment of antibodies fragments, conjugation with albumin, fatty acids and polymers, such as PEG, and by also modifying the amino acid sequence. (5) Long-acting insulins are based on the property of self-association and on the affinity of the insulin molecules for zinc, Zn^{2+}. Nevertheless, zinc complexion delays the onset activity of rapid insulins at a postprandial level, when the insulin action should be fast, therefore, in this case, these properties are reduced by altering the amino acid sequence. (5)(33)

Regarding the future systems, known as closed loop systems, the pulsatile secretion of insulin by pancreas will be mimic but only in response to glucose levels. Designed to be drug-device combinations that will monitor blood glucose levels, with an insulin pump to simulate endogenous insulin secretion. (5)(33) There are still some concerns concerning the possibility of pump malfunction leading to ketoacidosis risk and the need of continuously wear the device with higher costs and complexity. (34)

4.3.2 IDegLira and iGlarLixi co-formulations

Many studies have investigated the viability of using the combination of GLP-1RAs with insulin as a replacement for insulin basal-bolus therapy. In clinical practice, this combination separately in different formulations is already used, having several limitations. (35)(36) Fixed-dose combination, in a single formulation, raises great interest by the fact of being different therapeutic classes acting at different points of the pathophysiological deficit in T2DM, having complementary actions together, with basal insulin reducing FPG and GLP-1RAs decreasing PPG. Besides also reduces the risk of adverse effects, hypoglycemia episodes and the number of injections, being a single formulation with one daily administration. (35)(36)

IDegLira was the first co-formulation of a long-acting basal insulin analogue, insulin deglutec (iDeg), and a GLP-1RA, liraglutide, to be approved under the name Xultophy® in 2014 by EMA and recently in 2016 by FDA. It is given once daily at any time of the day, by subcutaneous injection, based on dose steps, each step consisting of 1U of insulin deglutec and 0.036mg of liraglutide. Doses are adjusted for each patient, having different initial doses depending on the previous therapy. For patients not controlled with ODA the starting dose is 10 dose steps and for patients with previous GLP-1RA therapy or basal insulin, the starting dose is 16 dose steps. The maximum dose is 50U insulin and 1.8mg liraglutide, 50 dose steps. (35)(36)

IDeg is formulated with Zn^{2+} and phenol, which forms soluble multihexamers at the injection site, creating a subcutaneous depot. The zinc ions slowly diffuse into the blood stream allowing iDeg monomers to dissociate at a slow and steady rate. (35)(36)

IGlarLixi is a prefilled subcutaneous pen with fixed dose of insulin glargine (iGlar) and lixisenatide, available in two different strengths, 100U/ml + 33 µg/ml and 100U/ml + 50 µg/ml, recently approved in 2017 by EMA and in by 2016 FDA as Suliqua® and Soliqua®, respectively. (37)(38) It is indicated to once-daily administration, with maximum doses covering 15 to 60U of insulin glargine and 5 to 20µg of lixisenatide. The starting dosage is 15U (15U insulin glargine/5µg lixisenatide) in patients not controlled on less than 30U of basal insulin or lixisenatide, and 30 units (30U insulin glargine/10µg lixisenatide) in patients inadequately controlled on 30 to 60U of basal insulin. (38)

Insulin glargine, an improved long-acting basal insulin, is an analogue of human insulin, differing by some structural changes in both, A and B, insulin chains: the elongation of the B

chain with two arginine, and the replacement of the C-terminal asparagine by glycine in A chain, making it soluble at an acid pH. When administered, forms a precipitate in the subcutaneous tissue, which delays absorption and prolongs action. (37)(38)

4.3.3 Results obtained/clinical trials

To compare the efficacy and safety of iDegLira between insulin deglutec and liraglutide alone, a 26-week study, DUAL I, was performed in patients previously treated with metformin, with or without pioglitazone. In this first study, the primary outcome was the change in HbA_1c and secondary outcome included body weight and the number of hypoglycemic events. In another study, DUAL II, iDegLira was only compared to insulin degludec, in patients who previously received basal insulin. (35)(36)

In both of these phase III studies, the results were more favorable for the co-formulation, demonstrating a better glycemic control, lower adverse effects, commonly associated with GLP-1RAs and a decreased incidence of hypoglycemia episodes and weight gain insulin associated. The presence of liraglutide on the co-formulation covering PPG levels, allowed a reduction of the insulin dose to about 28% at the end of the DUAL I study. The number of patients experiencing nausea decreased significantly. The results of these studies are summarized in Table 5. (35)(36)

Table 5. *Comparative phase IIIa and IIIb clinical trial of iDegLira versus iDeg and Liraglutide* (35)(36)

	DUAL I			**DUAL II**	
	iDegLira	***iDeg***	***Liraglutide***	***iDegLira***	***iDeg***
HbA_1c	-1.9%	-1.4%	-1.3%	-1.9%	-0.9%
Body weight	-0.5kg	+1.6kg	-3.0kg	-2.7kg	0.0kg
Hypoglycemic events/ PYE	1.8	2.6	0.2	1.5	2.6

DUAL, Dual action of Liraglutide and iDegLira in type 2 diabetes; PYE, patient-year of exposure.

LixiLan-O trial (lixisenate and Lantus® insulin), was made to compare iGlarLixi to insulin glargine and lixisenatide monocomponents, in a population of insulin-naive patients and also on metformin therapy, a phase III study lasting 30 weeks. HbA_1c, body weight, PPG and FPG levels were evaluated, symptomatic hypoglycemia and the incidence of GI adverse effects were also documented. (37)(39) IGlarLixi presented advantages over its components separately concerning the PPG-lowering effect and mitigated weight. (39) Regarding FPG, results were similar to iGlar alone but greater when compared to lixisenatide.

The incidence of nausea and vomiting was also lower with iGlarLixi then with lixisenatide, 2.5% and 7.5% respectively. (37) Nevertheless, there were significantly fewer episodes of hypoglycemia with lixisenatide alone than with iGlarLixi, this occurred mainly in patients with HbA_1c levels>8%, which may be due to the higher doses of iGlad used in the combination. (37)(39) The results were presented in subpopulations of patients based on baseline HbA_1c (Table 6). (37)(39)

Table 6. *Comparative clinical trial of iGlarLixi versus iGlar and Lixisenatide* (37)(39)

LixiLan-O Trial	***IGlarLixi***		***iGlar***		***Lixisenatide***	
Baseline HbA_1c (%)	<8	≥8	<8	≥8	<8	≥8
HbA_1c (%)	-1.2	-1.9	-0.8	-1.6	-0.5	-1.1
FPG (mmol/L)	-2.8	-4.0	-2.2	-4.0	-0.8	-2.0
PPG (mmol/L)	-5.1	-6.9	-2.3	-4.2	-4.4	-5.1
Body weight (kg)	-0.7	0.1	0.5	1.6	-2.6	-2.1
Hypoglycemic events/PYE (%)	1.0	1.6	1.4	1.1	0.2	0.5

PYE, patient-year of exposure

Both formulations established additional benefits compared to their individually components. Between them, iDegLira showed less hypoglycemic episodes. (40) Besides, a clinical trial between liraglutide and lixisenatide, had greater glycemic results for liraglutide rather than lixisenatide (Table 7). (41) Regarding insulins, in BEGIN a phase III clinical trial, iDeg showed a lower glycemic control and higher weight gain (Table 7). (42)

Table 7. *Comparative clinical trials of co-formulations components* (40)(41)(42)

	iDeg	***iGlar***	***Liraglutide***	***Lixisenatide***
HbA_1c	-1.10%	-1.18%	-1.8%	-1.2%
Body weight	2.4kg	2.1kg	-4.3kg	-3.7kg
Hypoglycemic events/ PYE (%)	11.09	13.63	1.5	2.5
GI adverse effects	-	-	71.8%	63.9%
Clinical trial	BEGIN		-	

PYE, patient-year of exposure; BEGIN, basal-bolus type 2.

5. CONCLUSIONS

Fixed-dose combinations of GLP-1RAs and insulin have simplified treatment regimens and are particularly important for patients taking multiple medications. With synergic mechanisms, they attenuated adverse effects and problems of safety and tolerability.

Oral formulations of these combined drugs will provide better results by mimicking the endogenous pathways, having a safer profile and facilities in the administration. Mucoadhesive delivery systems may have a potential clinical application, a promising solution to the current difficulties of oral formulation therapies, an alternative to subcutaneous injections.

These add-on therapies are available in clinical practice for a relatively short period of time therefore, further investigations are needed to better assess their safety and efficacy.

The number of co-formulations with insulin and GLP1-RAs is still very small, however, they exist, indicating that their development is indeed technologically possible. In a very competitive market crowded with "me too" drugs, these type therapies could provide great advantages so more research will be certainly conducted at this level in the near future.

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