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Review Article

Importance of Information on Excipients with a Known Action or Effect in the Package Leaflet and an Oversight of the Situation in Albania

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ABSTRACT

Pharmaceutical dosage forms incorporate both Active Pharmaceutical Ingredients (APIs) and excipients, which aid in formulation and manufacturing processes. Excipients, often perceived as inert, can possess pharmacological effects or trigger adverse reactions, necessitating their declaration on medicine labels and package leaflets to ensure safe use. This review focuses on commonly used excipients in orally administered pharmaceuticals, highlighting their characteristics and potential adverse effects, particularly significant for over-the-counter medications where patient self-administration is common.

In the European Union (EU), regulations under Directive 2001/83/EC mandate the disclosure of excipients with known actions or effects on medicine labels and package leaflets. Conversely, Albania's regulatory framework, while aligning partially with EU directives, lacks specific guidelines for listing excipients with known effects in package leaflets, potentially compromising comprehensive patient safety information.

An observational study was conducted in the Albanian market to assess compliance with excipient information standards across various medicinal products. The study found that most products, except those from Canada and some Swiss companies, included information on excipients with known actions or effects in their package leaflets, despite varying regulatory requirements among exporting countries.

The discussion underscores the importance of regulatory harmonization to ensure consistent and adequate information on excipients, thereby enhancing medication safety and patient outcomes. It also identifies gaps in current regulatory frameworks, suggesting improvements for Albania to align more closely with EU standards and enhance patient protection.

In conclusion, addressing the information gap on excipients in pharmaceuticals is crucial for ensuring rational medication use and minimizing adverse effects. The findings stress the need for Albania to develop comprehensive guidelines and lists of excipients with known actions or effects, akin to EU standards, to enhance medication safety and regulatory compliance.

Keywords: Excipients; Adverse reactions; Regulatory landscape; Package leaflet; Observational study; Patient safety

INTRODUCTION

Pharmaceutical dosage forms contain both pharmacologically active compounds and excipients added to aid the formulation and manufacture of the subsequent dosage form for administration to patients [1]. While most excipients are considered inactive, some can have a known action or effect in certain circumstances while others may trigger undesirable effects due to intolerance a non-immune mechanism which leads to anaphylactic reactions and idiosyncrasies or allergies immune mechanism which may result in immediate or late hypersensitivity [2,3]. Unfortunately, excipients are difficult to avoid, therefore this information must be declared in the labelling and package leaflet of the medicine for its safe use.

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Following are presented the characteristics and adverse reactions of some of the most used excipients in pharmaceutical formulas for oral intake, being the latter the most commonly used medication administration route. This is important for all medicinal products, but especially for the inserts of over the counter medications, since it is presupposed that patients will use these drugs without the guidance of a physician [4].

- In young children, ethanol may cause hypoglycemia and hypoglycemic seizures. This awareness of the potential hazards of ethanol as an excipient has led to a push for a drop in the number of oral liquid medicines containing alcohol globally.
- In susceptible individuals, preservatives and dyes may cause adverse reactions.
- In diabetics, inadvertent intake of sugar-containing medicines may cause complications.
- In patients with phenylketonuria, aspartame may be harmful to take.
- In patients with rare hereditary intolerance to some sugars (e.g. fructose, glucose, galactose), their intake, or the intake of sucrose, maltitol (E 965), isomalt (E 953), sorbitol (E 420), sometimes above a certain quantity, may be harmful, etc.

Since the current law on drugs in Albania has been partially aligned with the directive 2001/83/EC of the European parliament and council regarding medicinal products for human use, a brief comparison between the EU and Albanian requirements for excipients with a known action or effect is presented [5].

EU regulatory landscape

The legal basis for requirements on excipient labelling in the EU is Article 65 of directive 2001/83/EC.

Marketing authorisation holders and applicants should list excipients on the medicine's labelling and in the package leaflet in line with the European Commission guideline on "Excipients in the labelling and package leaflet of medicines for human use". This guideline requires marketing authorisation holders to display excipients with a known action or effect in the following ways (Table 1).

Table 1: Display excipients with a known action or effect.

Type of excipient	Type of medicine	Type of information	Display location
Excipients with a known action or effect	All medicines	List of excipients	Labelling
		Agreed safety information	Package leaflet

These requirements apply to all medicines in the EU, irrespective of whether they are centrally or nationally authorised. The list of excipients that have a known action or effect, and which must appear on the labelling of all medicines in the EU, is available in the annex to the above EU guideline "Annex to guideline on 'Excipients in the labelling and package leaflet of medicines for human use"'. The annex also includes the safety information that must appear in the medicine's package leaflet for the listed excipients. EMA may revise the annex to update the required safety information on existing excipients, or to add new excipients [6].

Albanian regulatory landscape

In Albania, the legal basis for requirements on excipients labelling is the law on medicines and pharmaceutical service no. 105/2014 and the regulation for granting the marketing authorization of drugs and their classification in the Republic of Albania, Decision of the Council of Ministers no.299, 8.4.2015 (hereinafter regulation). The law only states that it is mandatory for all excipients with a known effect to be listed in the outer packaging of the medicinal product, and in the same way for all excipients of the product to be listed in the package leaflet. The Regulation gives a few further recommendations, including the requirement for injectables, topical and ocular products to have all their excipients listed in the outer packaging.

Therefore, there is no requirement in Albania to have the safety information related to excipients with a known action or effect in the package leaflet. There is no guideline stating which are the excipients with a known action or effect that should be listed in the labelling. Unlike EU regulatory landscape, it lacks the proposed safety recommendation text for the package leaflet depending on the route of administration, the threshold etc. This deficiency may indicate low emphasis on the respective aspects of product information requirements by regulators in Albania.

Availability of correct and adequate information about medicines is an important aspect in ensuring rational use of medicines and hence facilitating safety of medicines during therapy. The safe use of all medicines depends on users reading the labelling and package leaflet carefully and accurately and being able to assimilate and act on the information presented.

Package leaflets have proven to be a good source of information to the prescribers and patients whereby they have been useful in highlighting important information pertaining proper use and handling of the medicines. The information provided in the package leaflets is much needed also to decrease chances of negative effects related to medicines use.

It was therefore considered interesting to carry out an observation in the Albanian market about the presence in the leaflet of safety information for excipients with a known action or effect.

LITERATURE REVIEW

In Albania, by law, medicinal products from the following countries can be registered and sold in the market:

- Albania (domestic products).

- EU member states, USA, Canada, Turkey, Switzerland, Israel, Japan, Australia.
- Balkan countries solely when already registered and in the market in their respective countries.

Having present that products that come from the EU have the adequate information in the package leaflet about excipients with a known action or effect because of the requirement in their own countries, having present also that according WHO, the competent drug regulatory authorities of USA, Canada, Switzerland, Japan and Australia are amongst the world's stringent ones, it was also expected that products imported from those countries would give this kind of information.

An observation then was made in the Albanian market targeting mainly Albanian medicinal products, those coming from Balkan countries, Turkey and Israel with the aim of controlling if they give information in the package leaflet regarding excipients with a known action or effect. The observation included both prescription and OTC products, without making any particular distinction between them.

The observation focused on two directions:

- Collecting information about the legal requirements of each country on regard.
- Collecting leaflets from the Albanian pharmacies to check for the presence of such information.

Notwithstanding the fact that products imported from USA, Canada, Switzerland, Japan and Australia were supposed to give this kind of information, they were partly included in the observation by only collecting leaflets from the market.

Regarding the number of controlled products, for each company found to be present in the market, the leaflets of at least 10% of its registered medicinal products were evaluated, however not less than 2 leaflets per company.

From the National Register of registered medicinal products in Albania, the following data were obtained:

- 322 Albanian products, from a single company, actually circulating the market.
- 31 Kosovo products, from a single company, actually circulating the market.
- 60 Bosnian products, from 4 different companies; the products of 3 of them were found circulating the market.
- 88 Serbian products, from 3 different companies; the products of 3 of them were found circulating the market.
- 123 Macedonian products, from 3 different companies; the products of 3 of them were found circulating the market.
- 653 Turkish products, from 38 different companies; the products of over 12 of them were found circulating the market.
- 1 single product from Israel, not found to be circulating the market.
- 1 single product from Montenegro, not found to be circulating the market.
- 7 USA products, from 2 different companies, neither actually found in the market.
- No Japanese products (with Japanese MAH) are registered in Albania.
- 7 Australian products, from a single company, none actually found in the market.
- 119 Swiss products, from 8 different companies; the products of 6 of them were found circulating the market.
- 12 Canadian products, from 3 different companies; the products of 1 of them were found circulating the market.

In total, 94 leaflets were collected and read in line with the aim of the observation.

In the website of each competent authority was searched for the document related to the rules on the excipients with a known action or effect on the package leaflet of medicinal products. In absence of such information in the website, the competent authority was contacted by email.

- Montenegro has a recommendation to refer to the guideline of EMA for excipients.
- Bosnia and Herzegovina has an Annex VI of the ordinance on the conditions for granting marketing authorization dedicated to excipients.
- Turkey has translated into local language the Annex to EU guideline on 'Excipients in the labelling and package leaflet of medicines for human use".
- North Macedonia has translated into local language the Annex to EU guideline on 'Excipients in the labelling and package leaflet of medicines for human use".
- Kosovo, likewise Albania, doesn't have such guideline.
- For Serbia, no relevant information was found in the documents published in their website.
- For Israel, no relevant information was found in the documents published in their website.

From the analysed leaflets, it results that all of them, except Canadian products and the products of a Swiss company, present the information on excipients with a known action or effect in the package leaflet. This is good news for the Albanian patients, however it does not lift the duty of the Competent Authority to compile a dedicated guideline as the majority of countries have.

DISCUSSION

Due to the fact that some of the companies whose products were included in this observation, have an obligation in their countries to comply with the requirement for providing in the leaflets the appropriate information for excipients with a known action or effect, it was expected that their leaflets would be compliant to this rule.

Kosovo products were a surprise to have included such information not having the guideline in Kosovo, however it seems that the Marketing Authorization Holder, for export and development purposes, has exceeded the local regulatory framework.

The same can be confirmed for Albanian products, which, although numerous in number, have implemented the information based on the Annex to EU guideline on 'Excipients in the labelling and package leaflet of medicines for human use'. Regardless of the fact that the local medicines have implemented this information without having the detailed help or obligation

from the competent authority, this cannot however be left to the will of the company. The leadership of the DRA in the company can change, as well as the leadership of the company, causing their work practice to change as well, posing risk of potential harm to the patients. Furthermore, locally manufactured medicines may have in their formulation other excipients with known action or effect despite those included in the Annex of the EU guideline, for which the Albanian competent authority should take deliberate efforts to ensure that the relevant recommendations are available legally in Albania.

Canada and Switzerland may use other mechanisms to inform patients in their countries, e.g. through medical doctors who have access in other product information, such as the summary of product characteristics, however that is not applicable in Albania, therefore even for these products, an improved legal framework and an increased attention from regulators would be helpful.

CONCLUSION

The excipients in drug formulations have been described as inert because they do not have an active role in the prevention or treatment of particular ailments. This has led to the misconception among physicians, pharmacists, drug manufacturers and the public that excipients are harmless and unworthy of mention. The preventive measures of the European regulatory authorities show us that the former information vacuum on excipients may have contributed to unnecessary illness which is no longer acceptable.

Likewise, in Albania, what portion of health problems after taking medicinal products is due to excipients, is not known because in clinical practice some of the reactions caused by excipients may be commonly and mistakenly attributed to the medication active principle and it should be the target for future studies in Albania because the public deserves to be better protected.

There is a need for the regulatory authorities in Albania to:

- Complete the legal framework by adding the requirements for the package leaflet related to excipients with a known action or effect and also.
- To provide a list similar to that of the Annex of the EU guideline with the concerned excipients listed and the appropriate warning safety instructions clearly and explicitly written in Albanian language. Without this list, the actual legal requirement of stating in the outer package the excipients with a known action or effect, is practically incomplete and not applicable for mainly Albanian and Kosovo products, therefore not adequate.

Insistance on having adequate and thorough information on all medicines given to the patients is of paramount importance for the protection of their health and realizing maximum benefits of treatment, and hence compulsory inclusion of detailed and accurate information on excipients should be emphasized.

LIMITATIONS

The limitations encountered during the study were that the Competent Authorities of Serbia and Israel did not answer through email. In the documents published in their websites, nothing available in English was found related to the excipients with a known action or effect and their presentation in the package leaflet.

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