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Possibilities of applying information technologies and digitalization in pharmacovigilance, with special reference to safety interventions at the level of drug prescription

Author:

Viola Macolić Šarinić

European Medicines Agency

Amsterdam, Netherlands

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INTRODUCTION

Risk minimisation measures (RMMs) in pharmacovigilance are one of the most important tools used in the post-authorisation phase in a human medicinal product (MP) lifecycle to maintain its benefit/risk balance positive and ensure the safe use of medicine. The RMMs are part of the Risk management plan (RMP) of the product which are already set in the time of granting marketing authorisation (MA) by the regulatory authority (routine and additional RMM). In addition, they can be introduced later during the post-authorisation safety surveillance phase as an outcome of a signal assessment, assessment of the Periodic update safety report (PSUR), assessment of the final report of a post-authorisation safety study (PASS) or as an outcome of a safety referral for a specific medicinal product / active substance or a class of products. This refers to the Pharmacovigilance system in the European Union (EU) which is laid down in Regulation (EC) No 726/2004, Directive 2001/83/EC, and Commission Implementing Regulation (EU) No 520/2012 (1-3).

Montenegro as an EU accession candidate country has transferred the EU Directive into the national legislation. With that the same regulatory obligations regarding RMMs apply.

This paper discusses the possibilities of using healthcare information technologies and digitalization in pharmacovigilance to implement RMMs for a specific medicinal product, with additional reference to safety interventions at the step of electronic drug prescribing (E-prescribing) when available.

RISK MINIMISATION MEASURES: IMPLEMENTATION VIA DIGITAL TOOLS

In the EU a set of measures are drawn up to facilitate the introduction and facilitation of the pharmacovigilance activities laid down in the EU legislation (1-3). The set of measures is called "Good pharmacovigilance practices" (GVP) which are European medicines agency's (EMA) and Heads of medicines agencies' (HMA) documents. They are published at the EMA corporative website (4). The GVPs apply to marketing authorisation holders (MAHs) in the EU, the EMA, and the national regulatory authorities (NRA) of the 27 member states and Norway and Island (4). As the GVPs are publicly available they have been used in many countries outside the EU as well and served as a basis for the development of their own national guidelines on pharmacovigilance bringing the example of Nigeria (5).

The actual EU GVP guideline which refers to RMM is the *GVP module XVI guideline on Risk minimisation measures: selection of tools and effectiveness indicators* is under the third revision, and it is foreseen to be finalized and come into effect in 2023 (6). The EMA communicated to the companies (MAHs) through its stakeholders' meetings that the GVP XVI text under revision could be already used for local implementation as no major editorial changes after receiving the comments from the public consultation are envisaged.

We distinguish two kinds of Risk minimisation measures (RMM):

- Routine, and
- Additional

The routine risk minimisation measure is the safety information given through the Summary of Product Characteristics (SmPC) and the Patient Information Leaflet (PIL) for healthcare professionals (HCP) and patients and consumers in the EU. In the EU these documents must be distributed by the MAHs, but also must be published at the EMA corporative website for centralized authorised products (CAPs) in all official European languages and at the national regulatory authorities' websites for national authorized products (NAPs). The obligation of the HCPs is to familiarize themselves with the information for prescribing and dispensing of the medicinal product, and for the patients there is the possibility to consult the PIL as part of the medicinal product packaging or via the available web sites in their national languages.

In view of the possible implementation of the SmPC in healthcare or prescribing databases the development of an electronic SmPC (e-SmPC) is important which is ongoing on level of the EU regulatory network. This project was launched already at the beginning of 2020 by the EU regulatory network (EMA and HMA). Digital platforms open additional possibilities to disseminate the Product information (PI) electronically. This can address some of the current limitations (e.g., the current PI is not interoperable with other electronic health systems such as e-

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prescription and electronic health records) and better meet patients' and healthcare professionals' needs for accessible, trustworthy, and up-to-date information on medicines available at the right time (7). The lead is taken by the EMA, and the aim is to develop the technology to support the implementation of the different sections of the SmPC in different digital tools for an easier and focused overview and faster search for key information for HCPs (prescribers and dispensers) and eventually for the patients (7, 8). This important work which is again accelerated in 2022 (after the pandemic pause) is of importance for the integration of the PI for the Montenegro's medicinal and healthcare authority as well and must be followed closely to be able to integrate the digitalized national system to the EU one especially focusing on Centralized authorised products (CAPs).

This paper focuses primary on the additional RMMs (aRMMs) which are categorized as Educational materials (EM), Direct healthcare professional communications (DHPCs), Pregnancy prevention programmes (PPPs) and Controlled access programmes. aRMMs are imposed for important identified and potential risks which are listed in the Risk management plan (RMP) for the concerned product. The section XVI.B.3 of the GVP Module XVI (6) highlights the possible tools which should be used to disseminate these additional RMMs introducing also the possibility to use digital tools: *"As digital technology advances, the potential of electronic dissemination, such as through web and app-based mechanisms, allowing for fast dissemination of updated information to the appropriate target audience(s) and for interactions between patients and healthcare professionals, or for safety systems independent from location, may be considered in addition to paper-based materials"* (6). The regulator introduces the digital tool in parallel to paper-based materials and sees it in the moment as a support but not as a standalone dissemination tool for a respective RMM.

Educational materials (EM)

Educational materials (EM) are imposed by the regulatory authority and developed by the MAH (as per RMP) for encouraging discussions between HCPs and patients in relation to the safety concern(s) and RMM when the objectives of RMM cannot be reached with the SmPC and PL alone. The EM must not be a copy of the SmPC and/or PIL but should be linked to these documents. In case of digital EM, it can be referred to SmPC for prescribers to a hyperlink (PDF) but also integrate the electronic SmPC when it becomes available in the prescribing database. Addendum I of the GVP module XVI gives further guidance on how to develop educational materials for HCP and patients (6).

As per GVP XVI (Rev 3) EMs have been divided in several categories (6). Here the EMs are listed which could be suitable to be integrated in the prescribing database to support safe prescribing of medicines:

- Guides for patients or healthcare professionals for risk minimisation

These guides have the objectives, among others, to enhance awareness of a specific risk associated with the medicinal product and risk factors the patient has and herewith guides the patient selection. In addition, EMs are aimed to instruct how to prevent, how to early recognise and timely manage Adverse drug reactions (ADRs) during the treatment and highlighting additional monitoring regiments during the treatment (blood sampling, diagnostic

tests, ECG etc). Guidance on the preparation or administration of the product where these processes are complex, e.g., in the case of patient/caregiver-administered infusions at home can also be given through these EMs.

The implementation of these guides in the prescription database could alert the prescriber on the key safety elements from the guide with the possibility to electronically view the Guide and send the link to the patient guide to the patient or print the patient guide directly when the medicine is prescribed (Physician) or later when the medicine is dispensed (Pharmacists).

- Healthcare professional checklists for risk minimisation

A healthcare professional checklist is a tool that lists actions aiming to support the prescriber or dispenser to check and record the presence or absence of certain clinical circumstances for risk minimisation. It is to be considered in situations where the safe and effective use of a medicinal product involves complex approaches and decision-making regarding the diagnosis, treatment, prescribing or dispensing, or when the treatment carries a high risk of medication errors (6).

The checklists can be important in the time of prescribing or in the time of dispensing. The checklist should be integrated in the prescription database in the way that the mandatory checklist has to be filled out before the system allows that the prescription is issued (prescriber) or before the medicinal product is handed out (dispenser).

Typical objectives of checklists include to check for contraindications, warnings, concomitant medicines or certain diagnostic test parameters, exclude pregnancy before and during treatment, use of contraception, inform about possible medication errors etc (6).

- Patient cards

A patient card is a tool that reminds the patient of (a) certain action(s) to take for risk minimisation or aims to ensure that information regarding the patient's current treatment with the medicinal product and its risks is held by the patient at all times and used as a communication aid with healthcare professionals. It is to be considered in situations where it is essential for risk minimisation that this information is always readily available to the patient and healthcare professionals (6).

These cards are mostly attached to the outer packaging of the dispensed medicines, but the opportunity to integrate them in the prescriber digital tool should not be omitted as there is the opportunity to print the card (paper format) and hand it out to the patient during the time of prescription/handing out the medicinal product. It has to be aimed for that the patient card could be stored in a digital format at the smart phone of the patient (wallet) and that the prescribing database has the option to send the link to the patients mobile phone to be downloaded in the digital form.

<u>Direct healthcare professional communications (DHPC)</u>

A direct healthcare professional communication (DHPC) is a safety communication tool that may also serve as an additional RMM. It is to be considered in situations where it is deemed important that all relevant HCPs in the given jurisdiction are timely informed of a risk and actions to take for risk minimisation (6).

The DHPC is an "one point in time" intervention, but it should be available to the prescribers/dispensers during the whole time this information is valuable and an obvious digital tool which can support this function is definitely an e-prescriber database. The DHPC has to be integrated in the prescribing database in the way when the medicinal product is prescribed this information and link to the DHPC "pops" up and bring it to the attention of the prescriber/dispenser of the medicinal product. Today the DHPCs are mostly available in a PDF format, but for the future an e-DHPC has to be introduced for a smoother integration of the letter.

The disadvantage of "popping" up of this kind of messages which could already be found in some EU member states is that all sort of communication is called "DHPC" and not only the defined safety one (GVP XVI Annex) (6). This leads to an over information and cases are described that prescribers turn off this link as this is too disturbing for them, and with this also the safety letters will not show up. This has to be tackled in the way that it has to distinguished between information on the medicinal product which covers shortage, other regulatory information, and the real safety DHPC. There is an example that in one member state in their e-prescriber database more than 3000 of such letters are integrated and published in the database in the last 2 years which are eventually turned off by most of the prescribers to be shown when prescribing. In a national unpublished survey, they also address them as "disturbing".

Pregnancy prevention programmes (PPP)

A pregnancy prevention programme (PPP) is a set of tools that aims at minimising exposure to a medicinal product during pregnancy. It is to be considered in situations where the product has teratogenic effects (6). This is the most discussed part of the GVP module XVI, and it relates to the definition and objectives of a PPP. Different views are expressed – to have a strong framework on what has to be fulfilled to call the program "pregnancy prevention" and in the other way to have elements of the PPP and be more flexible in what has to be used in certain situations.

The typical objectives of the PPP are to avoid that female patient are pregnant when starting the treatment and avoid that female patient become pregnant during and, if relevant, for a specific period after stopping treatment (6).

Here a combination of different routine and additional RMM has to be envisaged and as mentioned above several type of educational materials could be integrated in the prescription database – guidance for HCPs and patients with integrated checklists before issuing a prescription. The control access tools (see below) should be part of the e-prescribing algorithm which would allow the issuing of the prescription for the medicinal product only if it is ensured that a pregnancy test is carried out and negative results are verified by the healthcare professional before prescribing or dispensing of the medicinal product. In the e-prescription database an algorithm can be introduced which restricts the amount to be prescribed in a single prescription, often to a maximum supply of 30 days for example.

Controlled access programmes (CAP)

A CAP is a tool or set of tools that seeks to control access to a medicinal product beyond the level of control applied to medicinal products by means of routine RMM. It may restrict the time period of validity of a prescription or the maximum amount to be prescribed in a single prescription or require a visual reminder as part of the labelling of the outer packaging. CAPs should be considered and applied only in exceptional situations of an important safety concern with a severe impact on the patient or the child exposed in utero, or a significant public health impact, considering the nature of the risk and the likelihood that this risk cannot be managed by other RMM. (6)

Tools for CAP which can be applied by their own or in combination and could be integrated into the e-prescription database per GVP XVI (revision 3) (6) are as follow:

- Controlled prescription and supply systems

This envisages tracking up of the prescription or dispensing the products (batch number, date of prescription/dispensing)

- Centre accreditation systems

The system alerts that the prescription can be done only in certain accredited hospitals/pharmacies for example with an integrated algorithm that only these institutions or individual prescriber can prescribe/dispend the medicine.

- Forms for patient information exchange between prescriber and dispenser

Integration of forms in the prescriber database to ensure that the physician / pharmacist is informed about legally required test results before the product is dispensed, e.g., pregnancy test. This information exchange can take place.

- Dispensing forms

A dispensing form is a tool that supports risk minimisation during dispensing. It is to be considered in situations where it is intended to e.g., manage dispensing complex medicines, those requiring certain monitoring or testing within limited time before dispensing or those that require that certain information is transmitted from one healthcare professional to another (6). This part is important on the level of the pharmacist dispensing the medicine. This algorithm should be in place to allow that after prescription the dispension is made in the right way and will allow dispensing the medicine only when all the requirements are fulfilled.

Dissemination plans

The GVP XVI (rev 3) is emphasising the importance of the submission of plans for the dissemination of RMM by the MAHs which were agreed with the NRAs to HCPs and patients (6). The GVP module is mostly focused on the paper based dissemination of RMM (additional and routine), but this should also apply when implementing the RMM in digital databases and using of digital tools.

The MAH has to plan how the integration of the RMMs in the prescriber database has to happen in collaboration with the NRA (and healthcare provider) as they have to prepare the documents in line with the agreed key elements for digital integration. The GVP talks about periodically repeated delivery of educational materials to patients and HCPs which would not apply any more if digitally integrated – only the updates have to be planned if there is a change in the EM.

MEASURING THE EFFECTIVENESS OF THE IMPLEMENTED RMMS

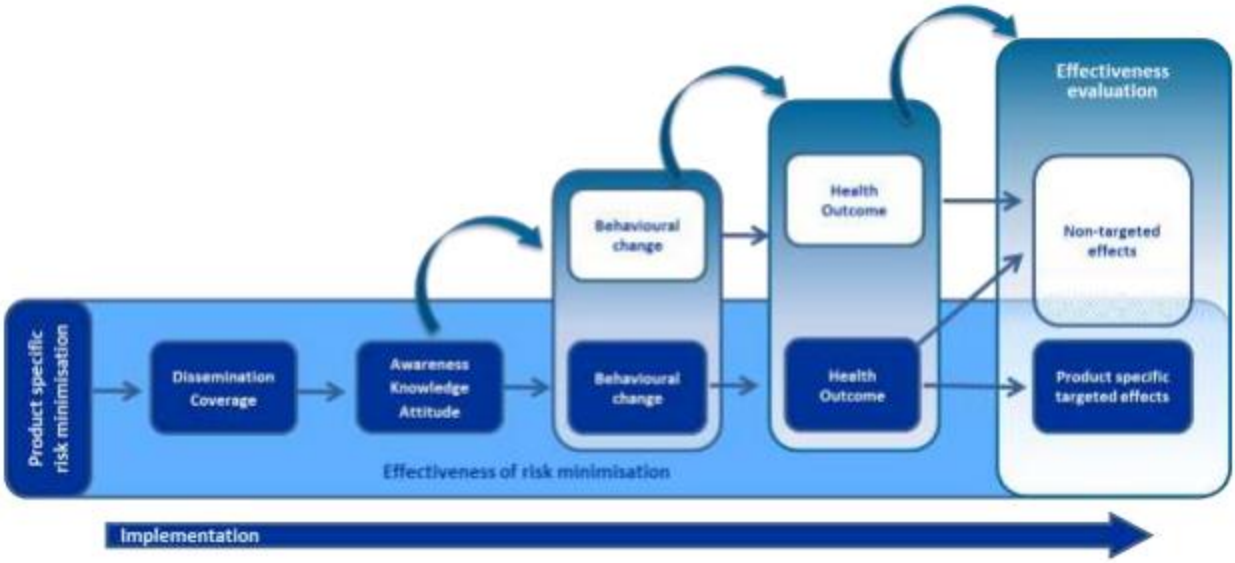
The European legislation (1-3) lays down that the risk minimisation measures (aRMM) have to be measured by their effectiveness to understand if the measures can ensure the positive benefit/risk balance for the medicinal product where the aRMM are introduced. For additional RMMs this is done by requesting Post authorisation studies (PASS) to the MAHs by the regulatory authority (PRAC or NRAs for products marketed only in that MS) which can be imposed (part of marketing authorisation (MA) decision and listed in the RMP) and non-imposed (listed only in the RMP).

The GVP guideline XVI (3rd revision) (6) elaborates this requirement in more details. The principles are described as follow (6): *"MAHs shall monitor the outcome of RMMs which are contained in the RMP, or which are laid down as conditions of the marketing authorisation pursuant to Articles 21a, 22 or 22a 518 [DIR Art 104 (3) (d)]. NRAs shall monitor the outcome of RMM which are contained in RMPs or measures that are laid down as conditions to the marketing authorisations [DIR Art 107h (1), REG Art 28a]. Monitoring RMM outcomes is intended to evaluate the effectiveness of RMM and may include both routine and additional RMM. Any study measuring the effectiveness of RMM is a PASS [DIR Art 1 (15)] and the guidance for conducting a PASS in GVP Module VIII should be followed for studies evaluating the effectiveness of RMM in addition to the specific guidance in this GVP module. The guidance on methods for effectiveness evaluation in GVP Module XVI - Addendum II should be followed and protocols for qualitative studies be included in the pharmacovigilance plan of the RMP (see GVP Module V)".*

The GVP XVI module (rev 3) highlights for the first time the evaluation of the intended and unintended outcomes (6). The Table XVI.1 on effects of regulatory actions on medicinal products is shown below (6):

	Intended	Unintended
Switching	RMM recommends that patients are switched to alternative therapy	Patients are switched to a treatment that has a less favourable safety profile
Spill-over effect	RMM recommends that the treatment is no longer used in a certain patient population and patients are switched to alternative therapy	Treatment is withheld in a patient population that is not targeted by the RMM and where the treatment can be used
Non-treatment	RMM no longer recommends the use of a medicine in indications where the therapeutic benefit is no longer considered to outweigh the risks	No alternative medicine is used in some patients of the target population to treat the condition even though alternatives are available
Lack of adherence	N/A	RMM is not adhered to in the target population
Additional prescribing	RMM recommends the use of a medicine in the target population in combination with another therapy (e.g. as preventive measure)	RMM no longer recommends the use of a medicine in the target population, but treatment is continued in combination with another medicine (e.g. to treat adverse reactions) and the recommendation is not adhered to

Furthermore, the figure XVI.1 “The approach to effectiveness evaluation of risk minimisation includes measuring medicinal product specific targeted effects and, as appropriate, relevant non-targeted effects associated with the use of the concerned and other medicinal products” from GVP module XVI (rev 3) (6) is of most importance to understand not only the regulatory impact but the wider impact on the healthcare system and to public health in its whole:



The e-prescription database is not only the digital basis and tool to implement the risk minimisation measures – e-SmPC and additional Risk minimisation measures but also the tool to measure the impact of these measures implemented in the way that studies on drug utilisation can be performed, patient characteristics and their health outcome can be followed up.

As prescription databases and healthcare data bases are in a development phase in most of the member states only a few databases are available for such analysis from Germany, Italy, Spain, and the Scandinavian countries. Also, many of the study aims cannot yet be performed as the data is insufficient (not enough data, short time used, not fully populated etc.)

In that regard it is essential to agree on the key elements a digital prescription/healthcare database has to have to be able to query the database in an efficient way.

In the case that the efficacy study on RMM in place goes beyond the efficacy of the RMM ensuring the safe use of a specific medicinal product the PASS has to be conducted by the national regulatory authorities or in the case of the EU the EMA has to contract such studies outside the specific RMP for a specific product. To be transparent on the protocols and outcome and these studies EMA has set a specific web link at the EMA corporate web site where the link to the study documents can be found. The outcomes of the studies have to be used in the regulatory safety procedures for the individual concerned medicinal products by the Marketing authorisation holder and have to be considered during the assessment of the documents by the EMA and NRAs. In the last ten years of the EU pharmacovigilance legislation coming in force EMA has contracted several institutions to conduct research projects

collecting and analysing real-world data from clinical practice to help monitor the safety and effectiveness of medicines (9). The following studies were performed:

- Changes in alternative treatments for pain and cough in children after introduction of risk minimisation measures for codeine (10)
- Codeine prescribing and use of the treatment of pain in children (11)
- Covid-19 vaccines awareness and adherence to risk minimisation measure for thrombosis with TTS (12)
- Diclofenac prescribing and use in patients with cardiovascular risk (13)
- EU Risk minimisation implementation in clinical guidelines (14)
- Fluoroquinolones: use and prescribing patterns in patients with tendinitis, tendon rupture and aortic aneurism/dissection (15)
- Hydrozyzine prescribing and use in patients at the risk of QT prolongation and cardiac arrhythmia (16)
- Methotrexate awareness and adherence to measure avoiding dosing errors (17)
- Ranitidine-containing medicines: exposure and use patterns with alternative treatments (18)
- Retinoid awareness and adherence during pregnancy or potential childbearing potential (19)
- Retinoid prescription and use patterns during pregnancy or childbearing potential (20)
- Single arm studies with historical controls for cancer drug development (21)
- Trade-offs between benefits and harms of drugs in cancer patients (22)
- Strengthening use of real -world data in medicines development (23)
- Valproate awareness and adherence during pregnancy or potential childbearing (24)
- Valproate prescription and use patterns during pregnancy or potential childbearing (25)

The diclofenac PASS (13) was commissioned by the EMA under the PRAC strategy on measuring the impact of pharmacovigilance activities (26) which is of interest for this project as the study aims are comparable to the study project in Montenegro determinizing the:

- How medicines containing diclofenac are prescribed before and after the Article 31 referral from 2013 (27)
- Prescriber compliance with product information warnings about cardiovascular risk factors
- Prescriber compliance with the product information recommendation to avoid diclofenac in patients with certain cardiovascular diseases
- Drug use and prescribing patterns for alternative treatments in patients who previously used diclofenac

The final results of the study were made available in March 2019 and are published in the EU PAS Registry (28). The results of the study were as follow: The cohorts consisted of 5.6 million in Denmark, 5.3 million in Scotland, 4.2 million in England and 1 million in the Netherlands. The most common indication for diclofenac in all countries among those assessed was osteoarthritis. In all countries diclofenac prescribing fell during the overall observation period. The 2013 EMA regulatory intervention was associated with a significant: immediate reduction in diclofenac initiation in the Netherlands (-0.42%, 95%CI -0.66% to -0.18%), England (-0.09%, 95%CI -0.11% to -0.08%) and Scotland (-0.67%,

95%CI -0.79% to -0.55%) but no significant immediate impact on diclofenac discontinuation; a falling trend in diclofenac initiation in the Netherlands (-0.03%, 95%CI -0.06% to -0.01%) and Scotland (-0.04%, 95%CI -0.05 to -0.02%), and no statistically significant rising trend in diclofenac discontinuation. The overall conclusion of the study is that the 2013 EMA referral was associated with reductions in overall diclofenac prescribing the extent of which varied by country and type of exposure. Although significant reductions in diclofenac initiation occurred, patients with contraindications continued to be prescribed diclofenac, the extent of which varied by country and target condition. Understanding reasons for such variation may help to guide the design or dissemination of future safety warnings (29, 30, 31). In this study the prescription rate for different patient populations were analysed pre- and post-introduction of the aRMMs by the EMA. The study does not analyze how the risk minimisation measures were disseminated to the HCPs and patients in the concerned member states and it does not address the possible use of digital tools in approaching the information by the prescribers, dispensers, and patients but it is seen as key in the conclusion of the study report.

The project in Montenegro has the opportunity not only to address the prescription of diclofenac pre and post introduction of the RMM in Montenegro but also to analyze the impact of the digital tool (prescriber database, e-prescription) on the prescription of the medicine in the right dose avoiding patients at risk (cardiovascular disease).

The above mentioned PASSs commissioned by EMA and conducted to measure the effectiveness of the introduced RMMs do not distinguish the impact between the paper based RMMs and RMMs dispended through digital tools such as national e-prescription databases at all (10-25) but it is seen as key factors on which future studies have to be designed for.

KEY FINDINGS

Key Findings #1

In the EU the relevant legislation and Good pharmacovigilance practice (GVP) guidance bases the implementation of RMM in principle on paper based routine (SmPC and PIL) and additional risk minimisation measures (RMM). Only the latest revision of the GVP module XVI (Revision 3) is mentioning digital tools as tools for a potential for disseminating RMM, but also only in additional to paper based information. The discussion on the implementation and key principles for the implementation of the digital tools for RMM is ongoing on the level of the EU – in the first place the implementation of e-SmPCs and additional RMMs such as educational materials and DHPCs.

Key Findings #2

No research so far was done to understand the differences between paper based RMMs and RMMs implemented through digital tools. The reason could be the underdevelopment of e-prescription databases or other digital tools in the last 10 years when the measurement of the impact of RMMs in the EU became mandatory. This is an area which needs further investigation.

Key Findings #3

Some unpublished data from EU member states suggest that an overload of safety data in e-prescription databases could lead to the opposite effect when prescribers delete the safety information which appears in the e-prescription database. Some unpublished data suggests that this kind of information seen by the prescribers as an unpleasant, not useful, and annoying feature. Additional research in this regard has to be initiated.

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CONCLUSION

The implementation of the RMM in the e-prescription databases in Montenegro starting with diclofenac RMMs is a pioneer's step forward in tailoring the optimal way of disseminating the RMMs with the consequence of rational and safe prescribing in changing the prescribers' behaviour where the individual patient is protected, and the public health is enhanced.

To achieve the optimal implementation of the RMM especially the development of the key elements on e-SMPC/PIL has to be followed up closely in Montenegro which will bring the optimal environment to implement all information on EU centralised procedures (CAP) medicines as well.

It is not known if the implementation of the RMMs through digital tools actually brings a better knowledge to the prescriber, dispenser and patients and it is not known if this way of dissemination of the safety information enhances the behavior of the physicians, pharmacists, and patients for a safer use of medicines as this was not part of PASSs conducted in the EU so far. This should be in particular investigated as there is lack of this information Europe wide.

Further implementation of RMM through digital tools for other medicines beyond diclofenac, which is serving as a pilot, will put Montenegro's healthcare system to the leading countries in Europe in implementing new IT technologies and in this way enhances the needed close collaboration between the regulatory network and the healthcare system, as both have the same aim to make medicines safer in their use and improve public health.

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Joint EU-MNE Programme for
Employment, Education and Social Welfare

WP5

Prescribing and consumption of diclofenac in patients with or at high risk of cardiovascular diseases after new recommendations related to its cardiovascular adverse effects

Author:

Silva Dobrić

University of Defence

Faculty of Medicine of the Military Medical Academy

Belgrade, Serbia

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1. Introduction

In 2013, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) concluded that the effects of diclofenac on the heart and circulation when given systemically were similar to those of selective COX-2 inhibitors and recommended to apply the same cardiovascular (CV) precautions as for selective COX-2 inhibitors in to appropriate sections of the Summary of Product Characteristics (SPC) and Patient Information Leaflet (PIL) or Package Leaflet of systemic formulations of diclofenac. These new recommendations include (European Medicine Agency, 2013):

Summary of Product Characteristics

Section 4.2 Posology and method of administration:
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4 Special warnings and precautions for use).
Section 4.3 Contraindications:
Established congestive heart failure (CHF) (NYHA II-IV), ischemic heart disease (IHD), peripheral arterial disease (PAD) and/or cerebrovascular disease (CVD).
Section 4.4 Special warnings and precautions for use:
Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration.
As the CV risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.
Section 4.8 Undesirable effects:
Clinical trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high dose (150mg daily) and in long term treatment. (see section 4.3 and 4.4 for Contraindications and Special warnings and special precautions for use).

Package Leaflet

Section 2 "What you need to know before you take diclofenac containing medicinal product"

Do not use diclofenac:
- if you have established heart disease and /or cerebrovascular disease e.g. if you have had a heart attack, stroke, mini-stroke (TIA) or blockages to blood vessels to the heart or brain or an operation to clear or bypass blockages
- if you have or have had problems with your blood circulation (peripheral arterial disease)

Make sure your doctor knows, before you are given diclofenac
- if you smoke
- if you have diabetes
- if you have angina, blood clots, high blood pressure, raised cholesterol or raised triglycerides.

Side effects may be minimised by using the lowest effective dose for the shortest duration necessary.

Conditions and diseases listed above as contraindications and precautions are common conditions among the general population and therefore the target population is large.
Considering the high consumption of non-steroidal antiinflammatory drugs (NSAIDs), and especially diclofenac, around the world, non-compliance with these recommendations can have serious consequences for public health. Therefore, it is very important to investigate to what extent the mentioned recommendations influenced the prescription of diclofenac to patients with CV diseases or diseases that represent a risk for their development.

2. Analysis of literature data

So far, only one study has been conducted, the aim of which was to establish the the impact of EMA recommendations on CV contraindications (IHD, CHF, PAD, CVD), and special warnings and precautions (hypertension, hyperlipidaemia, diabetes mellitus), which were a part of EU SPC for diclofenac, in prescribing of this medicine to patients with CV diseases/risk for CV diseases (Morales et al, 2020). The study was conducted in four European countries: Denmark, Holland, England and Scotland. The data sources for prescribing diclofenac in these countries were register of medicines that also included the data on prescribing diclofenac (Denmark), data on prescribing it in primary and secondary healthcare including pharmacies (Netherlands), data on prescribing it in primary healthcare (England) and data on dispensing diclofenac in pharmacies (Scotland). In all of the above countries, implementation of SPC with new CV safety information resulted in decrease in prescribing diclofenac. Results have shown that EMA recommendations have led to significant *immediate* (first three months after introducing EMA recommendation) absolute decrease in prescribing diclofenac in all countries to patients with IHD, PAD and hyperlipidaemia, in Netherland**s**, England and Scotland to patients with hypertension and diabetes, and in England and Scotland to patients with CHF and CVD. Within the time period after three months following the adoption of EMA recommendation (*post-intervention*) a significant decrease has been noted in prescribing diclofenac in Netherlands to patients with IHD, PAD, hypertension, hyperlipidaemia and diabetes and in Scotland to patients with CHF, IHD, PAD and hypertension. In England, the rates of prescribing diclofenac have gradually descended, while in Denmark the changes related to prescribing practice had been more prominent after the earlier analysis of EMA experts on CV safety risks of systemic administration of diclofenac in 2012 (Figures 1-4).

In the conclusion of this study the authors indicate that, although a significant decline in prescribing diclofenac has been reached, thanks to the introduction of EMA recommendations in clinical practice of these countries, to certain patients with CV diseases constituting contraindications for prescribing it, it is still prescribed, in a scope differing from one country to the other and depending on the type of the contraindication.

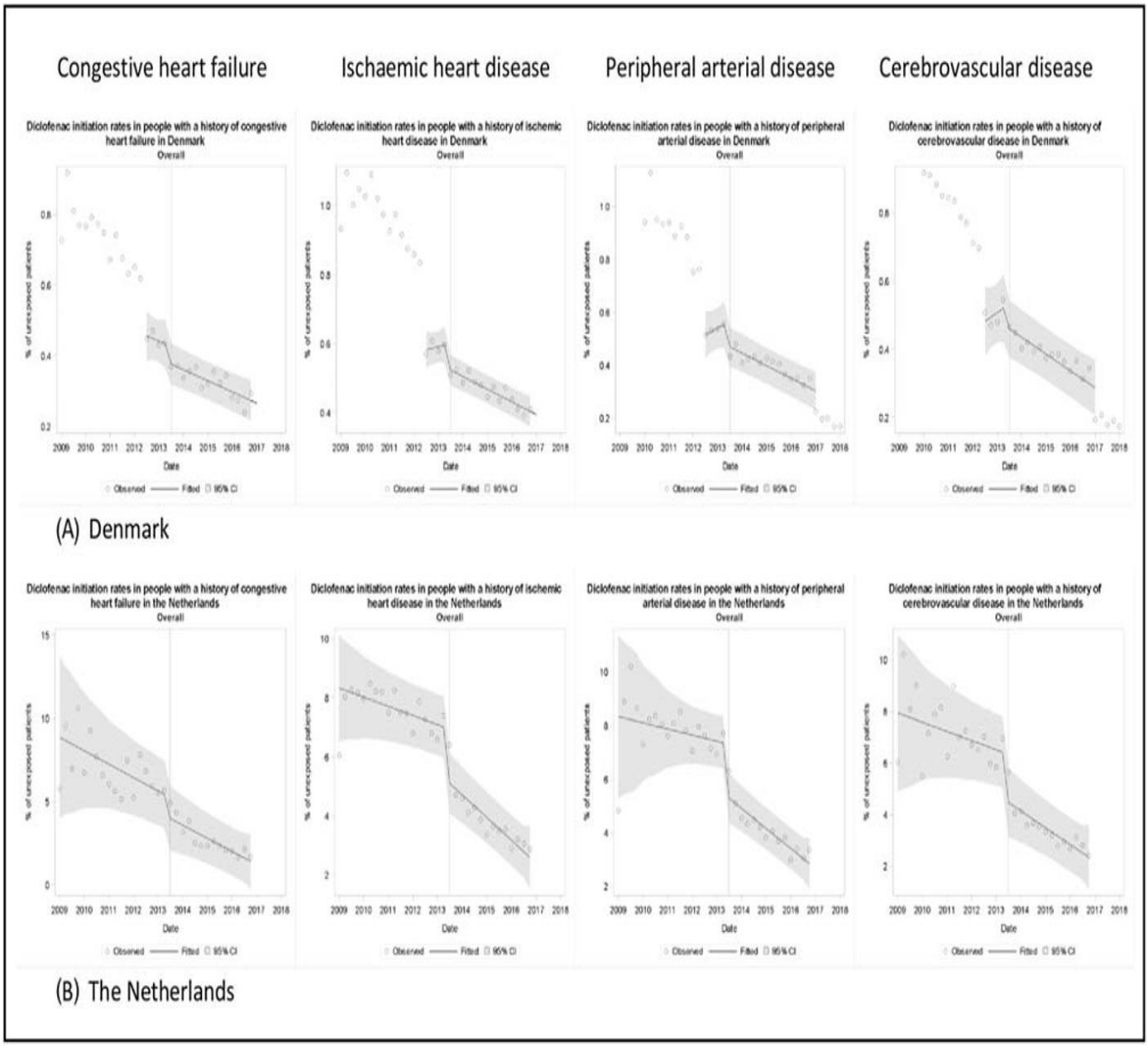

Figure 1. Diclofenac initiation rates in patients with new contraindications following the 2013 EMA regulatory action in (A) Denmark and (B) the Netherlands (Morales et al, 2020)

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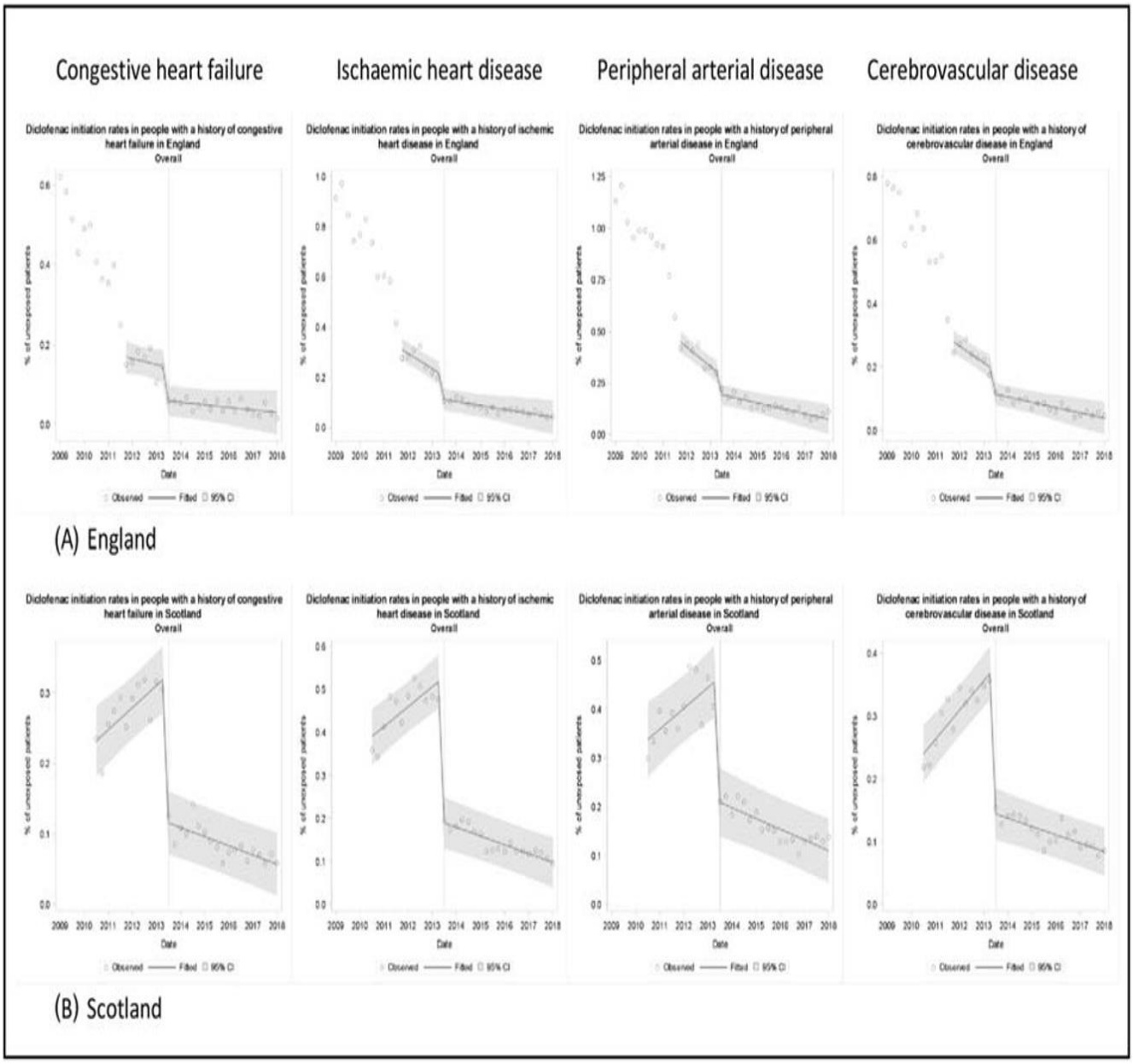

Figure 2. Diclofenac initiation rates in patients with new contraindications following the 2013 EMA regulatory action in (A) England and (B) Scotland (Morales et al, 2020).

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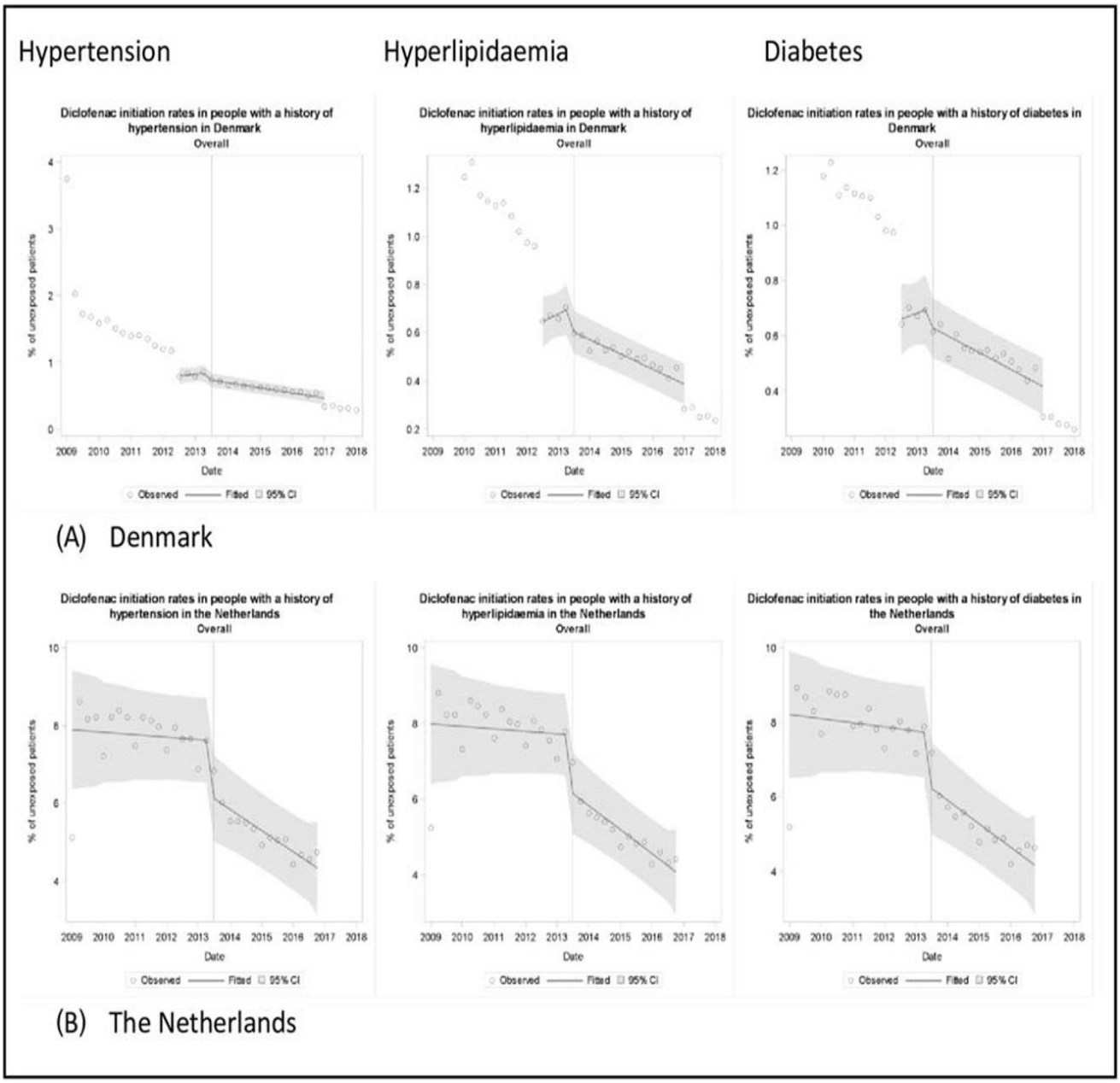
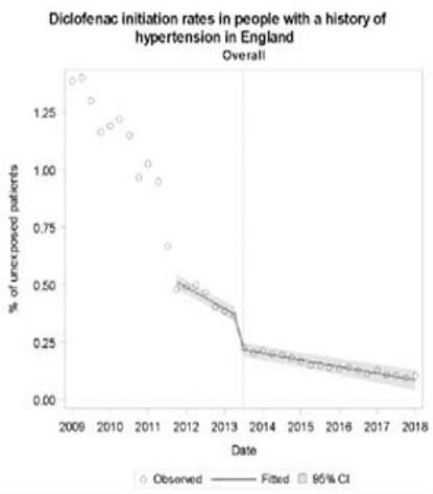
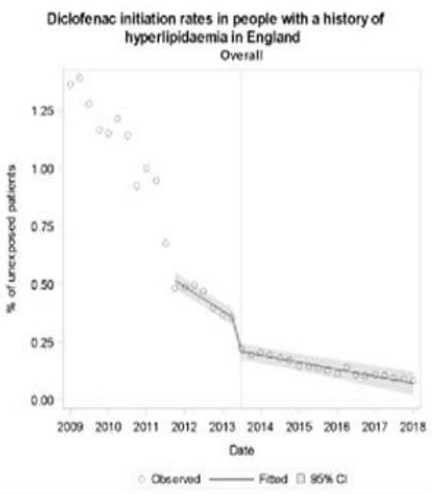


Figure 3. Diclofenac initiation rates in patients with new cautions following the 2013 EMA regulatory action in (A) Denmark and (B) the Netherlands (Morales et al, 2020)

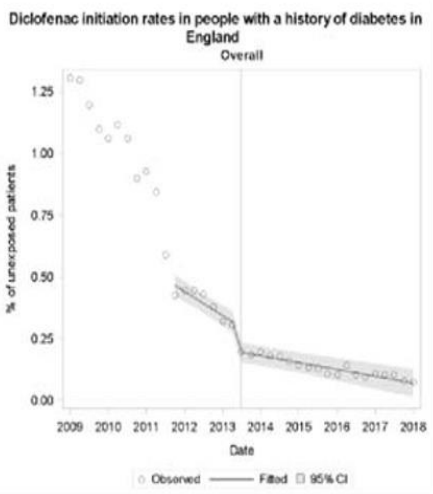
Hypertension



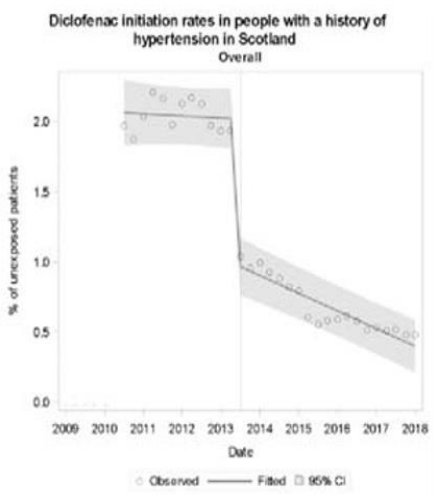
Hyperlipidaemia

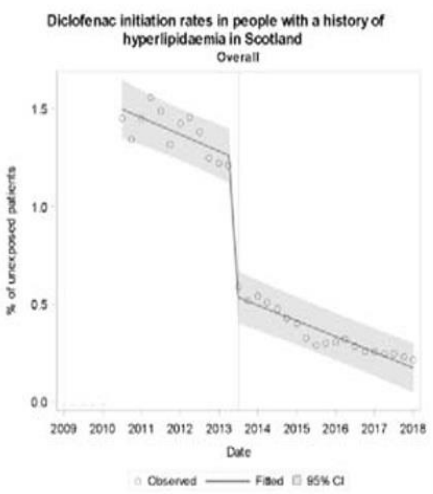


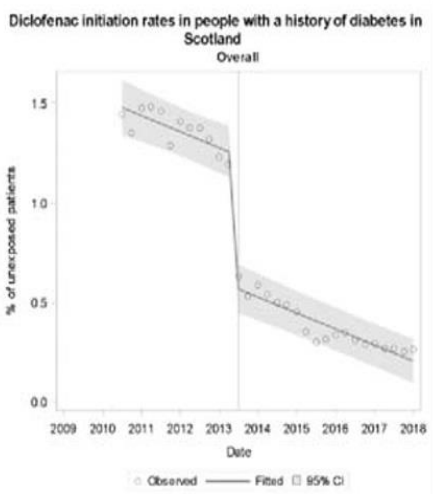
Diabetes



(A) England







(B) Scotland

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Figure 4. Diclofenac initiation rates in patients with new cautions following the 2013 EMA regulatory action in (A) England and (B) Scotland (Morales et al, 2020)

3. Analysis of data from the integrated health information system at the primary healthcare level (outpatient care settings) in Montenegro

Thanks to the improved integrated information system that was implemented in all healthcare centers on the territory of Montenegro (in total 18), it was possible to conduct an analysis of the impact of the EMA recommendation on the prescription of diclofenac in patients with or at high risk of CV diseases after new EMA recommendations related to its adverse CV effects. The analysis involved the prescription and consumption of systemic formulations of diclofenac at the outpatient care settings in Montenegro in that category of patients during the period 2016-2020. Namely, the new EMA recommendation on prescribing diclofenac to cardiac patients were also adopted in Montenegro, on the basis of approval of the Institute for Medicines and Medical Devices of Montenegro (CInMED), referred to the introduction of new contraindications, special warnings and precautions when prescribing systemic formulations of diclofenac to those patients. With reference to the newly introduced contraindications and special warnings and precautions, in 2015 CInMED implemented the additional measure of minimising (reducing) risks of unsafe prescribing of diclofenac in a way that it had notified healthcare professionals by a letter (*DHPC – Direct Healthcare Professional Communications*) of introduced restrictions in administering diclofenac in CV patients or in patients with diseases with known CV risk (Anonymous, 2015). Therefore, it was important to establish to what extent these regulatory measures influenced the prescription and consumption of diclofenac in this high-risk patient population, given the otherwise enormously high consumption of this drug in Montenegro (see Report 2: Consumption of non-steroidal antiinflammatory drugs (NSAID) with special reference to diclofenac, November 2021).

Data from the information system of the healthcare centres in Montenegro which were the subject of this analysis included:

- data on the patients who have s been prescribed the systemic formulations of diclofenac, with one of the CV diseases contraindicated for the administration of diclofenac (CHF, IHD, PAD, CVD)
- data on the patients who have been prescribed systemic formulations of diclofenac, with some of the diseases that pose risk factors for the development of CV diseases, for which there are special warnings and precautions in prescribing of diclofenac (hypertension, hyperlipidaemia, diabetes mellitus)
- data on the brand (protected) name of the medicine which contains diclofenac as active substance, on pharmaceutical form, strength (dose) and method of administration.

All patients treated in the level of primary healthcare, who had been prescribed systemic formulations of diclofenac, undergone verification of their diagnoses in their electronic medical records, according to the International Classification of Diseases (ICD), in order to identify if their's CV diseases or diseases with

known CV risk, were among those diagnoses, which in the current SPC for diclofenac were characterized as contraindication/ special warning or precautions for prescribing systemic formulations of the drug.
Diagnoses under the ICD that refer to medical conditions which in the SPC stand for contraindications for prescribing diclofenac include: congestive heart failure, ischemic heart disease, other heart diseases, large arteries diseases, small arteries and capillary diseases, heart diseases of pulmonary origin and diseases of pulmonary blood vessels, and cerebrovascular diseases.
Diagnoses according to ICD that refer to medical conditions which under SPC for diclofenac require special supervision of the patients are hypertension, hyperlipidaemia and diabetes mellitus.
Consumption of systemic formulations of diclofenac, prescribed in the level of the primary healthcare, was analysed by using the standard methodology of the World Health Organization, based on daily defined dose (DDD)/1000 inhabitants/day and Anatomic Therapeutic Chemical (ATC) classification of medicines: https://www.whocc.no/atc_ddd_index).
Within the observed period, in the level of primary healthcare in Montenegro, systemic formulations of diclofenac have been prescribed to patients with CV diseases and diseases which pose a risk factor for the development of CV diseases, constituting a contraindication or require precautions for prescribing it. Although the total number of patients who have been prescribed systemic formulations of diclofenac has reduced in that period (from 94,269 to 79,168 patients), that trend has not been observed in case of the patients with CV diseases where, with the exception of 2019, there has been the trend of increase in their number despite the existence of safety risk for its administration. With regard to the total number of patients who in the course of 2016, 2017, 2018, 2019 and 2020 were prescribed the systemic formulations of diclofenac, 16%, 18%, 24%, 15% and 20% of them, respectively, had a CV disease posing a safety risk for the administration of this medicine (Table 1).

Table 1. Total number of patients and number of patients with cardiovascular (CV) diseases/risk for CV diseases (contraindications and special warnings and precautions for use) who have been prescribed systemic formulations of diclofenac, during a five-year period (2016-2020)

Year	Number of patients on diclofenac therapy	Number (%) of patients with CV diseases on diclofenac therapy
2016	94,269	15,602 (16)
2017	95,112	17,060 (18)
2018	93,598	22,923 (24)
2019	93,435	14,530 (15)
2020	79,168	15,702 (20)

Within the observed period, prescribing of systemic formulations of diclofenac to patients with CV diseases, or with diseases posing a risk factor for the development of CV diseases, expressed in the number of prescribed diclofenac packaging, marks the growth trend in the first three years (2016-2018), with a decline in prescribing in 2019 and 2020, in relation to 2018 (Figure 1).

Table 2 provides distribution of the patients according to the diseases posing the CV safety risk for the administration of diclofenac, who were prescribed the medicine in the period 2016-2020 in the level of the PHC in Montenegro. The highest number of these patients who had contraindication in administration of diclofenac, had the ischemic heart disease (39.7%), while the highest number of patients to whom the medicine could be prescribed, but with increased precautions, had hypertension (77.4%).

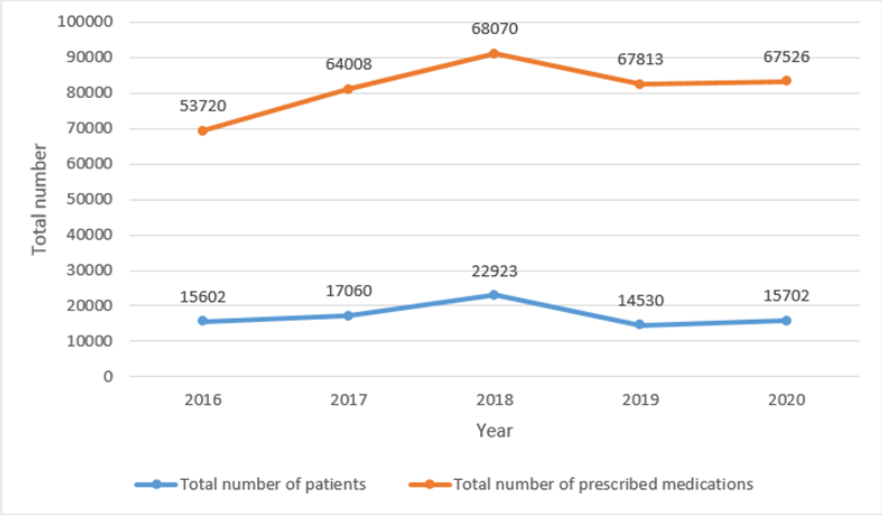

Figure 1. Total number of prescribed systemic formulations of diclofenac and number of patients with cardiovascular (CV) diseases/risk for CV diseases (contraindications and special warnings and precautions for use) who have been prescribed them, during a five-year period (2016-2020)

Table 2. Number of patients with cardiovascular (CV) diseases/ risk for CV diseases who have been prescribed systemic formulations of diclofenac, during a five-year period (2016-2020) (according to the primary diagnosis)

Diseases	2016	2017	2018	2019	2020	Total
CV diseases						
Congestive heart failure	95	87	102	63	40	387
Ischemic heart disease	753	785	1004	619	569	3,730
Other heart disease	507	488	597	369	330	2,291
Diseases of arteries, small arteries and capillaries	151	156	221	154	141	823
Cerebrovascular disease	371	390	529	374	364	2,028

Diseases of the heart of pulmonary origin and diseases of the blood vessels of the lungs	14	20	46	26	28	134
Diseases-risk factor for CV disaeses						
Hypertension	10,561	11,713	15836	10,025	11,013	59,148
Hyperlipidemia	330	350	403	263	289	1635
Diabetes mellitus	2,820	3,071	4,185	2,637	2,928	15,641
Total	15,602	17,060	22,923	14,530	15,702	85,817

If the consumption of systemic formulations of diclofenac is analysed with patients with the above CV diseases, expressed in the number of DDD/1000 inhabitants/day, its continuous growth has been noted. Within the observed period, the consumption was increased from 4.6 to 6.3 DDD/1000 inhabitants/day, which is the increase of 36.91% (Figure 2). Consumption of systemic formulations of diclofenac in CV patients, to whom administration of this medicine has been contraindicated, accompanies the trend of prescribing them to the patients within the observed period. Namely, in the period 2016-2018 there was a noticeable increase in diclofenac consumption in this group of the patients, while in 2019 and 2020 a mild decline in that consumption was noted. On the other hand, consumption of systemic formulations of diclofenac in patients with diseases-risk factors for the development of CV diseases, to whom diclofenac has to be prescribed with special precaution, records continuous increase. Consumption of diclofenac in these patients records increase from 4.1 in 2016 to 5.8 DDD/1000 inhabitants/day in 2020, which is the increase of 41.46% (Figure 2).

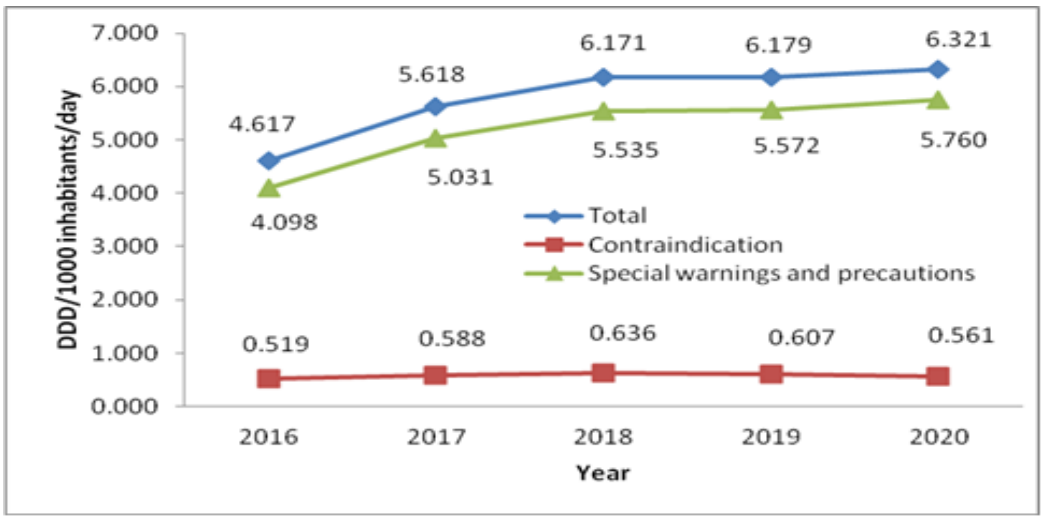

Figure 2. Total consumption of systemic formulations of diclofenac in patients with cardiovascular (CV) diseases/risk for CV diseases (contraindications and special warnings and precautions for use) expressed as the number of DDD/1000 inhabitants/day during a five-year period (2016-2020)

Analysis of consumption of systemic formulations of diclofenac marked as the number DDD/1000 inhabitants/day during the five year period (2016-2020) with regard to the CV diseases, or diseases designated as CV risk factors, which are the contraindication or require special precautions in administration of medicine, also shows that the drug, although contraindicated, was prescribed mostly to the patients suffering from ischemic heart disease (with 40,7% of those patients), while among the diseases requiring intensified precautions for the administration of diclofenac, hypertension dominated in its consumption (with 77.2% patients of this group) (Table 3).

Table 3. Consumption of systemic formulations of diclofenac expressed as the number of DDD/1000 inhabitants/day during a five-year period (2016-2020) in patients with cardiovascular (CV) diseases/ risk for CV diseases

Disaeses	2016	2017	2018	2019	2020	Total
CV diseases						
Congestive heart failure	0.0313	0.0300	0.0283	0.0210	0.0181	0.1286
Ischemic heart disease	0.2077	0.2457	0.2615	0.2466	0.2252	1.1867
Other heart disease	0.1384	0.1487	0.1519	0.1336	0.1241	0.6966
Diseases of arteries, small arteries and capillaries	0.0384	0.0420	0.0471	0.0460	0.0487	0.2222
Cerebrovascular disease	0.1010	0.1175	0.1381	0.1485	0.1355	0.6407
Diseases of the heart of pulmonary origin and diseases of the blood vessels of the lungs	0.0026	0.0050	0.0112	0.0122	0.0115	0.0426
Diseases-risk factor for CV disaeses						
Hypertension	3.1617	3.8670	4.2565	4.3121	4.4586	20.0613
Hyperlipidemia	0.0873	0.0987	0.0966	0.0951	0.1004	0.4781
Diabetes mellitus	0.8434	1.0638	1.1797	1.1636	1.1994	5.4499

If the consumption of systemic formulations of diclofenac is analysed in patients with CV diseases, in relation to the type of systemic formulation of diclofenac (oral, parenteral, rectal), the permanent growth in consumption of oral formulation, decline in consumption of parenteral formulations since 2017 and permanent drop in consumption of rectal formulations of the drug have been recorded within the observed

period. Oral formulations of diclofenac made 98% of total consumption of its systemic formulations (Table 4).

Table 4. Consumption of systemic formulations of diclofenac expressed as the number of DDD/1000 inhabitants/day during a five-year period (2016-2020) in relation to the route of administration of systemic formulations of the drug

Route of administration	2016	2017	2018	2019	2020
Oral	4.523	5.520	6.079	6.091	6.262
Parenteral	0.090	0.095	0.091	0.086	0.060
Rectal	0.004	0.003	0.002	0.001	0.000

DDD – daily defined dose.

Analysis of consumption of systemic formulations of diclofenac, presented in the number of prescribed packaging of diclofenac to targeted population, indicates the highest consumption of diclofenac in patients with ischemic heart disease (40.3%), other CV diseases (25.8%) and cerebrovascular diseases (19.2%), when speaking of the diseases which are contraindicated for its administration (Table 5), and in patients with hypertension (76.6%) and diabetes mellitus (21.5%), when speaking about the diseases that require special warnings and precaution for its use (Table 6).
Diclofenac was most frequently prescribed to target population in formulations for oral administration, in a strength of 75 mg (63.7% in relation to other systemic formulations and doses of the drug). However, it was also prescribed in a dose of 100 mg where, in case the patients took it twice a day, the total daily dose exceeded the maximum permitted one of 150 mg. A contribution of 100 mg oral formulations of diclofenac in relation to its other doses and formulations amounted to 18.8% (Table 5).
Similarly, prescribing of oral formulations of diclofenac 75 mg and 100 mg, in patients with diseases requiring increased precautions for its prescribing, amounted for 70.7% and 21.1%, respectively, in relation to other systemic formulations and strengths of the drug (Table 6).

Comment

Analysis of the data on prescribing systemic formulations of diclofenac in Montenegro in the period 2016-2020 shows that, despite new contraindications and precautions when prescribing it to patients with or at high risk for CV diseases, the drug was widely prescribed to that category of patients. Namely, out of the overall number of patients who were prescribed diclofenac in that period, in average, almost every fifth patient had one of the CV diseases posing a contraindication or requiring special precaution when using it. Besides, in that period, diclofenac consumtion increased by 36.91% in patients with or at high risk of CV diseases. The highest number of cardiology patients (39.7%), who were contraindicated the use of diclofenac

and whom the medicine was prescribed to, had the IHD, while the highest number of patients (77.4%) whom the drug could be prescribed, but with increased precautions, had hypertension. IHDs constitute serious, clinically significant conditions which in the patients taking diclofenac may lead to increase of their morbidity, mortality and increase the costs of healthcare due to the necessary treatment of these patients.
This analysis showed that oral formulations of diclofenac in the dose of 75 mg were the most commonly prescribed drug formulations at the outpatient care settings in Montenegro (63.7%) compared to its other systemic formulations and doses. However, oral 100 mg formulations of diclofenac also made a significant contribution, which is potentially a risk factor for aggravation of CV diseases when taking into account that maximum daily dose of diclofenac is 150 mg.
Bearing in mind the high consumption of diclofenac in Montenegro as well as its safety risk in patients with CV diseases, CInMED, as routine measure of minimizing (reducing) the risks, allocated to all systemic formulations of diclofenac the dispensing mode exclusively with physician's prescription, aiming at necessary physician's supervision of administering the drug. However, despite that, it is obvious that diclofenac is nonrationally prescribed, even in cases posing contraindications for administering it, which may result in serious consequences for population health regarding the huge consumption of the drug. That is why it is necessary to take additional measures (regulatory and educational) aimed at raising awareness of healthcare professionals of the need to comply with the recommendations when prescribing diclofenac to patients with CV diseases, but not only diclofenac, but also other drugs with recognized safety risks.

Table 5. Number of prescribed packages of diclofenac to patients with cardiovascular (CV) diseases (contraindications) in different strengths (doses) and pharmaceutical forms during a five-year period (2016-2020)

Congestive heart failure	Oral administration			Parenteral administration	Rectal administration	Total
	50 mg	75 mg	100 mg	75 mg/3 ml	50 mg	
2016	4	188	138	20	-	350
2017	6	204	100	44	-	354
2018	5	219	59	71	-	354
2019	-	174	32	57	-	263
2020	-	153	32	5	-	190
Ischemic heart disease	Oral administration			Parenteral administration	Rectal administration	Total
	50 mg	75 mg	100 mg	75 mg/3ml	25mg, 50mg	
2016	58	1,298	820	275	8	2459
2017	76	1,710	763	339	10	2898
2018	36	2,189	420	329	9	2983
2019	2	2,026	445	297	1	2771
2020	1	1978	295	98	-	2372
Other heart disease	Oral administration			Parenteral administration	Rectal administration	Total
	50 mg	75mg	100mg	75 mg/ 3ml	50mg	
2016	92	861	496	338	1	1,788
2017	50	1,078	382	373	-	1,883
2018	28	1,269	211	381	-	1,889
2019	9	1,120	195	262	1	1,587

2020	2	1,078	152	224	-	1,456
Diseases of arteries, small arteries and capillaries	Oral administration			Parenteral administration	Rectal administration	Total
	50 mg	75 mg	100 mg	75 mg/3 ml	50 mg	
2016	6	289	64	241	1	601
2017	15	322	68	172	1	578
2018	3	370	56	227	-	656
2019	-	325	99	199	-	623
2020	1	369	68	176	2	616
Cerebrovascular diseases	Oral administration			Parenteral administration	Rectal administration	Total
	50 mg	75 mg	100 mg	75 mg/3 ml	12.5 mg, 25 mg, 50mg	
2016	24	525	272	338	6	1165
2017	22	673	264	297	-	1256
2018	10	848	126	323	-	1307
2019	1	896	216	346	1	1460
2020	1	828	173	233	-	1,235
Diseases of the heart of pulmonary origin and diseases of the blood vessels of the lungs	Oral administration			Parenteral administration	Rectal administration	Total
	50 mg	75 mg	100 mg	75 mg/ 3ml	50 mg	
2016	-	23	1	4	-	28
2017	-	37	6	9	-	52
2018	-	95	1	3	-	99
2019	-	105	10	-	-	115
2020	-	99	-	-	-	99

Table 6. Number of prescribed packages of diclofenac to patients with diseases that pose a risk for cardiovascular (CV) disease (special warnings and precautions) in different strengths (doses) and pharmaceutical forms during a five-year period (2016-2020)

Hypertension	Oral administration			Parenteral administration	Rectal administration	Total
	50 mg	75 mg	100 mg	75,mg/3 ml	12.5 mg, 25 mg, 50 mg	
2016	971	20,816	11,563	2,719	137	36,206
2017	1042	28,230	11,097	3,016	104	43,489
2018	529	35,487	7,635	2,748	65	46,464
2019	183	34,918	9,096	2,531	57	46,785
2020	142	38,028	7,414	1,735	16	47,335
Hyperlipidemia	Oral administration			Parenteral administration	Rectal administration	Total
	50 mg	75 mg	100 mg	75 mg/3 ml	50 mg	
2016	27	556	342	70	3	998

2017	36	710	282	124	-	1,152
2018	10	840	120	86	-	1,056
2019	2	789	169	117	-	1,077
2020	-	864	149	90	-	1,103
Diabetes mellitus	Oral administration			Parenteral administration	Rectal administration	Total
	50 mg	75mg	100 mg	75 mg/ 3ml	12.5 mg, 25 mg, 50 mg	
2016	250	5,469	3,052	1,328	26	10,125
2017	294	7,816	2,901	1,326	9	12,346
2018	151	9,662	2,224	1,220	5	13,262
2019	21	9,274	2,520	1,314	3	13,132
2020	54	10,077	2,083	902	4	13,120

4. Conclusion and recommendation

Despite new recommendations from regulatory bodies on new contraindications and precautions for the use of diclofenac in patients with or at high risk of cardiovascular diseases, recent research conducted in fourth European conutries (England, Scotland, Denmark and Netherlands) as well as this analysis on prescription and consumption of systemic formulations of diclofenac in Montenegro show that the drug is still prescribed to risk groups. This finding is particularly relevant to Montenegro. Due to this, it is necessary to design more efficient measures of reducing CV risks from the use of diclofenac which would significantly improve the public health.

As previously suggested, one of the measures would be to improve the electronic prescription software by a warning to a doctor who prescribes diclofenac to a patient who has diagnoses that are contraindications or require special monitoring of the patient as well as include a recommendation on alternative therapy (eg. paracetamol, naproxen, ibuprofen at a dose of less than 1200 mg/day).

Also, it is necessary to continue monitoring the prescription and consumption of diclofenac, especially in risk groups such as cardiac patients.

CInMed, in cooperation with faculties from the medical scientific field, should be more involved in the education of health workers regarding the rational use of medicines.

5. References

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