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

WP3

Assessment of compliance or deviation of diclofenac prescribing in PHC

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Table of Contents

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1. Introduction

In regard to the diclofenac project it is important to develop the environment to conduct comprehensive research on prescribing patterns of systemic diclofenac by HCP from PHC (indication, dose, duration of therapy, comorbidities, medicines in concomitant use with diclofenac). It is important to establish the degree of compliance or deviation of diclofenac prescribing in PHC with evidence based CinMED recommendation via the product information and in line with the EU recommendation by the EMA pharmacovigilance and risk assessmnet Committee (PRAC) and diseminated to the EU memberstates through the CMDh. There is the need to provide analysis and assessment of prescribing of diclofenac in PHC as possible main reason of non-rational cosumption of diclofenac in Montenegro and use the data as for timely introduction of the health policy makers and PHC institutions on the results obtained to optimise the prescription of diclofenac in regard to the risk minimisation measures implemented in 2013 and improvement of the awareness of the importance of rational prescription of medicines using diclofenac as the vechicle of such principle also for other medicines.

As already outline in the first document The EU pharmacovigilance legislation from 2010 is introducing the obligation to the pharmacovigilance system to measure the additional risk minimisation impact in health care and with that the (Directive 2010/84/EC and Regulation (EU) No1235/2010) and following this obligation the EMA and the PRAC have created a dedicated working group in 2014 to look into the impact of important safety changes in prescribing and using medicines in public health. The only study which has been ferforemed for the impact of the diclofenac safety changes was the study of Daniel Morales from the University Dundee et al under the lsupervision of the EMA, UK to understand the impact of the EMA recommended new contrindications and changes to the product information due to cardiovascular safety concerns across Europe for diclofenac in 2013, with the aim to measure their impact among targeted populations (1,2). The conclusion of this important pioneer study is that although significant reductions in diclofenac initiation occurred, patients with contraindications continued to be prescribed diclofenac, varied by country and target condition. Understanding reasons for such variation may help to guide the design or dissemination of future safety warnings (2).

2. Discussion

The data source which have been used in the diclofenac study by Morales and al were validated population data sources from four European countries which were the the Danish Register of Medicinal Products, which records all outof-hospital prescriptions and allows linkage of drug exposures to inpatient and outpatient hospital contacts and death data; The Dutch PHARMO Database Network, which contains combined data from primary and secondary healthcare settings in the Netherlands and the outpatient pharmacy database; The United Kingdom Clinical Practice

Research Datalink (CPRD), which contains primary care data; and finally the Scottish Prescribing Information System (PIS), which records all medicines dispensed from pharmacies in Scotland that can be record-linked to demographic data, Scottish Morbidity Records and death registrations for the entire population (2). The Montenegrian data base has the advantage to have the primary care data and the data from the pharmacies as the database is combined but it is is very difficult from the database to understand what is the primary diagnose why diclofenac is prescribeb and to follow the duration of therapy and the final outcome of the patient. Using the basic model of Morales and al. putting the different patinets into subgroups with the different contraindications has to be done to better understand the overall outcome ot the patinet not only in the treatment why diclofenac was introduced itself.

Tables and surches which could allow why diclofenac was introduced in the first place (primary diagnosis for the treatment) and the outcome of other diseases have to be better defined.

As the first starting point to make it easier for the prescriber the clinical diagnosis are proposed and integrated into the database (the proposed etext is in montenegrian language to be implented into the software programe):

PORUKE UPOZORENJA U PZZ

1. Slijedi lista dijagnoza koje su kontraindikovane za primjenu diklofenaka. Potrebno primijeniti poruke upozorenja za ove dijagnoze kao i poddijagnoze u okviru ovih dijagnoza, ukoliko postoje.

MKB-10: I20
Dijagnoza: Stezanje u grudima
Latinski naziv: Angina pectoris
MKB-10: I21
Dijagnoza: Akutan infarkt (izumiranje tkiva) srca
Latinski naziv: Infarctus myocardii acutus
MKB-10: I22
Dijagnoza: Ponovljen akutni infarkt srca
Latinski naziv: Infarctus myocardii recidivus acutus
MKB-10: I23
Dijagnoza: Akutna komplikacija posle akutnog infarkta srca
Latinski naziv: Complicatio acuta post infarctum cordis acutum
MKB-10: I24
Dijagnoza: Druge akutne ishemijske bolesti srca
Latinski naziv: Morbi cordis ishaemici acuti alli
MKB-10: I25
Dijagnoza: Hronicna ishemijska bolest srca
Latinski naziv: Morbus cordis ischaemicus chronicus

MKB-10: I26
Dijagnoza: Zacepljenje krvnih sudova pluca
Latinski naziv: Embolia pulmonis
MKB-10: I27
Dijagnoza: Druge bolesti srca plucnog porekla
Latinski naziv: Morbi cordis pulmonales alii
MKB-10: I28
Dijagnoza: Druge bolesti krvnih sudova pluca
Latinski naziv: Morbi vasorum pulmonis alii
MKB-10: I42
Dijagnoza: Oboljenja srcanog misica
Latinski naziv: Cardiomyopathia
MKB-10: I43
Dijagnoza: Oboljenje misica srca u drugim bolestima
Latinski naziv: Cardiomyopathia in morbis aliis
MKB-10: I50
Dijagnoza: Nedovoljna funkcija srca
Latinski naziv: Insufficientia cordis
MKB-10: I60
Dijagnoza: Krvarenje ispod paucinaste mozdanice
Latinski naziv: Haemorrhagia subarachnoidalis
MKB-10: I61
Dijagnoza: Krvarenje u mozgu
Latinski naziv: Haemorrhagia cerebri
MKB-10: I62
Dijagnoza: Drugo netraumatsko krvarenje u mozgu
Latinski naziv: Haemorrhagia intracranialis non traumatica, alia
MKB-10: I63
Dijagnoza: Infarkt mozga-izumiranje tkiva mozga
Latinski naziv: Infarctus cerebri
MKB-10: I64
Dijagnoza: Apopleksija - Mozdana kap, neoznacena kao krvarenja ili infarkt mozga
Latinski naziv: Apoplexia cerebri ut haemorrhagia sive infarctus non specificata
MKB-10: I65
Dijagnoza: Zapusenje premozdanih arterija i suzenje premozdanih arterija brz infarkta mozga
Latinski naziv: Occlusio arteriae praecerebralis et stenosis arteriae praecerebralis sine infarctus cerebri
MKB-10: I66
Dijagnoza: Zapusenje arterije mozga i suzenje arterije mozga bez infarkta mozga
Latinski naziv: Occlusio arteriae cerebri et stenosis arteriae cerebri sine infarctu
MKB-10: I67

Dijagnoza: Druge bolesti krvnih sudova mozga
Latinski naziv: Morbi cerebrovasculares alli
MKB-10: I68
Dijagnoza: Bolest krvnih sudova mozga u drugim bolestima
Latinski naziv: Morbi cerebrovasculares in morbis aliis
MKB-10: I69
Dijagnoza: Posledice bolesti krvnih sudova mozga
Latinski naziv: Sequelae morbi cerebrovascularis
MKB-10: I70
Dijagnoza: Ateroskleroza - zakrecavanje velikih krvnih sudova
Latinski naziv: Atherosclerosis
MKB-10: I71
Dijagnoza: Aneurizma - ograniceno prosirenje srcanice i rascep srcanice
Latinski naziv: Aneurysma aortae et dissectio aortae

MKB-10: I72
Dijagnoza: Aneurizme drugih krvnih sudova
Latinski naziv: Aneurysmata alia
MKB-10: I73
Dijagnoza: Druge bolesti perifernih krvnih sudova
Latinski naziv: Morbi vasorum periphericorum alii
MKB-10: I74
Dijagnoza: Zacepljenje arterije i stvaranje krvnog ugruska u arterijama
Latinski naziv: Embolia ateriarum et thrombosis arteriarum
MKB-10: I77
Dijagnoza: Druge bolesti arterija i malih arterija
Latinski naziv: Morbi arteriales et arteriolares alli
MKB-10: I79
Dijagnoza: Bolesti arterija, malih arterija i kapilara u drugim bolestima
Latinski naziv: Morbi arteriales, arteriolares et capillares in morbis aliis

Tekst poruke upozorenja: U kartonu ovog pacijenta postoje dijagnoze koje su kontraindikovane za propisivanje diklofenaka. Kod ovog pacijenta odnos korist/rizik od primjene diklofenaka nije povoljan (pozitivan).

2. Slijedi lista dijagnoza za koje postoji pojačan oprez u slučaju propisivanja diklofenaka. Potrebno primijeniti poruke upozorenja za ove dijagnoze kao i poddijagnoze u okviru ovih dijagnoza, ukoliko postoje.

MKB-10: I10
Dijagnoza: Povisen krvni pritisak, nepoznatog porekla
Latinski naziv: Hypertensio arterialis essentialis (primaria)

MKB-10: I11
Dijagnoza: Bolest srca uzrokovana povisenim krvnim pritiskom
Latinski naziv: Morbus cordis hypertensivus
MKB-10: I12
Dijagnoza: Povisen krvni pritisak bubreznog porekla
Latinski naziv: Morbus renalis hypertensivus
MKB-10: I13
Dijagnoza: Bolest srca i bolest bubrega uzrokovana povisenim krvnim pritiskom
Latinski naziv: Morbus cordis et morbus renis hypertensivus
MKB-10: I15
Dijagnoza: Sekundarno povisen krvni pritisak
Latinski naziv: Hypertensio arterialis, secundaria
MKB-10: E10
Dijagnoza: Šećerna bolest, insulinozavisan oblik
Latinski prijevod: Diabetes mellitus ab insulino dependens
MKB-10: E11
Dijagnoza: Šećerna bolest, insulinonezavisan oblik
Latinski prijevod: Diabetes mellitus ad insulino independens
MKB-10: E12
Dijagnoza: Šecerna bolest kod pothranjenosti
Latinski prijevod: Diabetes mellitus malnutritionalis
MKB-10: E13
Dijagnoza: Druga oznacena secerna bolest
Latinski prijevod: Diabetes mellitus alius,specificatus
MKB-10: E14
Dijagnoza: Šećerna bolest, neoznacena
Latinski prijevod: Diabetes mellitus,non specificatus
MKB-10: E78
Dijagnoza: Poremecaji metabolizma masti i drugi poremecaji masti u krvi
Latinski prijevod: Disordines metabolismi lipoproteiniet lipidaemiae alii
MKB-10: Z72.0 Pušenje

Tekst poruke upozorenja: U kartonu ovog pacijenta postoje dijagnoze koje zahtijevaju poseban oprez u doziranju i dužini primjene diklofenaka. Kardiovaskularni rizik se može povećati povećanjem doze i trajanja terapije. Diklofenak treba primjenjivati u najnižim efikasnim dnevnim dozama, u najkraćem vremenskom periodu.

3. Slijedi lista dodatnih poruka u slučaju odabira dijagnoza za koje postoji pojačan oprez prilikom propisivanja diklofenaka. Različite poruke upozorenja se kreiraju u slučaju odabira oralnih (tablete, kapsule), rektalnih (supozitorije) i parenteralnih (injekcije) formulacija diklofenaka

Tekst poruke upozorenja za oralne formulacije diklofenaka (tablete, kapsule) svih jačina: Preporučena maksimalna dnevna doza je 150 mg. Kod blažih slučajeva, kao i kod dugotrajne terapije, 75 do 100 mg dnevno je obično dovoljno. Neželjena dejstva (kardiovaskularna i gastrointestinalna) se mogu svesti na najmanju moguću mjeru korišćenjem najniže efektivne doze u najkraćem vremenskom periodu neophodnom za kontrolu simptoma.

Tekst poruke upozorenja za parenteralne formulacije diklofenaka (injekcije): Preporučena maksimalna dnevna doza je 150 mg. Ne treba primenjivati duže od dva dana; ukoliko je neophodno, terapija se može nastaviti diklofenak tabletama ili supozitorijama. Neželjena dejstva (kardiovaskularna i gastrointestinalna) se mogu svesti na najmanju moguću mjeru korišćenjem najniže efektivne doze u najkraćem vremenskom periodu neophodnom za kontrolu simptoma.

Tekst poruke upozorenja za rektalne formulacije diklofenaka (čepići): Preporučena maksimalna dnevna doza je 150 mg. Neželjena dejstva (kardiovaskularna i gastrointestinalna) se mogu svesti na najmanju moguću mjeru korišćenjem najniže efektivne doze u najkraćem vremenskom periodu neophodnom za kontrolu simptoma.

4. Conclusion

The health care database does capture all the diagnosis of the patient but in most of the cases it is not clear why diclofenac is prescribed in the first place and for how long. The long term outcome of the patient has to be captured – evaluation of the risk factor.

Update of the software is done with the aim to better infrom the HCPs on who should not get diclofenac but in the same time it is important to understand which medicinal product the patient has got instead (ibuprofen with a better safety profile, lesser dose or different pain killers as for exemple opiates).

Deteiled protocols have to be developed to adress these questions with adjustment of the database to easy brows trhrough the data and prepare the database for other medicinal products which have to be followed in the same manner.

The development of such of protocols are of highest importance as till today we do not have real answers and outcomes of studies which are ongoing and looking into real world data which coud give us the answer of these important publich health questions in pharmacovigilance (3).

4. Literature

1. SmPC – diclofenac (CinMED)

2. D.R. Morales et al. Impact of EU regulatory label changes for diclofenac in people with cardiovascular disease in four countries: interrupted time series regression analysis. BrJClinPharmacol.2020;1-12
3. GVP module XVI revision 3 (public consultation) Guideline on good pharmacovigilance practices (GVP) - Module Risk Minimisation Measures (europa.eu) (April 2021)

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Analysis of diclofenac consumption 2009-2020

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Table of Contents

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1. Introduction

Diclofenac is a non-steridal antiinflamatory drug (NSAD) which is indicated in most countries for relief of all grades of pain and inflammation in a wide range of conditions, which includes arthritic condition such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout; acute musculo-skeletal disorders such as periarthritis tendinitis, tenosynovitis, bursitis and other painful conditions resulting from trauma, including fracture, low back pain, sprains, strains, dislocations, orthopaedic, dental and other minor surgery (1).

On 28 June 2013, the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) in the European union (EU) endorsed by majority a new safety advice for diclofenac-containing medicines for systemic use. The new advice aims to minimise the risks of effects on the heart (like myocardial infarction) and circulation (Cardiovascular side effects) from these medicines. This was followed by a review (so called article 31 safety referral) by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) which found that the effects of systemic diclofenac on the heart and circulation are similar to those of selective COX-2 inhibitors. This applies particularly when diclofenac is used at a high dose and for long-term treatment. The PRAC therefore recommended that the same precautions already in place to minimise the risks of blood clots in the arteries with selective COX-2 inhibitors should be applied also to diclofenac. The CMDh position was sent to the European Commission, which confirmed it and took a final legally binding for all diclofenac containing medicines in the EU decision on 25 September 2013. This is not the first review on NSAIDs and systemic diclofenac, as thhe safety of NSAIDs has been closely monitored by regulatory authorities in the EU for several years. Reviews of these medicines were carried out in 2005, 2006 and 2012 have confirmed that NSAIDs as a class are associated with a small increased risk of arterial thromboembolic events especially in patients with underlying cardiovascular conditions or with certain cardiovascular risk factors, which in some cases has led to miocardial infarction or stroke, particularly if used at high dose and for long periods. A class warning in the product information (Summary of Product Characteristics and Patient leaflet) of this risk is in place and the product information for all NSAIDs recommends that these medicines be used at the lowest effective dose for the shortest period of time necessary to control symptoms. As the risk is known to be somewhat higher with the subgroup of NSAIDs the selective COX-2 inhibitors, increased measures to minimise risk are recommended in their product information which applies from 2013 also for diclofenac. The PRAC review of diclofenac which resultes in the above mentioned safety recommendationwas started at the request of the UK medicines regulatory agency, the MHRA, in October 2012 in response to findings from the 2012 review of NSAIDs. The latter identified a small increased risk of these cardiovascular side effects with diclofenac compared with other NSAIDs – an increase similar to that seen with the COX-2 inhibitors. The cardiovascular risk with any NSAID depends on a person's underlying risk factors, such as high blood pressure and cholesterol levels and also any underlying cardiovascular conditions. About 8 people in 1,000 at moderate risk of heart disease are likely to have a heart attack over one year. In the case using higher doses and for prolonged time diclofenac the overall number of heart attacks

in people at moderate risk would be expected to increase by around 3 cases per year for every 1,000 people treated with diclofenac (from 8 expected to 11 observed per 1,000 people per year) (2).

To diseminate the new safety information on the level of the EU member states on 15 November 2013 a Direct health coomunication (DHPC) letter was send to health care proffesionals (HCPs) by the Marketing authorisation holders (MAHs) in collaboration with the National regulatory agencies (NCAs) where the contraindications for the use of diclofenac were highlighted emphesising the need that the medicinal product has to be used by the patient by the lowest effective dose in the lowest possible treatment time. The Croatian example of the DHPC letter is given (3).

As Montenegro is an EU candidate country and is in the phase of the implementation of the the Aqui in the national legislation, CinMED (previous CALIMS) has acted upon this recommendation coming from the EU updateting the national diclofenac SmPCs for systemic use and sent out a DHPC with the warnings. As one of the CinMED resposibilitiy is closely monitoring of medicinal product consumption in Montenegro it is realised that the consumption is still very high also after the warning is introduced and it is is seen as a threat to public health regarding cardiovascular safety of treated patients with diclofenac.

2. Discussion

CinMed (former CALIMS) has realized that the consumption in DDD/1000/day is at leas 4 times higher than in the countries in the region especially when using data from the Croatian (EU memember state from 2013) medical utility program which is ongoing from 2004. Table 1. shows the consumption of systemic diclofenac in Croatia from 2004 in DDD/1000/day. It is important to highlight that from 2011 diclofenac is prescription only medicine (in line with the earlier EU safety recomedations on cardiovacular risk of NSAIDs), and the additional risk minimisation measure (DHPC) was introduced in 2013 (one offf, but the letter is still available on the NCA's website). In all the shown years the diclofenac consumption is in the first 25 most prescribed (used) medicines (4).

Table 1. Consumption of systemic diclofenac in Croatia from 2004-2020 (DDD/1000/day):

INN	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Diclofenac consumtion	19.41	16.86	11.3	14.56	13.13	14.52	14.01	12.47	13.17	12.82	12.16	12.26	12.38	11.77	11.76	11.38	11.63

As Norway was the pioneer in drug utility science and medical consupmtion activities, the Norwegian data were also taken into account to understand the consumption of diclofenac as Norway as an EEA country has to follow the EMA (EC) decissions in the medical area as well. The data shown for Norway are slightly different as they do not show the consumption of an INN by DDD/1000/day, but as a percentege of an individual personal use in the country per year

(5). Table 2 is showing the percentage of usage of diclofenac in Noway per an individual per year (Norway has 5,2 million inhabitants). The percentage is high and dicofenac is actually still among the 5 most prescribed/used medicine in Norway, behind paracetamol as the most prescribed/used painkiller in about 9% of patinets (2013 the DHPC with the warnings and the PI update for diclofenac was introduced).

Table 2. Diclofenac usage from 2011 till 2020 in Norway (individual use % in 5,2 million population).

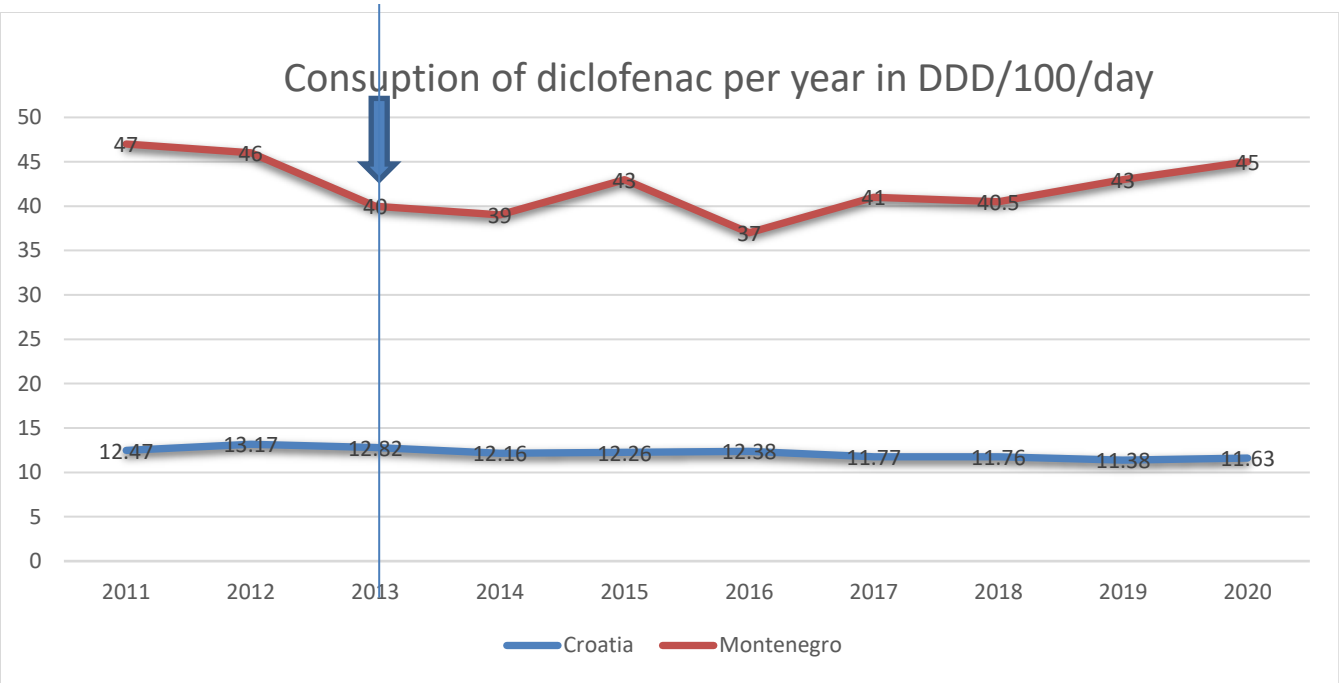
INN	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Diclofenac usage per individual (%)	9.2	8.9	8.2	7.1	6.9	6.3	6.1	5.8	5.5	5.1

Bringing the data from Montenegro into these data it can be seen that it is disproportionally high in comparison to the use in the two countries which were chosen as comparators. Having the data in DD/1000/day we can see that is over or around 40 DDD/1000/day with no change seen after the introduction of the additional minimisation measures in 2013. Table 3 shows the utility data for Montenegro:

Table 3. Consumption of systemic diclofenac in Montenegro from 2011 till 2020

INN	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Diclofenac consumtion	38	46	47	46	40	39	43	37	41	40.5	43	45

Figure 1. Diclofenac consumption 2011-2020 in Croatia and Montenegro (Norway is not shown as the numbers are expressed differently) The arrow indicates the implenetation of the PI warning and the aRMM (DHPC)



If we look into the consumption curve in Croatia we see that it stays very much the same from 2011 – it lowers only very little in contrast to the observation in Montenegro where we see a decrease from 46 DDD/1000/day to 39 in 2014 after the 2013 introduction of warning, but with again a slow increase to the same number of consumption in 2020.

The EU pharmacovigilance legislation from 2010 is bringing the obligation to the pharmacovigilance system to measure the additional risk minimisation impact in health care and with that the (Directive 2010/84/EC and Regulation (EU) No1235/2010) the EMA and the PRAC have created a dedicated working group looking into the impact of important safety changes in prescribing and using medicines in public health. In this regard the impact of the diclofenac safety change was investigated. Under the European Medicines Funding Framework with the grant/award number aEMA/2014/50/RE a study in four countries (Denmark, The Netherlands, England and Schotland) was initiated under the lead investigator Daniel Morales from the University Dundee, UK to understand the impact of the EMA recommended new contrindications and changes to the product information due to cardiovascular safety concerns across Europe for diclofenac in 2013, with the aim to measure their impact among targeted populations (6). The conclusion of this important pioneer study is that although significant reductions in diclofenac initiation occurred, patients with contraindications continued to be prescribed diclofenac, varied by country and target condition. Understanding reasons for such variation may help to guide the design or dissemination of future safety warnings (6). This study shows the importance that a continuous work on communication, education

of the healthcare profesionals and the patients has to be performed where the use of the database introduced by CinMED could be used and adapted to achive this goal. Importantly what is understood from the study performed on the level of the EU that the warnings are understood, but not implented in the health care system and clinical work and not reflected in the clinical guidelines.

The EU (EMA nad HMA) GVP Module XVI on Risk minimisation measures (revision 3) which was at public consultation till April 2021 and now is in the stage of finalisation points out that putting measures on one medicinal product (warnings and restriction of use) (7) can lead to a use of another or more products which a known and better safety profile but also can go in the direction of use of another product with a less safe profile which has to be closely monitored as well. Figure 2 is taken from the GVP XVI module which shows non-targeted effectivness when putting in place measures for one product (activ substance):

Figure 2. Non targeted effectivness in product specific riks minimisation measures (from GVP module XVI (7)):

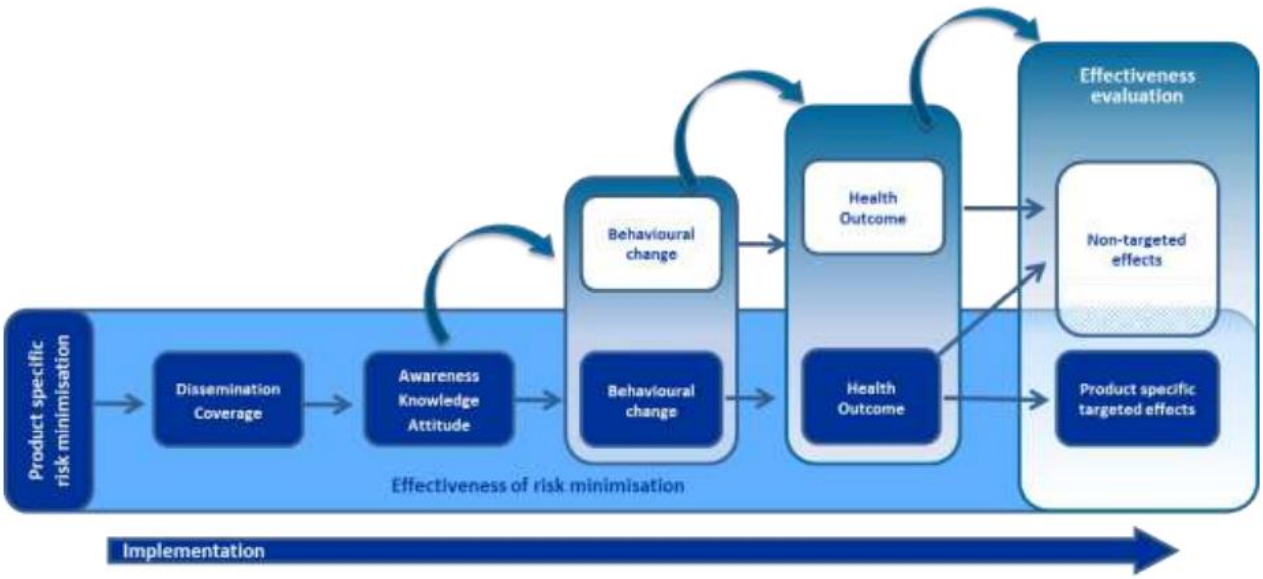


Figure XVI.1.: The approach to effectiveness evaluation of risk minimisation includes measuring medicinal *product-specific targeted effects* and, as appropriate, relevant *non-targeted effects* associated with the use of the concerned and other medicinal products

This situation can be ilustrated with the consumption of other NAIDs such as ibuprofen. In the drug consumtion data from Croatia it can be observed that in line with the decreasing of the use of diclofenac the use of ibuprofen is rising highly. The question which cannot be answered from the data is how high the ibuprofen dose per individual patient is – if the dose is increasing over 1200 mg per day the simmilar risk is reached as for the patients receiving parenteral diclofenac. In Norway for exmple the consumation of ibuprofen stays stable with no fluctuation, where paracetamol is leading as pain killing medicine. In Croatia paracetamol is in the 50 most prescribed medicines only three years ago and it is low with abot 6 DDD/1000/day. See also Table 4 and 5.

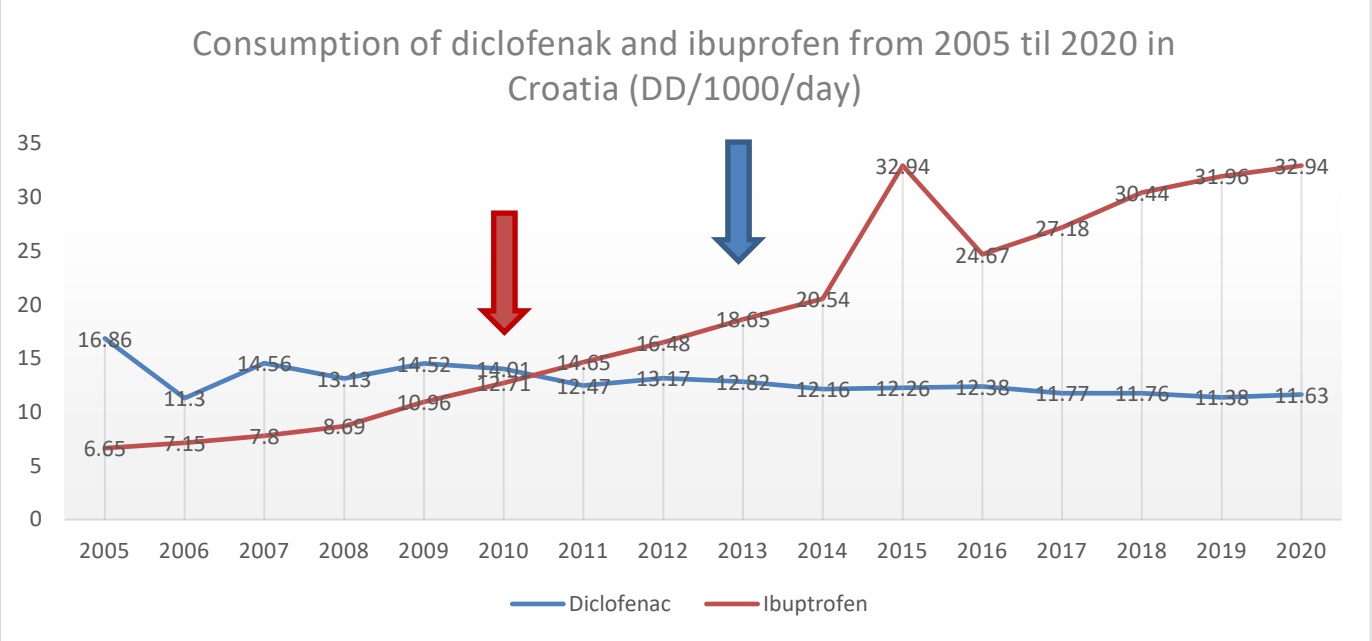
Table 5. Consumption of ibuprofen in Croatia 2004-202 (DDD/1000/day)

INN	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Ibuprofen _consumption	NA	6.65	7.15	7.8	8.69	10.96	12.71	14.65	16.48	18.65	20.54	32.94	24.67	27.18	30.44	31.96	32.94

Table 6. Consumption of ibuprofen in Norway (% of individuals taking ibuprofen per year in 5,2 million inhabitants)

INN	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Ibuprofen consumption	4.4	4.3	4.3	4.3	4.3	4.3	4.4	4.2	4.3	4.2

Figure 3. Consumption of diclofenac and ibuprofen in 2005 till 2020 Croatia



The blue arrow shows the introduction of the risk minimisation measure – warning and contraindication for diclofenac. The red arrow shows another risk minimisation measure - the change of diclofenac from the OTC status to prescription only status in Croatia. The Croatian e-prescription database captures only the prescriptions reimburesd by the state insurance health institution (HZZO) and does not capture OTC saled products which does not allowi additional reaerch on the dose and use of ibuprofen in patient who are contraindicated to use diclofenac. But, the graph shows the impact of the use of other medcicines (see Figure 3 and GVP XVI) from the same class which has to be monitored to insure public health and understand the risk minimisation measures putting on individual medicines. Montenegro's medical and prescriprion database can be fine tuned to capture all the datta of basic interest in pharmacovigilance impact research.

4. Conclusion

The healthcare database where all the prescription are captured with all diagnoses of the patients should be used in the following way allowing to answer healthcare questions which can guide the healthcare practices and as the final aim protecting public health:

- Information about warning and contraindications which should not appear only once in a time when the DHPC is sent but be there continuesly present to remind the prescriber when and for how long to prescribe the medicine
- Give clinical guidelines with concrete diagnoses when the medicinal product is contraindicated

- To be able to follow other medications of the patient which he/she will get instead of the medicine which is contraindicated for the patient's condition (follow the safety profile of the other medicine given in supstitution)
- To be able to follow concrete patients with contraindications – for diclofenac patients with cardiac failure, stroke, (NYHA II-IV)
- Combine prescription data (physicians) and OTC (pharmacists) in prescribing and despensing diclofenac – this feature is not available in the databases of western and northern EU countries
- Prescription only medicines – using as safety risk minimisation measure
- Have an alert system to the physiscians not to prescribe diclofenac in patinets in high risk and pharmacists not to despence diclofenac if the medicine is OTC
- Use the system to understand and improve risk minimisation measures introduced through the regulatory system in the light of examples from other countries given

4. Literature

1. SmPC – diclofenac (CinMED)
2. EMA referral outcome - https://www.ema.europa.eu/en/medicines/human/referrals/diclofenac-containing-medicines (approached September 2021)
3. DHPC – Pismo zdravstvenim radnicima o uvodjenju novih kontraindikacija i upozorenja nakon ocjene kardiovaskularne sigurnosti diklofenaka provedene u zemljama Europske unije www.halmed.hr/Farmakovigilancija/Pisma-zdravstvenim-radnicima/ (approached September 2021
4. Potrosnja lijekova HALMED https://www.halmed.hr/Promet-proizvodnja-i-inspekcija/Promet/Potrosnja-lijekova/Izvjesca-o-prometu-lijekova/
5. Consumption of diclofenac in Norway www.fhi.no/en/hn/drug/
6. D.R. Morales et al. Impact of EU regulatory label changes for diclofenac in people with cardiovascular disease in four countries: interrupted time series regression analysis. BrJClinPharmacol.2020;1-12
7. GVP module XVI revision 3 (public consultation) Guideline on good pharmacovigilance practices (GVP) - Module Risk Minimisation Measures (europa.eu) (April 2021)

Joint EU-MNE Programme for
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WP3

Consumption and consequences of diclofenac use in patients with cardiovascular diseases

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Table of Contents

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1. Introduction

The cardiovascular (CV) risks of non-aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) remain a major safety concern after rofecoxib's (a COX-2 selective NSAID) thromboembolic properties were revealed (Brresalier et al., 2005). Since diclofenac is the most frequently used NSAID in low, middle, and high income countries, and is available over the counter in most countries, its cardiovascular risk profile is of major clinical and public health importance. 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 CV precautions as for selective COX-2 inhibitors. Due to the uneven response to these recommendations in prescribing diclofenac in European countries, in 2017, the EMA has again called for a safety assessment of diclofenac (European Medicines Agency, 2017).

To examine the cardiovascular risks of diclofenac initiation compared with initiation of other traditional non-steroidal anti-inflammatory drugs, initiation of paracetamol and no initiation (no drug use), Schmidt et al. (2018) conducted a series of 252 nationwide cohort studies in line with the strict design criteria of a clinical trial. Data were from Danish national population-based health registries from 1996 to 2016. Eligible for inclusion were all adults without malignancy; schizophrenia; dementia; or cardiovascular, kidney, liver, or ulcer diseases. The study ultimately included nearly 1.4 million diclofenac initiators, 3.9 million ibuprofen initiators, and slightly more than 290,000 naproxen initiators, as well as 764,781 healthcare-seeking paracetamol initiators matched by propensity score and about 1.3 million healthcare-seeking noninitiators also matched by propensity score.The focus was on the risk of major adverse CV events within 30 days of initiation.

Results of the study indicate that the adverse-event rate among diclofenac initiators increased by:
- 50% compared with noninitiators (incidence rate ratio 1.5, 95% confidence interval 1.4 to 1.7),
- 20% compared with paracetamol or ibuprofen initiators (both: 1.2, 1.1 to 1.3), and
- 30% compared with naproxen initiators (1.3, 1.1 to 1.5).

In addition, compared with noninitiators, the event rate for patients beginning diclofenac increased for each component of the combined endpoint:
- 1.2 (1.1 to 1.4) for atrial fibrillation/flutter
- 1.6 (1.3 to 2.0) for ischemic stroke
- 1.7 (1.4 to 2.0) for heart failure
- 1.9 (1.6 to 2.2) for myocardial infarction
- 1.7 (1.4 to 2.1) for cardiac death.

Although the relative risk of major adverse cardiovascular events was highest in individuals with low or moderate baseline risk (that is, diabetes mellitus), the absolute risk was highest in individuals with high baseline risk (that is, previous myocardial infarction or heart failure).

Diclofenac initiation also increased the risk of upper gastrointestinal bleeding at 30 days, by approximately 4.5-fold compared with no initiation, and by 2.5-fold compared with initiation of ibuprofen or paracetamol, and to a similar extent as naproxen initiation.

Authors of this stude conclude that diclofenac poses a cardiovascular health risk compared with non-use, paracetamol use, and use of other traditional non-steroidal anti-inflammatory drugs. Considering its cardiovascular and gastrointestinal risks, they suggest that there is little justification to initiate diclofenac treatment before other traditional NSAIDs.

Having in mind above mentioned, it is of great importance to know to what extent is diclofenac prescribed to patients with CV diseases, ie. in conditions where its use is contraindicated [established congestive heart failure (HF) (NYHA II-IV), ischemic heart disease (IHD), peripheral arterial disease (PAD) and/or cerebrovascular disease] or requires caution and careful monitoring of the patient (hypertension, hyperlipidaemia, diabetes mellitus, smoking) and what are the consequences of its administration to such patients.

2. Analysis of diclofenac use in patients with cardiovascular diseases

The risk of cardiovascular events in patients with established cardiovascular diseases who used diclofenac has been examined in several studies listed below.

Gislason et al. (2009) estimated the risk of cardiovascular events in patients with established heart failure. The study population was taken from a Danish registry database and it covered a period of 10 years. There were 107,092 patients surviving first hospitalisation from heart failure and 36,354 patients using at least one prescription of NSAID after discharge. They report the following hazard ratios for diclofenac compared to no use of any NSAID:

- death: 2.08 (95% CI:1.95-2.21)
- hospitalisation because of HF: 1.35 (95% CI: 1.24-1.48)
- hospitalisation due to acute myocardial infarction (AMI): 1.36 (95% CI: 1.12-1.64).

In a separate paper, using the same database, Gislason et al. (2006) studied the risk of death or reinfarction (after surviving a first myocardial infarction) associated with the use of NSAIDs. The study period was seven years, with 58,432 patients surviving a first myocardial infarct and 6193 receiving diclofenac. They reported the following hazard ratios for diclofenac versus no NSAID:

- death: 2.40 (95% CI: 2.09-2.80)
- reinfarction: 1.54 (95% CI: 1.23-1.93).

Schjerning Olsen et al. (2011) examined the risk of death and recurrent myocardial infarction in patients with prior myocardial infarction, specifically looking at the time to event. A Danish database of 83,677 patients, of whom 13.4% took diclofenac post-myocardial infarction was used. The authors report that the increased risk of death and myocardial infarction among those taking diclofenac as compared to no NSAID use appeared from the beginning of treatment and had the highest hazard ratio of 3.26 (95% CI: 2.57-3.86).

Ray et al. (2009) studied patients who had been recently hospitalised for coronary heart disease using 48,566 patients from the Saskatchewan and UK General Practice Research Databases. The cohort represented more than 111,000 person-years of follow up. They report that current users of diclofenac had an increased risk of serious cardiovascular disease/death of 1.38 (95% CI: 1.18- 1.61) compared to non-use of any NSAID.

Lamberts et al. (2013) studied patients taking NSAIDs post first-time myocardial infarction using a Danish registry database. The study period was 10 years and included 97,458 patients, 2.2% of whom used diclofenac. They reported that diclofenac was associated with an increased mortality at one year, hazard ratio 1.13 (95% CI: 1.04-1.20) compared to no use.

Taking these facts into account, it was to be expected that after the EMA recommendations about new contraindications and warnings for prescribing diclofenac in people with CV diseases from 2013, the use of diclofenac in target population will decrease.

Morales et al. (2020) conducted the study aimed to measure the impact of these new EMA recommendations among patients with contraindications [congestive HF, ischemic heart diseases (IHD), PAD, cerebrovascular diseases] and warnings (hypertension, hyperlipidemia, diabetes) from Denmark, the Netherlands, England and Scotland.

Results showed that the EMA regulatory action was associated with significant immediate absolute reductions in diclofenac initiation in all countries for IHD (Denmark −0.08%, 95% CI −0.13, −0.03; England −0.09%, 95% CI −0.13 to −0.06%; the Netherlands −1.84%, 95% CI −2.51 to −1.17%; Scotland −0.34%, 95% CI −0.38 to −0.30%), PAD and hyperlipidaemia, the Netherlands, England and Scotland for hypertension and diabetes, and England and Scotland for CHF and CVD. Post-intervention there was a significant negative trend in diclofenac initiation in the Netherlands for IHD (−0.12%, 95% CI −0.19 to −0.04), PAD (−0.13%, 95% CI −0.22 to −0.05), hypertension, hyperlipidaemia and diabetes, and in Scotland for CHF (−0.01%, 95% CI −0.02 to −0.007%), IHD (−0.017, 95% CI −0.02, −0.01%), PAD and hypertension. In England, diclofenac initiation rates fell less steeply, while in Denmark changes were more strongly associated with the earlier EMA regulatory action.

The authors of this study concluded that the outcome of the 2013 EMA regulatory action on the cardiovascular safety of diclofenac had a significant impact on reducing diclofenac initiation among patients with cardiovascular disease contraindications and cautions, although some patients with contraindications still continue to be prescribed diclofenac in all countries.

Although similar studies have not been conducted in Montenegro, given the consistently high consumption of diclofenac in the country (given in the Repot 2), it can be assumed that it is largely prescribed to patients with cardiovascular diseases that are contraindications or require caution for its use.

3. Conclusion and recommendation

Despite new recommendations from regulatory bodies on new contraindications and precautions for the use of diclofenac in patients with cardiovascular diseases, recent research shows that the drug is still prescribed to risk groups.

Given the high consumption of dicolofenac in Montenegro, it is a realistic assumption that this drug is largely prescribed to patients in whom its use is contraindicated or must be carried out with great caution.

In order to reduce the use of diclofenac in Montenegro to at-risk groups of patients, in addition to the warnings that should appear to the physician trying to prescribe diclofenac to such patients, it would be preferably to include a recommendation on alternative therapy (eg. paracetamol, naproxen, ibuprofen at a dose of less than 1200 mg/day).

Using new IT tools that enable a wide range of prescription database searches, it is necessary to continuously conduct prescribing and consumption analyses of drugs of interest, in this case diclofenac, to obtain reliable indicators of (ir)rational use of the drug that will be the basis for taking necessary regulatory measures that will enable its safe and optimal use.

4. References

Bresalier RS et al. (2005). Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med; 352:1092-102.

European Medicines Agency (2017). European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Call for information on effectiveness of risk minimisation on diclofenac (Referral EMEA/H/A-31/1344). February 2017.

Gislason G.H. et al. (2006). Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction. Circulation. 113(25): 2906-13.

Gislason G.H. et al. (2009). Increased mortality and cardiovascular morbidity associated with use of nonsteroidal antiinflammatory drugs in chronic heart failure. Arch Intern Med.169(2):141-9.

Lamberts M. Et al. (2013). Ongoing treatment with non-steroidal anti-inflammatory drugs at time of admission is associated with poorer prognosis in patients with first-time acute myocardial infarction. Int J Cardiol. 168(2):832-37.

Morales RD et al. (2020). Impact of EU regulatory label changes for diclofenac in people with cardiovascular disease in four countries: Interrupted time series regression analysis. Br J Clin Pharmacol. 2020:1-12.

Ray W.A. et al. (2009).. Cardiovascular risks of nonsteroidal antiinflammatory drugs in patients after hospitalization for serious coronary heart disease. Circ Cardiovasc Qual Outcomes. 2 (3): 155-63.

Schjerning Olsen A.M. et al. (2011). Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: a nationwide cohort study. Circulation. 123 (20): 2226-35.

Schmidt M. et al. (2018). Diclofenac use and cardiovascular risks: series of nationwide cohort studies. BMJ: 362:k3426.