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

WP 3 - Conducting of the Drug utilisation study – DUS of diclofenac, scientific analysis of obtained data on prescribing of diclofenac in PHC, preparational activities for publication of data in scientific journals

---

DEV 3.1 - Analysis of obtained data on prescribing patterns of diclofenac in PHC

Authors:

Veselinka Vukicevic, Institute for Medicines and Medical Devices (CInMED)

List of authors with affiliation

This project is co-funded by the European Union

The project is implemented by

Table of Contents

This project is co-funded by the European Union

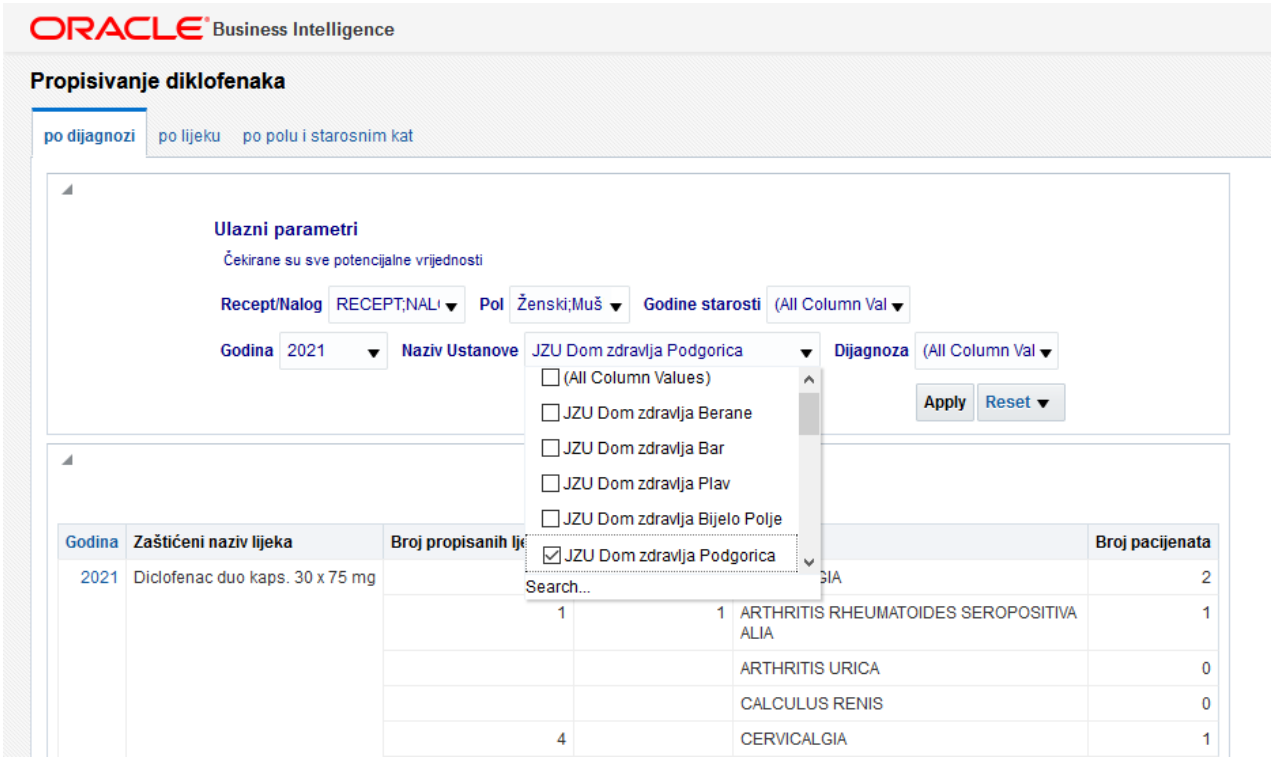
The project is implemented by

1. Introduction

As a part of the project, Data Warehouse System (DW) containing cleansed, catalogued and transformed data on prescribing of diclofenac in primary healthcare (PHC) was formed. A Business Intelligence tools (BI) were created for searching and analysing the data collected on the PHC level. The analysis of data on the prescription of diclofenac on the PHC level is enabled by the diagnosis, trade name, as well as by the gender and age category of the patient. Regarding age, patients are grouped into 6 categories: up to 17 years of age, 18 to 44 years, 45 to 64 years, 65 to 74 years, over 75 years of age and unknown age. Along with that, the BI tool enables search by the potential interaction of diclofenac with the other medicines used concomitantly, and the analysis of anamnestic data in order to determine the reason behind the prescription of diclofenac in a specific situation. Data analysis depending on whether the prescribed form of diclofenac is intended for oral, parenteral or rectal administration is also enabled. The analysis of the prescribing practice by individual Montenegrin health care institutions is enabled – data are available for 18 primary health care centers in Montenegro. As for the period of time the available data relates to, the data is available for 2016, 2017, 2018, 2019, 2020 and 2021 and they are constantly updated during the implementation of the project. The available data are analysed in line with the information on medicine (Summary of Product Characteristics) and valid recommendations on the use of diclofenac. Approved indications, counter-indications, measures of caution and special warnings for use of the medicine are taken into consideration, as well as interactions with other medicines and other types of interaction. In line with this, there are 3 main sets of project reports:

1. Reports on diclofenac prescriptions and consumption
2. Reports on interaction of other medicines prescribed with diclofenac to patients
3. Reports on medical treatment of patients with prescribed diclofenac medicines.

These reports provide analiysis of the large amount of obtained data on prescribing diclofenac in PHC.



2. Analysis of the available data

2.1 Analysis of prescribing of diclofenac according to the diagnosis

Available data on diagnoses that were used in prescribing of diclofenac in PHC were analysed. The finding was that the prescribing of diclofenac in the time period covered by the project is connected with an extremely high number of diagnoses. Diclofenac has been prescribed for more than 4 thousand different diagnoses in the PHC during 2016 – 2021 time period.

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

WP3

Report"Efficacy and safety profile of diclofenac – an overview"

Author:

Silva Dobrić

University of Defence

Faculty of Medicine of the Military Medical Academy

Belgrade, Serbia

This project is co-funded by
the European Union

The project is implemented by

Table of Contents

This project is co-funded by the European Union

The project is implemented by

1. Introduction

Diclofenac is a proven, commonly prescribed nonsteroidal anti-inflammatory drug (NSAID) that has analgesic, anti-inflammatory, and antipyretic properties, and has been shown to be effective in treating a variety of acute and chronic pain and inflammatory conditions. Generally, NSAIDs, and among them especially diclofenac, are the most widely used drugs in the world. It is estimated that 14 million Americans age 45 and older use NSAIDs daily. As the population continues to age, the United States Centers for Disease Control and Prevention (CDC) expects a marked rise in the use of this drug class that will mirror the expected increased prevalence of painful conditions, such as osteoarthritis and inflammatory diseases. It then comes as no surprise that the rate of adverse events associated with NSAID consumption will also likely escalate. Previous studies have shown that 5% to 7% of hospital admissions result from adverse effects and toxicity with non-aspirin NSAIDs contributing to 11% to 12% of those admissions (1, 2).
Having in mind these facts, the objectives of this overview are:

- Outline the mechanisms of action of diclofenac
- Review the indications for therapy with diclofenac
- Summarize the efficacy and potential adverse effects of diclofenac
- Give the proposals for more rational and safer diclofenac use

2. Method

The PubMed and SCOPUS databases were searched in August 2021 with aim to select articles dealing with efficacy, safety, tolerability (withdrawals) and toxicity of diclofenac in comparison with other NSAIDs, published in the last 20 years (2000 to 2020). Abstracts and full text articles in a language other than English were excluded. The relevance of each citation identified was assessed in a two-tiered approach. First, the titles and abstracts were screened for eligibility, and those fulfilling the selection criteria were included in the next stage. Only articles available in full text were analysed.
This report mostly presents the results of large meta-analyses and randomized clinical studies published in the mentioned period.

3. Mechanism of action

As with all NSAIDs, diclofenac exerts its action via inhibition of prostaglandin synthesis by inhibiting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) and, consequently, by inhibiting the synthesis of prostanoids such as prostaglandin-E2 (PGE2), prostacyclins, and thromboxanes, which are essential components of the inflammatory and nociceptive response (Figure 1) (3).

Diclofenac inhibits COX-1 and COX-2 relatively equally, although evidence suggests that it has selective COX-2 inhibition, about four times that of the inhibition of COX-1 during *in vitro* experimentation. This value is far from the

reported 20-fold selectivity of COX-2 inhibition of the more selective COX-2 inhibitors like rofecoxib, but diclofenac's activity can be compared more accurately to that of celecoxib (4-6). Diclofenac is regarded as one of the most effective inhibitors of the production of PGE2. Like other NSAIDs, it also has effect in blocking the production of thromboxanes, especially thromboxane-B2 (TXB2) (4, 5).

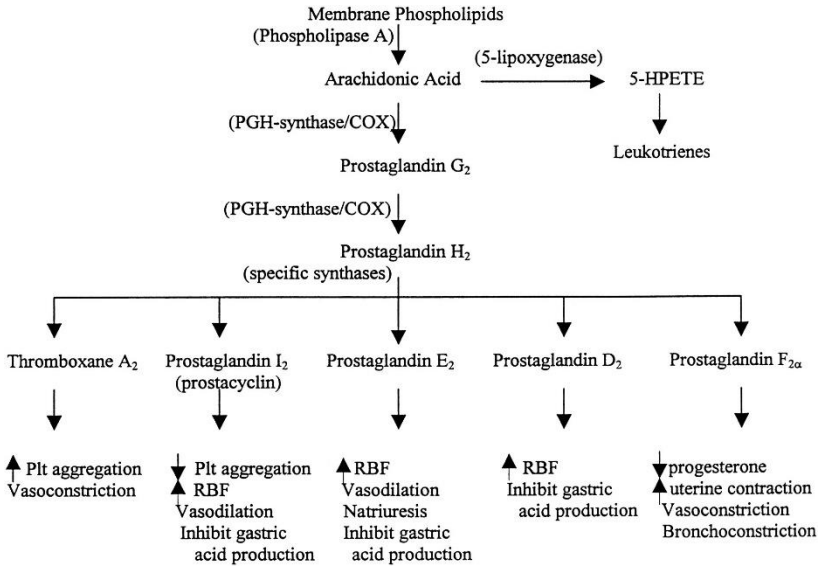


Figure 1. Arachidonic acid pathway

COX-1 is a constitutively active enzyme that is expressed almost ubiquitously over the human body. The level and activity of COX-1 are thought to be rather stable and participates in the maintenance of normal activity of platelets, blood flow into renal tissues, and protection of the gastric mucosa from harmful acidity, among other processes (3). COX-2 is an inducible enzyme that is overly expressed during times of tissue damage and in the presence of inflammatory mediators that also have nociceptive properties and induce pain. These include thromboxanes, leukotrienes, and prostaglandins. Diclofenac's effect of COX-2 inhibition appears to occur mostly at the site of target tissues such as synovial fluid and joint capsules. However, the inhibition of COX enzymes in other tissues, such as the stomach, may cause the depletion of many protective substances and can lead to the development of gastric irritation, for example (6, 7). Many of these mechanisms of action are considered putative by the clinical community.
Diclofenac's peripheral analgesic effects are attributable to its activity in decreasing the availability of sensitized peripheral pain receptors via down-regulation, which appears to be accomplished by stimulating the L-arginine nitric oxide cGMP pathway via activation of ATP-sensitive potassium channels. Also, evidence suggests that diclofenac has activity in reducing the previously increased levels of substance P, a known pro-inflammatory neuropeptide with nociceptive activity in the synovial fluid of patients with rheumatoid arthritis (5). The mechanism of action of

diclofenac inhibiting downstream arachidonic acid metabolite production may explain its efficacy in treating actinic keratosis and preventing progression to more malignant disease. This way, topical diclofenac may inhibit the production of epithelial growth factors that would otherwise promote angiogenesis and inhibit apoptosis in proliferating tissue. However, this mechanism is still subject to testing and debate (8).

5. Indications

As mentioned above, diclofenac is is the most widely prescribed NSAID worldwide. In general, it is used in the treatment and management of acute and chronic pain associated with inflammatory conditions, especially those involving the musculoskeletal system such as osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Although it can help to manage the symptoms of pain during inflammatory processes, it cannot reverse or prevent chronic joint damage seen with osteoarthritis and rheumatoid arthritis (10).
Topically, it can be used for treating actinic keratosis (8, 9).
In many countries, diclofenac is also approved for ophthalmic administration for the treatment of eye pain, redness, and swelling in patients who are recovering from cataract or laser surgery, during eye surgery, to prevent the pupil of the eye from becoming smaller, and to relieve eye symptoms of seasonal allergies such as hay fever (10).
Diclofenac has been used off-label to treat biliary colic, corneal abrasion, fever, gout, migraine, myalgia, and post-episiotomy pain. Its rectal administartion has been recomended in prophylaxis of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Studies have also elucidated the benefits of using diclofenac post-operatively to reduce the need for rescue analgesia in patients after surgery (10).
In general, in many countries diclofenac 1% gel was approved for over-the-counter (OTC) distribution in the management of arthritic pain. Otherwise, the drug is only available via prescription (10).

According to the Montenegrin Institute of Medicines and Medical Devices (CInMED) data, diclofenac is marketed in Montenegro in the dosage forms for systemic administration (75 mg modified-release capsules, 75 mg gastro-resistant capsules, 50 mg gastro-resistant tablets, 1% gel, 75 mg/3 mL solution for, 50 mg suppository, 100 mg prolonged-release tablets, 50 mg film-coated tablets, 75 mg tablets, 100 mg modified-release tablets, 50 mg coated tablets), as well as in forms for topical use (1% gel for application on the skin and 0.1% eye drops) (https://www.cinmed.me/).

6. Administration

Diclofenac containing medicinal products are available in different formulations, such as tablets, capsules for oral administration [including immediate-release (IR), gastro-resistant, soluble effervescent, extended-release (ER), combined IR and ER formulations], suppositories for rectal administration and solutions for intravenous or intramuscular injection.

Diclofenac preparations pair the drug with a salt such as sodium, potassium, or epolamine salt. Diclofenac sodium can be administered orally as a tablet or suspension, intramuscularly in solution, intravenously in solution, topically in the form of gel or eye drops on the skin and eye, respectively or by rectal route as a suppository. Diclofenac potassium is available for oral administration in oral tablet or suspension forms. Diclofenac epolamine is available as a transdermal patch (10).

When orally administered, diclofenac is absorbed rapidly and binds to albumin in the plasma. The drug concentrates in synovial fluids, where it renders its targeted action as an NSAID for relief musculoskeletal inflammation and ailments. It has both extended-release and immediate-release forms that vary in doses. Oral administration of diclofenac, like other NSAIDs, carries the risk of gastrointestinal upset and is recommended to consume the medication with food or milk in all age groups. In addition, there are formulations of diclofenac combined with misoprostol to mitigate gastrointestinal adverse effects. It is common practice for clinicians to prescribe gastric acid-reducing therapies such as proton pump inhibitors (PPI) for concomitant use with NSAIDs to reduce the risk of more serious gastrointestinal (GI) adverse reactions. Recommendations may include taking over-the-counter antacids as a form of gastroprotection (10).

Oral diclofenac sodium can be administered in ER or iIR tablets in 25 to 150 mg tablets to achieve a total daily dose of 100-150 mg per day. These doses are for ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis (10).

Topically, diclofenac sodium is available in gel preparations ranging from 1% to 3% concentrations.

Gel with 1% to 2% diclofenac sodium is indicated for topical administration for osteoarthritis for up to 16 g per day for monoarthritis joints and up to 32 g per day for polyarthritic joints (10).

The 3% diclofenac sodium preparation is reserved for treating actinic keratosis and is to be applied twice daily as hybrid therapy (8, 9).

Intravenous diclofenac sodium can be administered as a 37.5 mg bolus injection every 6 hours for acute moderate to severe pain. Intramuscular diclofenac solution comes as a 75 mg/3 mL solution for managing moderate to severe pain, and administration is generally by injection into large muscle groups such as the thigh or buttocks. Ophthalmic preparations are administered as 1 to 2 drops per affected eye four times daily following cataract surgery and for treatment of photophobia and eye pain.

Generally, diclofenac potassium is administered in either 25 mg or 50 mg doses 1 to 4 times per day for total doses between 50 to 200 mg per day. This treatment is the indicated regimen for migraines, osteoarthritis, generalized pain, primary dysmenorrhea, and rheumatoid arthritis.

Diclofenac epolamine is available as a 1.3% transdermal patch to be applied twice daily over the affected area to relieve pain and inflammation (10).

Diclofenac, like other NSAIDs, should be administered at the lowest effective dose to achieve clinical goals to limit the risk of adverse reactions and toxicity (10).

7. Efficacy

Systemic forms of diclofenac

Diclofenac was first released in Japan in 1974. It is mainly used for pain relief and therefore treats a wide variety of conditions. For the treatment of acute pain, actual gudelines suggest using traditional NSAIDs including diclofenac as a second line agent after paracetamol for moderate pain (11, 12).
The comparative analgesic effects of NSAIDs for acute pain was evaluated by the Oxford Pain Group and formulated into a league table based on systematic reviews of randomised, double-blind, single dose post-operative studies (Table 1). They report the number needed to treat (NNT) to achieve at least 50% reduction in pain compared to placebo for diclofenac 100 mg was 1.9 (95% CI 1.6-2.2) (13). The comparative efficacy of diclofenac was among the best of the NSAIDs.
There is little evidence from longer term efficacy studies versus placebo. Trelle et al. (14) in their systematic review conducted extensive searching to find randomised controlled trials of any NSAID versus placebo that had 100 patient years of follow up and found none for diclofenac. Despite the relative paucity of evidence for diclofenac versus placebo, diclofenac is generally regarded as efficacious. In more recent trials, where COX-2 inhibitors were compared to standard treatment, diclofenac has often been used as the standard treatment. A systematic review was conducted by Pavelka (15) about the efficacy of diclofenac in osteoarthritis. The review reported that diclofenac has been studied in comparisons with many different NSAIDs and other treatments for pain and provides similar efficacy to these other treatments. Often these other treatments (that is COX-2 inhibitors) have been trialled against placebo and this provides good indirect evidence for the efficacy of diclofenac.
It has been shown that rectal NSAIDs may reduce the risk of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. On the basis of findings from several previous meta-analyses, rectal NSAIDs, primarily diclofenac or indomethacin have been recommended by the European Society of Gastrointestinal Endoscopy (ESGE) and Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) guidelines to prevent post-ERCP pancreatitis for all risk patients (17, 18). Efficacy and safety of these two NSAIDs in the post-ERCP parncreatitis prophylaxis has recently been confirmed in a systematic review of 16 randomized controlled trial involving 6458 patients at risk for development of post ERCP parncreatitis (19).

Table 1. The comparative analgesic effects of NSAIDs for acute pain

Analgesic	Number of patients in comparison	Percent with at least 50% pain relief	NNT	Lower confidence interval	Higher confidenc interval
Valdecoxib 40 mg	473	73	1.6	1.4	1.8
Ibuprofen 800	76	100	1.6	1.3	2.2
Ketorolac 20	69	57	1.8	1.4	2.5
Ketorolac 60 (intramuscular)	116	56	1.8	1.5	2.3
Rofecoxib 50	1900	63	1.9	1.8	2.1
Diclofenac 100	411	67	1.9	1.6	2.2
Piroxicam 40	30	80	1.9	1.2	4.3
Lumiracoxib 400 mg	252	56	2.1	1.7	2.5
Paracetamol 1000 + Codeine 60	197	57	2.2	1.7	2.9
Oxycodone IR 5 + Paracetamol 500	150	60	2.2	1.7	3.2
Diclofenac 50	738	63	2.3	2.0	2.7
Naproxen 440	257	50	2.3	2.0	2.9
Oxycodone IR 15	60	73	2.3	1.5	4.9
Ibuprofen 600	203	79	2.4	2.0	4.2
Ibuprofen 400	4703	56	2.4	2.3	2.6
Aspirin 1200	279	61	2.4	1.9	3.2
Bromfenac 50	247	53	2.4	2.0	3.3
Bromfenac 100	95	62	2.6	1.8	4.9
Oxycodone IR 10 + Paracetamol 650	315	66	2.6	2.0	3.5
Ketorolac 10	790	50	2.6	2.3	3.1
Ibuprofen 200	1414	45	2.7	2.5	3.1

Topical forms of diclofenac

The efficacy of topical 1% diclofenac for the treatment of pain and inflammation has been well studied in short-term studies. Zacher et al. (20) conducted an evidence-based review about the efficacy of topical diclofenac. They concluded, based upon published randomised controlled trials, that diclofenac is an effective treatment for painful inflammatory conditions. The topical 3% diclofenac is used solely for the treatment of actinic keratosis and its efficacy in this indecation has also been established.

8. Safety

Examining the recent literature regarding the safety of diclofenac, cardiovascular safety is the most published topic. The gastrointestinal (GI) and hepatic adverse effects of diclofenac are well known and the

recent literature on this is summarised. There were no other significant safety issues identified in the review of the recent literature.

Cardiovascular safety

Despite the relatively rare incidence of serious cardiovascular events in trials of NSAIDs, the following systematic reviews of randomised controlled trials (RCTs) and observational studies clearly show increased risk of cardiovascular adverse effects in patients taking diclofenac.

Bhala et al. (21), in the systematic review published in August 2013, presented estimates of the rate ratio of major cardiovascular events for diclofenac versus placebo (major cardiovascular events being non-fatal myocardial infarction, non-fatal stroke, or death from a vascular cause). They reported a rate ratio of 1.41 (95% CI: 1.12-1.78). They also calculated an annual absolute effect size based on two different baseline risks. For 1000 patients taking diclofenac for one year who have a baseline risk of 2% per year, there would be seven extra major cardiovascular events. For 1,000 patients with a baseline risk of 0.5% per year there would be two extra major cardiovascular events (21).
Trelle et al. (14) in their 2011 systematic review performed an indirect estimate of the cardiovascular effects of diclofenac compared to placebo. They did not group the cardiovascular events together and report separately rate ratios for myocardial infarction 0.82 (95% CI: 0.29-2.20), stroke 2.86 (95% CI: 1.09-8.36) and cardiovascular death 3.98 (95% CI 1.48-12.7).
Kearney et al. (22) in their 2006 systematic review performed an indirect estimate of the effect of diclofenac in comparison to placebo for serious vascular events (defined as non-fatal myocardial infarction, non-fatal stroke, or vascular death). They found a rate ratio of 1.63 (95%CI 1.12-2.37).
Systematic reviews of observational studies also show increased risk of cardivascular adverse events in diclofenac-treated patients compared to those no treated with the drug (Table 2).

Table 2. Systematic reviews of observational studies with diclofenac versus non-use

Author (year) [ref.]	Title	Outcome	Relative risk
McGettigan et al. (2006) [23]	Cardiovascular risk and inhibition of cyclooxygenase. A systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2	Serious cardiovascular events	1.40 (95% CI: 1.16-1.70)
McGettigan et al. (2011) [24]	Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies	Major cardiovascular events	1.40 (95% CI: 1.27-1.55)
Singh et al. (2006) [25]	Risk of acute myocardial infarction with nonselective non-steroidal anti-inflammatory drugs: a meta-analysis	Acute myocardial infarction	1.38 (95% CI: 1.22-1.57)
Varas-lorenzo et al. (2011) [26]	Stroke risk and NSAIDs: a systematic review of observational studies	Stroke: diclofenac versus non-use	1.20 (95% ci: 1.05-1.36)

In following studies, the risk of cardiovascular events in patients with established cardiovascular diseases who used diclofenac has been examined.

Gislason et al. (27) 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 heart failure: 1.35 (95% CI: 1.24-1.48)
- hospitalisation due to acute myocardial infarction: 1.36 (95% CI: 1.12-1.64).

In a separate paper, using the same database, Gislason et al. (28) 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. (29) 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. (30) 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. (31) 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.

When considering safety of low versus high doses of diclofenac, studies show that the risk of serious cardiovascular events within the population of diclofenac users is higher among those who take higher doses (this is consistent across several definitions of high and low dose and different lengths of exposure). Results of these studies are given in Table 3.

Table 3. Cardiovascular adverse effects of diclofenac: dose response relationship

Author (year) [ref.]	Daily diclofenac dose	Relative risk
Garcia Rodriguez et al. [32]	Low-medium dfose High dose	1.51 (95% CI: 1.20-1.89) 1.80 (95% CI: 1.49-2.18)
Van Staa et al. [33]	< 150 mg > 300 mg	1.13 (95% CI: 1.04-1.22) 2.03 (95% CI: 1.09-3.77)
Gislason et al. [27]	< 100 mg > 100 mg	1.14 (95% CI: 0.91-1.43) 2.43 (95% CI: 1.74-3.40)
Gislason et al. [28]	< 100 mg > 100 mg	1.27 (95% CI: 0.92-1.76) 1.89 (95% CI: 1.40-2.55)
Fosbol et al. [34]	< 100 mg > 100 mg	0.96 (95% CI: 0.59-1.57) 2.01 (95% CI: 1.56-2.59)

According to these results are those from the study of Hasford et al. (35). They conducted an observational cohort study which examined the safety of short-term, low-dose diclofenac. In the cohort of 446 participants followed for 19 days, none reported a serious cardiovascular adverse event. This gives some support to the safety of the short term use of low-dose diclofenac.

Fosbol et al. [36] examined the cardiovascular risk associated with NSAIDs in otherwise healthy individuals. They used a Danish registry database and selected patients who had not had any contact with the hospital system for five years and had not used serious pharmacological treatments for two years. The study population comprised 1,028,427 individuals of whom 44.7% claimed at least one prescription for any NSAID. In this low-risk population they found an increased odds ratio of coronary death or non-fatal myocardial infarction to be 1.82 (95% CI: 1.43-2.33) among users of diclofenac as compared to no NSAID use. In a similar paper, Fosbol et al. [37] examined the cerebrovascular risk of NSAIDs in a healthy population and report that diclofenac was associated with an increased risk of stroke but did not quantify the risk in the article.

In general, the available evidence regarding cardiovascular safety of diclofenac suggests a less favourable cardiovascular risk profile compared to other NSAIDs such as naproxen and ibuprofen, and similar risks as those of COX-2 inhibitors.

Accordingly, cardiovascular safety of diclofenac and other NSAIDs has been continuously reviewed over the last years. The safety of diclofenac-containing products has been examined by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC). On 25 September 2013, the EMA released its safety advice for diclofenac (38). The Summary of Product Characteristics (SPC) and Package Leaflet changes that it recommended are provided below. A search of the websites of the major international regulators did not reveal any other changes to diclofenac.

The EMA recommended that the following text be inserted into the following sections.

A. 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 (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

Section 4.4 *Special warnings and precautions for use:*
Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking) should only be treated with diclofenac after careful consideration.
As the cardiovascular 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).

B. 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.

Gastrointestinal and hepatic safety

GI side effects of NSAIDs, especially upper GI bleeding, are well known. Unlike for cardiovascular risks, the recent literature has remained relatively quiet on the GI and hepatic adverse effects of NSAIDs in general and diclofenac specifically.

Castellsague et al. (39) conducted a systematic review of observational studies that report on the serious upper GI complications of individual NSAIDs (peptic ulcer perforations, obstructions and bleeding). They report a relative risk of 3.37 (95% CI: 2.55-4.46) for diclofenac compared to no use of any NSAID. Bhala et al. (21) in their systematic review and meta-analysis of individual participant data also report on upper GI complications (bleeding, perforation and obstruction) with a relative risk of 1.89 (95%CI: 1.16-3.09) for diclofenac versus placebo.

It is important to consider that studies have shown that GI damage occurs over extended periods of exposure to the adverse GI effects of NSAIDs. Therefore, clinicians frequently prescribe a gastroprotective agent such as a PPI or PGE2 analog to decrease acid production or increase gastroprotective activity, respectively.

NSAIDs, including diclofenac, can cause drug-induced hepatic damage and increases in liver transaminase levels. These events are usually transient and reversible. Although rare, patients exposed to long-term NSAID treatment can develop hepatitis and face a life-threatening adverse effect. These are more prevalent in patients taking long-term diclofenac for rheumatoid arthritis (40- 44). Female patients aged >50 years, with autoimmune disease, and those on other potentially hepatotoxic drugs, appear to be particularly susceptible. Liver function test abnormalities generally settle within 4-6 weeks of stopping the causative drug. However, some patients may develop acute liver failure and successful orthotopic liver transplantation may be undertaken in such patients. Recent *in vitro* animal studies have shown that the mechanism of diclofenac toxicity relates both to impairment of ATP synthesis by mitochondria, and to production of active metabolites, particularly n,5-dihydroxydiclofenac, which causes direct cytotoxicity. Mitochondrial permeability transition (MPT) has also been shown to be important in diclofenac-induced liver injury, resulting in generation of reactive oxygen species, mitochondrial swelling and oxidation of NADP and protein thiols (45).

Having in mind these facts, physicians and hepatologists must be vigilant to the hepatotoxic potential of diclofenac as well as other NSAIDs, as increased awareness, surveillance and reporting of these events will lead to a better understanding of the risk factors and the pathophysiology of NSAID-related hepatotoxicity.

Safety of topical diclofenac

Taylor et al. (47) conducted a systematic review looking at the safety profile of topical diclofenac in the treatment of musculoskeletal conditions. They included only randomised controlled trials. They do not report any major cardiovascular, GI or hepatic adverse events. The longest study duration in the review was 12 weeks.

There were no observational studies that looked into the safety of topical diclofenac identified in the literature searches. A non-systematic narrative review was found which commented on the fact that the literature regarding adverse events for topical diclofenac is limited and that there are no studies evaluating the long-term safety (5).

Pharmacokinetics of diclofenac after topical administration on the skin supports its systemic safety. Namely, when comparing 150 g/day of oral diclofenac to high-dose topical diclofenac 1% gel (48 g/day), the oral diclofenac had 40-fold higher peak plasma concentrations and the AUC_{0-24} was fivefold higher (47).

8. Analysis of regulatory status of diclofenac

There is consensus among regulators around the world regarding recommendations for the use of diclofenac in the approved indication area. Special emphasis in these recommendations is placed on the safety of the use of this drug.

9. Conclusions and recommendation

Diclofenac is widely used in the treatment of pain where there is an inflammatory component. It is available in oral, rectal and topical forms. The overall risk/benefit ratio of the drug remains favourable. However, it is necessary to constantly monitor their application in practice because according to recently published data, despite warnings regarding the use of the drug, it is still prescribed to patients with contraindications (48).

In Montenegro, 15 preparations of diclofenac have been approved (9 in the form of oral administration, 2 in the form of solution for injection, 2 as a 1% gel and one in the form of eye drops). Summaries of Product Characteristics and Patient Instructions for diclofenac preparations marketed in Montenegro contain all relevant data for the safe use of this drug. These documents are regularly updated following the recommendations of the European Medicines Agency. However, according to the data of CInMED, diclofenac is among 10 most used drugs in Montenegro in last several years, much more than in the region and EU countires. This speaks in favor of its irrational consumption.

Improvements to the existing integrated health information system in terms of the ability to monitor the prescribing of diclofenac to different categories of patients with regard to comorbidities, age, existing therapy, will allow to see the extent to which diclofenac is prescribed to risk groups and, consequently, indicate the need in which segments of the electronic prescription program should install a warning system that will signal to the attending physician to pay attention and consider whether that patient should be prescribed diclofenac with regard to diagnoses that are contraindications or precautions for its use. Therefore, the proposal is 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 (especially cardiovascular ones because of their high morbidity and mortality rates) or who is

on therapy with certain groups of drugs that, given concomitantly with diclofenac, can lead to serious complications (e.g. anticoagulants).
It is expected that this measure will help in more rational prescribing of diclofenac and ensuring its safer use.

10. References

1. Davis JS, Lee HY, Kim J, Advani SM, Peng HL, Banfield E, et al. Use of non-steroidal anti-inflammatory drugs in US adults: changes over time and by demographic. Open heart. 2017; 4(1):e000550.

2. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ Clinical Research. 2004; 329(7456):15-9.

3. Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. Arteriosclerosis, thrombosis, and vascular biology. 2011; 31(5):986-1000

4. Altman R,Bosch B,Brune K,Patrignani P,Young C, Advances in NSAID development: evolution of diclofenac products using pharmaceutical technology. Drugs. 2015; 75(8):854-77.

5. Gan TJ. Diclofenac: an update on its mechanism of action and safety profile. Curr Med Res Opin. 2010; 26(7):1715-31.

6. Grosser T, Fries S, FitzGerald GA. Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities. J Clin Invest. 2006; 116(1):15-31.

7. Takeuchi K,Amagase K, Roles of Cyclooxygenase, Prostaglandin E2 and EP Receptors in Mucosal Protection and Ulcer Healing in the Gastrointestinal Tract. Curr Pharm Des. 2018; 24(18):2002-11.

8. Pirard D,Vereecken P,Mélot C,Heenen M, Three percent diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses: a meta-analysis of the recent studies. Arch Dermatol Res. 2005; 24(18):2002-11.

9. Tampucci S, Carpi S, Digiacomo M, Polini B, Fogli S, Burgalassi S, et al. Diclofenac-Derived Hybrids for Treatment of Actinic Keratosis and Squamous Cell Carcinoma. Molecules (Basel, Switzerland). 2019; 24(9):1793. doi: 10.3390/molecules24091793.

10. Buckingham R (editor). Martindale: The Complete Drug Reference. 40th edition. London: The Pharmaceutical Press and the Royal Pharmaceutical Society; 2020.

11. Anekar AA, Cascella M. WHO Analgesic Ladder. [Updated 2021 May 18]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554435/

12. Agency Task Force Report: Updates, Gaps, Inconsistencies, and Recommendations. May, 2019. Retrieved from U. S. Department of Health and Human Services website: https://www.hhs.gov/ash/advisory-committees/pain/reports/index.html

13. Ong CK, Lirk P, Tan CH, Seymour RA. An evidence-based update on nonsteroidal antiinflammatory drugs. Clin Med Res. 2007; 5(1):19-34.

14. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086.

15. Pavelka K. A comparison of the therapeutic efficacy of diclofenac in osteoarthritis: a systematic review of randomised controlled trials. Curr Med Res Opin. 2012;28(1):163- 78.

16. Zacher J, Altman R, Bellamy N, Bruhlmann P, Da SJ, Huskisson E, et al. Topical diclofenac and its role in pain and inflammation: an evidence-based review. Curr Med Res Opin 2008 Apr;24(4):925-50.

17. Yokoe M et al. Japanese guidelines for the management of acute pancreatitis: Japanese Guidelines 2015. J Hepatobiliary Pancreat Sci. 2015; 22: 405–32

18. Dumonceau JM et al. Prophylaxis of post-ERCP pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - updated June 2014. Endoscopy 2014; 46: 799–815.

19. Hou Y-C, Hu Q, Huang J, Fang J-Y, Xiong H. Efficacy and safety of rectal nonsteroidal anti-inflammatory drugs for prophylaxis against post-ERCP pancreatitis: a systematic review and meta-analysis. Sci Rep. 2017; 7:46650. DOI: 10.1038/srep46650.

20. Zacher J, Altman R, Bellamy N, Bruhlmann P, Da SJ, Huskisson E, et al. Topical diclofenac and its role in pain and inflammation: an evidence-based review. Curr Med Res Opin 2008 Apr;24(4):925-50.

21. Bhala N, Emberson J, Merhi A, Abramson S, Arber N, Baron JA, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013 Aug 31;382(9894):769-79.

22. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclooxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. BMJ 2006; 332(7553):1302-8.

23. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. JAMA 2006 Oct 4;296(13):1633-44.

24. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. PLoS Med 2011 Sep;8(9):e1001098.

25. Singh G, Wu O, Langhorne P, Madhok R. Risk of acute myocardial infarction with nonselective non-steroidal anti-inflammatory drugs: a meta-analysis. Arthritis Res Ther 2006;8(5):R153.

26. Varas-Lorenzo C, Riera-Guardia N, Calingaert B, Castellsague J, Pariente A, Scotti L, et al. Stroke risk and NSAIDs: a systematic review of observational studies. Pharmacoepidemiol Drug Saf 2011 Dec;20(12):1225-36.

27. Gislason GH, Rasmussen JN, Abildstrom SZ, Schramm TK, Hansen ML, Fosbol EL, et al. Increased mortality and cardiovascular morbidity associated with use of nonsteroidal antiinflammatory drugs in chronic heart failure. Arch Intern Med 2009 Jan 26;169(2):141-9.

28. Gislason GH, Jacobsen S, Rasmussen JN, Rasmussen S, Buch P, Friberg J, et al. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardiaql infarction. Circulation 2006 Jun 27;113(25):2906-13.

29. Schjerning Olsen AM, Fosbol EL, Lindhardsen J, Folke F, Charlot M, Selmer C, et al. 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 2011 May 24;123(20):2226-35.

30. Ray WA, Varas-Lorenzo C, Chung CP, Castellsague J, Murray KT, Stein CM, et al. Cardiovascular risks of nonsteroidal antiinflammatory drugs in patients after hospitalization for serious coronary heart disease. Circ Cardiovasc Qual Outcomes 2009 May;2(3):155-63.

31. Lamberts M, Fosbol EL, Olsen AM, Hansen ML, Folke F, Kristensen SL, et al. 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 2013 Sep 30;168(2):832-7.

32. Garcia Rodriguez LA, Tacconelli S, Patrignani P. Role of dose potency in the prediction of risk of myocardial infarction associated with nonsteroidal anti-inflammatory drugs in the general population. J Am Coll Cardiol. 2008;52(20):1628-36.

33. van Staa TP, Rietbrock S, Setakis E, Leufkens HG. Does the varied use of NSAIDs explainthe differences in the risk of myocardial infarction? J Intern Med. 2008;264(5):481-92.

34. Fosbol EL, Folke F, Jacobsen S, Rasmussen JN, Sorensen R, Schramm TK, et al. Cause-specific cardiovascular risk associated with nonsteroidal antiinflammatory drugs among healthy individuals. Circ Cardiovasc Qual Outcomes 2010;3(4):395-405.

35. Hasford J, Moore N, Hoye K. Safety and usage pattern of low-dose diclofenac when used as an over-the-counter medication: results of an observational cohort study in a communitybased pharmacy setting. Int J Clin Pharmacol Ther. 2004;42(8):415-22.

36. Fosbol EL, Gislason GH, Jacobsen S, Folke F, Hansen ML, Schramm TK, et al. Risk of myocardial infarction and death associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) among healthy individuals: a nationwide cohort study. Clin Pharmacol Ther 2009 Feb;85(2):190-7.

37. Fosbol EL, Schjerning Olsen AM, Olesen JB, Andersson C, Kober L, Torp-Pedersen C, et al. Use of nonsteroidal anti-inflammatory drugs among healthy people and specific cerebrovascular safety. Int J Stroke 2014; 9(7):943-45.

38. European Medicines Agency. Assessment Report for diclofenac containing medicinal products (systemic formulations). Procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data (EMEA/H/A-31/1344). 25 September 2013 (EMA/544760/2013). Available at the website: https://www.ema.europa.eu/en/documents/referral/diclofenac-article-31-referral-prac-assessment-report_en.pdf.

39. Castellsague J, Riera-Guardia N, Calingaert B, Varas-Lorenzo C, Fourrier-Reglat A, Nicotra F, et al. Individual NSAIDs and upper gastrointestinal complications: a systematic review and meta-analysis of observational studies (the SOS project). Drug Saf 2012 Dec 1;35(12):1127-46.

40. Aithal GP, Day CP. Nonsteroidal anti-inflammatory drug-induced hepatotoxicity. Clin Liver Dis. 2007 Aug;11(3):563-75.

41. Lapeyre-Mestre M, de Castro AM, Bareille MP, Del Pozo JG, Requejo AA, Arias LM, Montastruc JL, Carvajal A. Non-steroidal anti-inflammatory drug-related hepatic damage in France and Spain: analysis from national spontaneous reporting systems. Fundam Clin Pharmacol. 2006 Aug;20(4):391-5.

42. Rostom A, Goldkind L, Laine L. Nonsteroidal anti-inflammatory drugs and hepatic toxicity: a systematic review of randomized controlled trials in arthritis patients. Clin Gastroenterol Hepatol. 2005; 3(5):489-98.

43. O'Connor N, Dargan PI, Jones AL. Hepatocellular damage from non-steroidal anti-inflammatory drugs. QJM. 2003; 96(11): 787-91. 4.

44. Laine L, Goldkind L, Curtis SP, Connors LG, Yanqiong Z, Cannon CP. How common is diclofenac-associated liver injury? Analysis of 17,289 arthritis patients in a long-term prospective clinical trial. Am J Gastroenterol. 2009; 104(2):356-62.

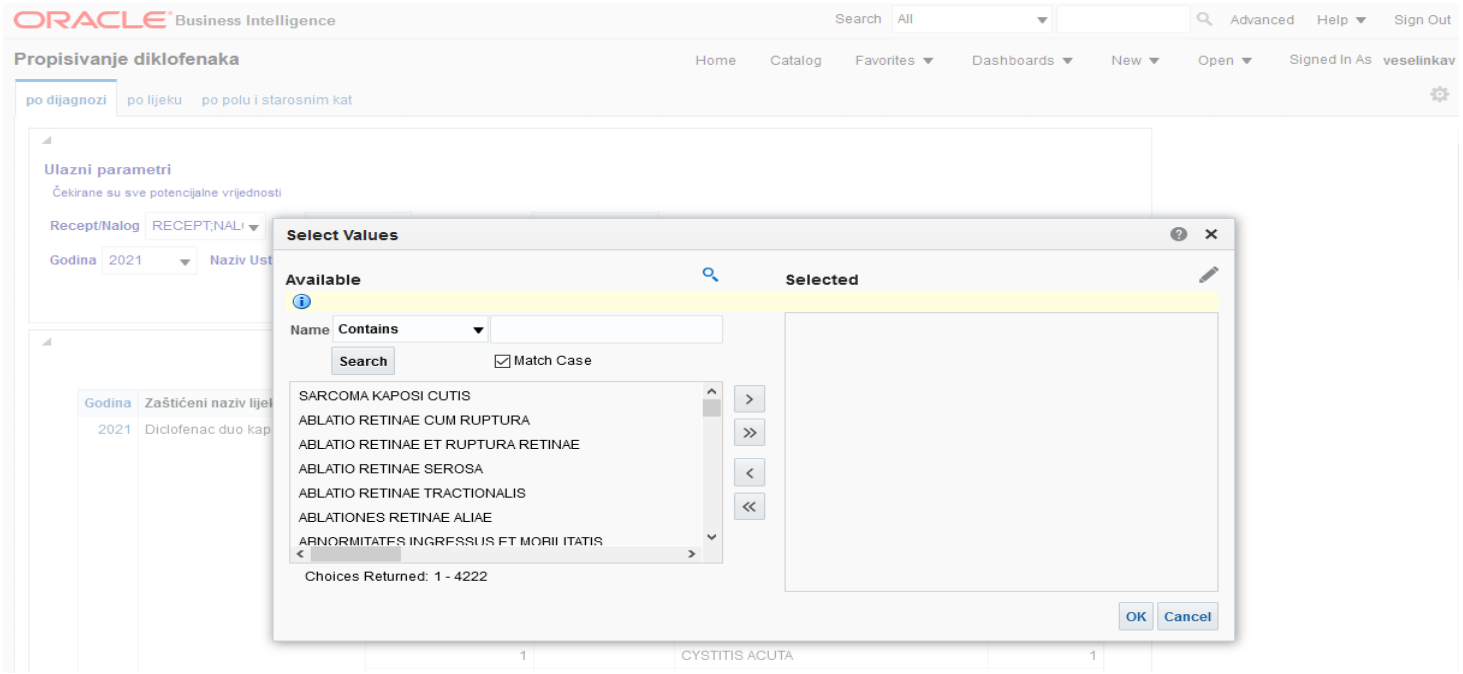
45. Syed M, Skonberg C, Hansen SH. Mitochondrial toxicity of diclofenac and its metabolites via inhibition of oxidative phosphorylation (ATP synthesis) in rat liver mitochondria: Possible role in drug induced liver injury (DILI). Toxicol In Vitro. 2016;31:93-102.

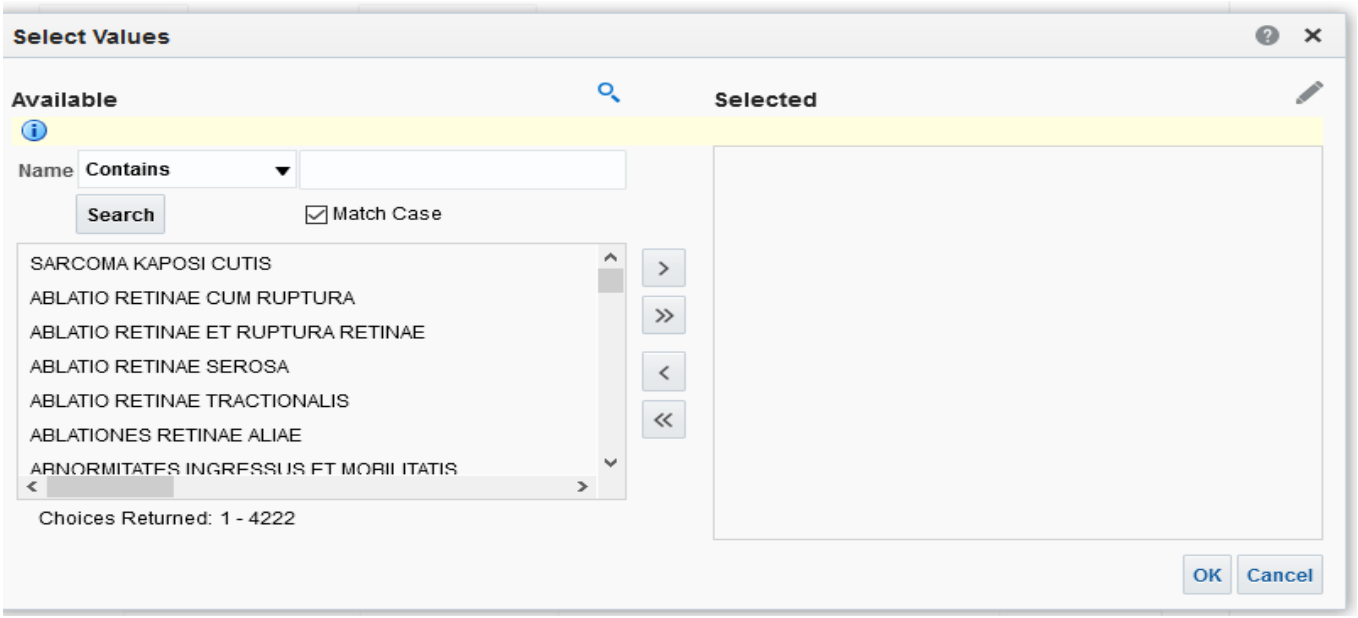
46. Taylor RS, Fotopoulos G, Maibach H. Safety profile of topical diclofenac: a meta-analysis of blinded, randomized, controlled trials in musculoskeletal conditions. Curr Med Res Opin. 2011;27(3):605-22.

47. Altman R, Barkin RL. Topical therapy for osteoarthritis: clinical and pharmacologic perspectives. Postgrad Med. 2009;121(2):139-47.

48. Morales RD, Hallas J, Merings MCR, Mackenzie SI, Bennie M, Morris C et al. Impact of EU regulatoryy label changes for diclofenac in poeple with cardiovascular disease in four countries: Interrupted time series regression analysis. Br J Clin Pharmacol. 2020; 1-12.

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

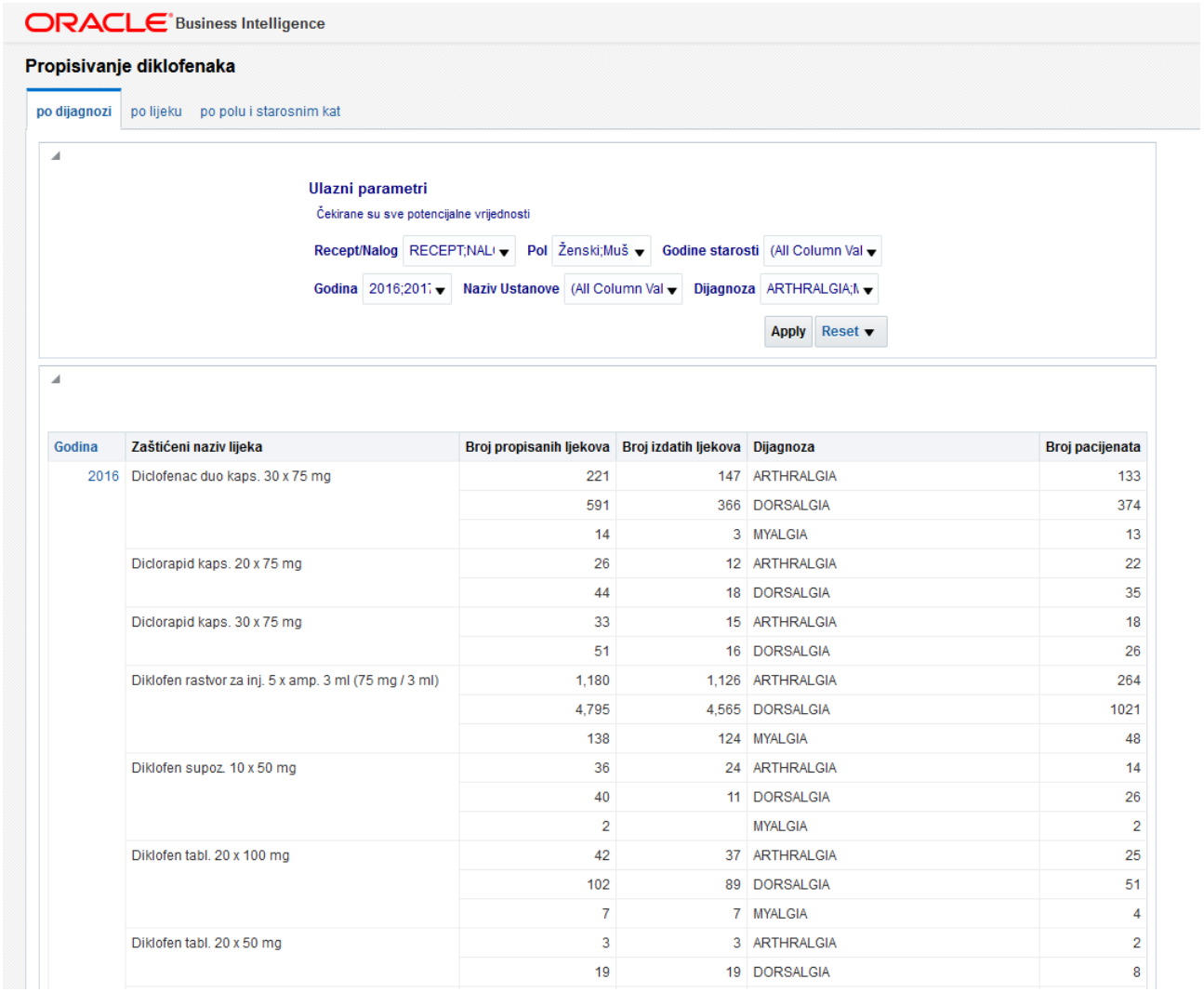




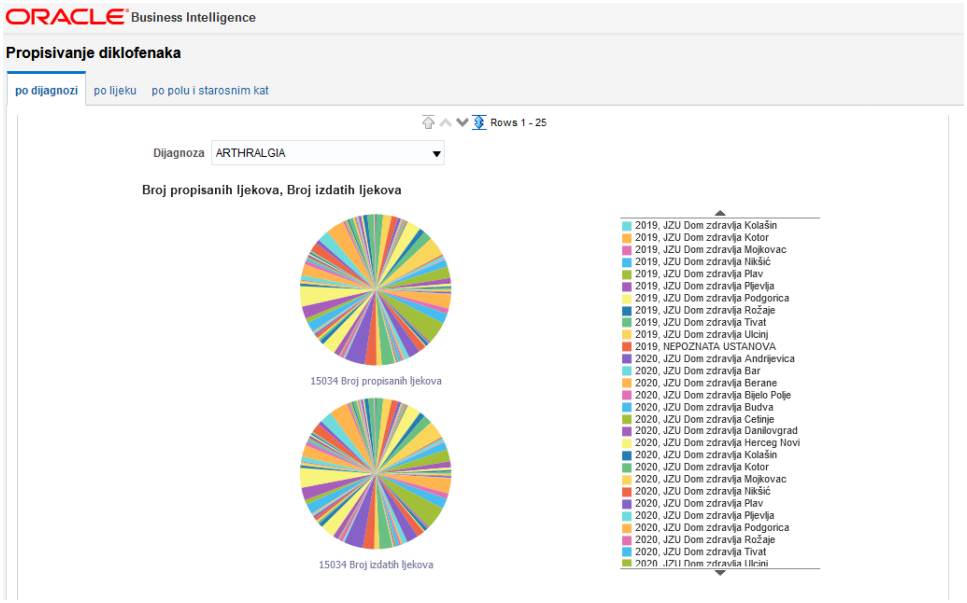
This project is co-funded by
the European Union

The project is implemented by

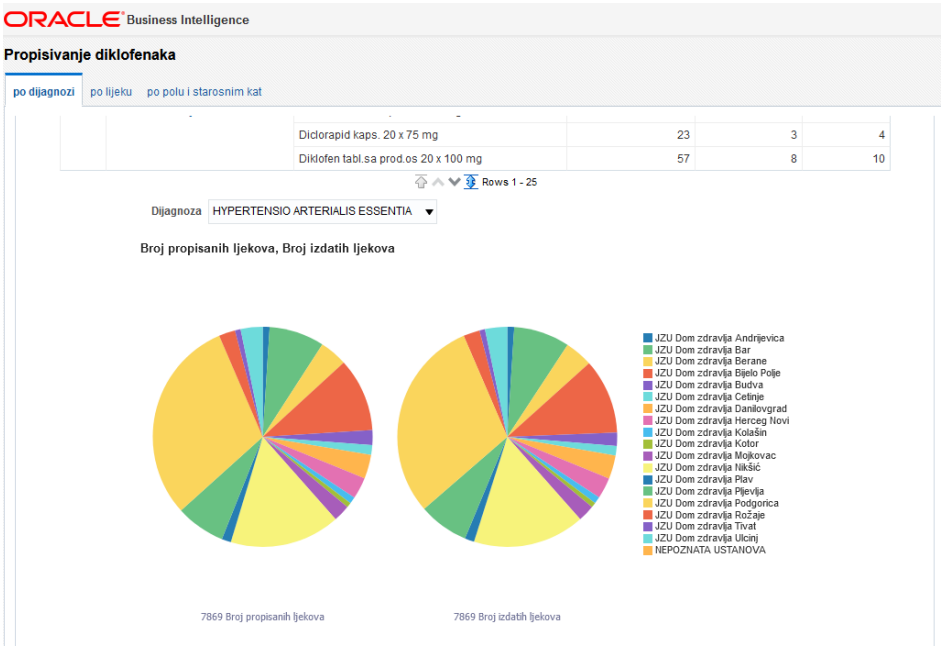
The analysis covered prescribing of diclofenac related to the diagnoses of inflammatory and painful conditions of the musculoskeletal system in line with the approved indications (arthralgia, myalgia, dorsalgia, sciatica, lumbosciatica, spondylosis, extremity pain, gonarthrosis, hip osteoarthritis).



Godina	Zaštićeni naziv lijeka	Broj propisanih ljekova	Broj izdatih ljekova	Dijagnoza	Broj pacijenata
2016	Diclofenac duo kaps. 30 x 75 mg	221	147	ARTHRALGIA	133
		591	366	DORSALGIA	374
		14	3	MYALGIA	13
	Diclorapid kaps. 20 x 75 mg	26	12	ARTHRALGIA	22
		44	18	DORSALGIA	35
	Diclorapid kaps. 30 x 75 mg	33	15	ARTHRALGIA	18
		51	16	DORSALGIA	26
	Diklofen rastvor za inj. 5 x amp. 3 ml (75 mg / 3 ml)	1,180	1,126	ARTHRALGIA	264
		4,795	4,565	DORSALGIA	1021
		138	124	MYALGIA	48
	Diklofen supoz. 10 x 50 mg	36	24	ARTHRALGIA	14
		40	11	DORSALGIA	26
		2		MYALGIA	2
	Diklofen tabl. 20 x 100 mg	42	37	ARTHRALGIA	25
		102	89	DORSALGIA	51
		7	7	MYALGIA	4
	Diklofen tabl. 20 x 50 mg	3	3	ARTHRALGIA	2
		19	19	DORSALGIA	8



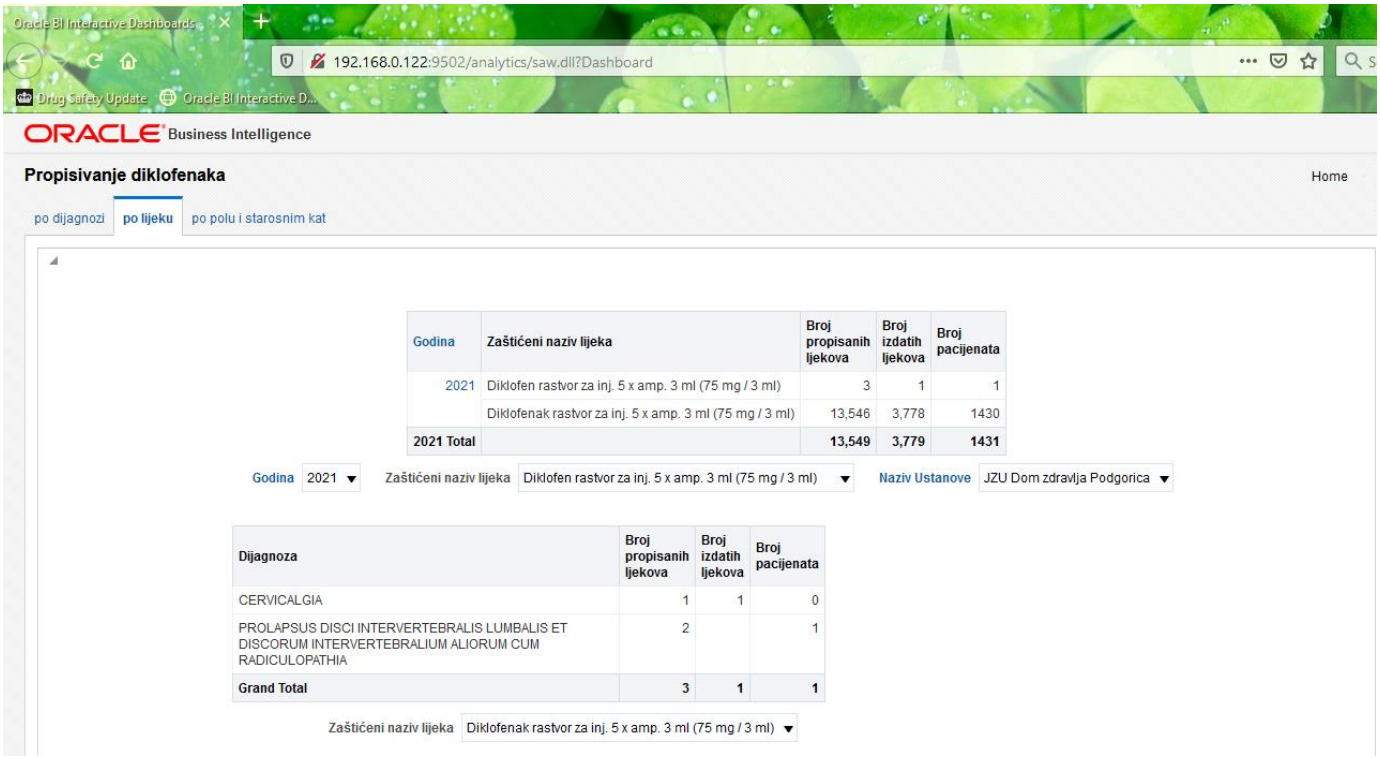
Prescribing of diclofenac related to other diagnoses was analysed as well, with a focus on the diagnoses related to the conditions that according to SPC require special caution in diclofenac use: primary arterial hypertension, insulin-dependent diabetes, hyperlipidemia, angina pectoris, dyspepsia, duodenal ulcer.



2.2 Analysis of prescribing according to the medicine

During the monitored period there were numerous pharmaceutical forms and strengths of diclofenac available at the market, under various trade names: Diclofenac duo capsules 30x75mg, Diclorapid capsules 20x75mg, Diclorapid capsules 30x75mg, Diklofen tablets 20x50mg, Diklofen extended-release tablets 20x100mg, Diklofen solution for injection 5x3ml (75mg/3ml), Diklofenak solution for injection 5x3ml (75mg/3ml), Diklofenak modified-release retard tablets 20x100mg, Diklofenak film-coated tablets 20x50mg, Naklofen duo capsules 20x75mg, Rapten K coated tablets 10x50mg, Rapten duo tablets 30x75mg, Rapten duo capsules 30x75mg, Rapten forte modified-release tablets 20x100mg, Voltaren F tablets 20x50mg, Voltaren rapid coated tablets 10x50mg, Naklofen suppositories 10x50mg, Diklofen suppositories 10x50mg, Voltaren suppositories 10x12.5mg, Voltaren suppositories 10x25mg, Voltaren suppositories 50mg.

Analysis based on the pharmaceutical form was performed in order to compare the share of specific pharmaceutical forms in prescribing practice.

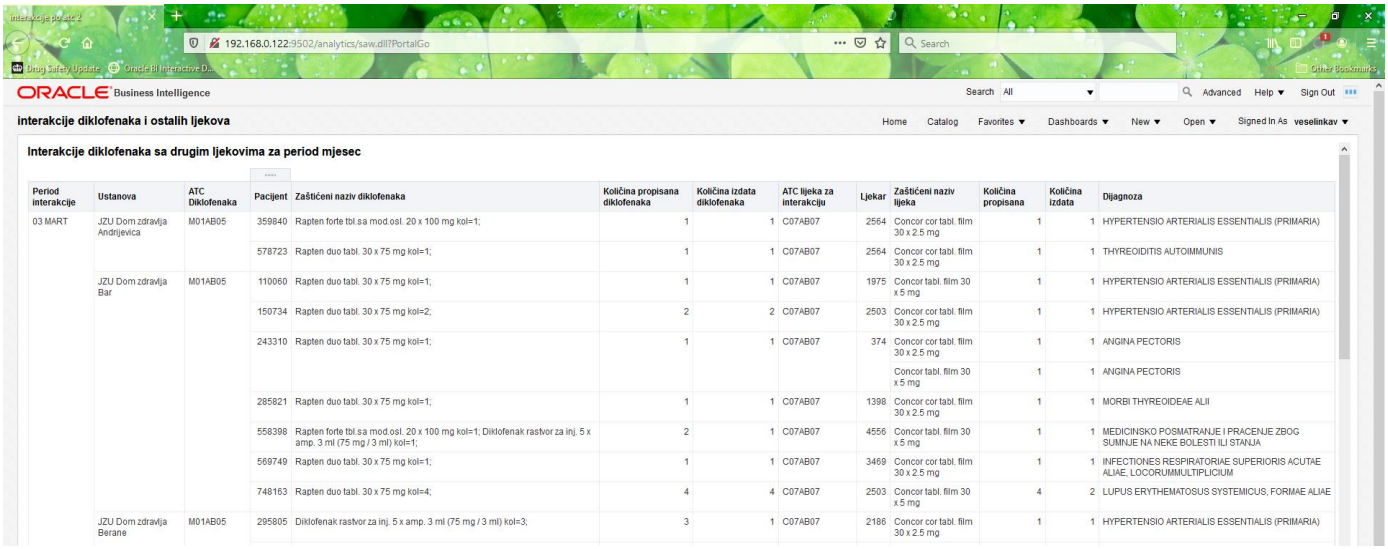


2.3 Analysis of prescribing of diclofenac according to the gender and age

We have analysed the share of men and women regarding diclofenac prescribing, as well as the shares of specific age groups among the patients.

2.4 Analysis of prescribing diclofenac concomitantly with the other medicines

Prescribing diclofenac concomitantly with other medicines was analysed. It was also analysed if diclofenac was prescribed as concomitant medicine during a short or longer time period and which diagnoses are most commonly used in these situations. Potential interactions were analised regarding diferent groups of medicines according to ATC classification.

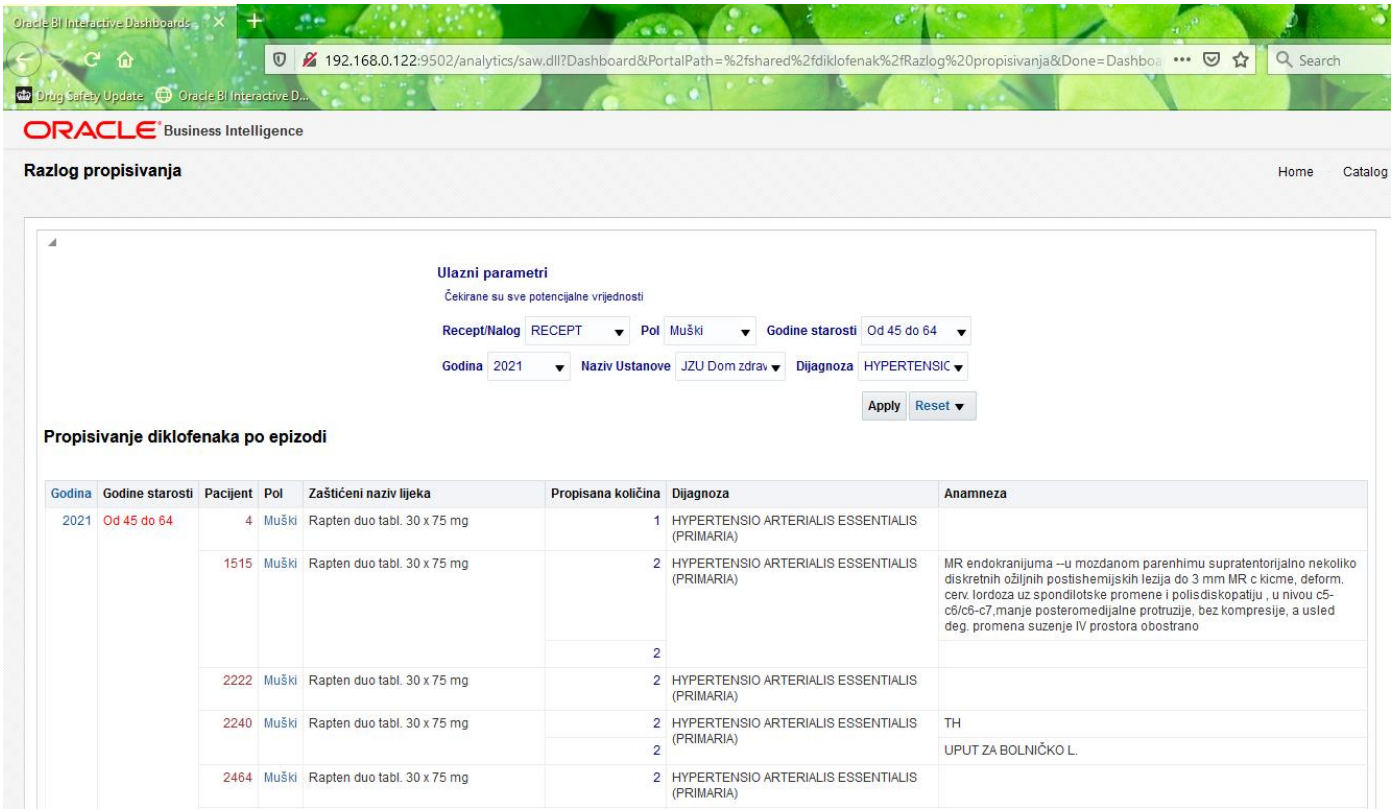


Period interakcije	Ustanova	ATC Diklofenaka	Pacijent	Zaštićeni naziv diklofenaka	Količina propisana diklofenaka	Količina izdata diklofenaka	ATC lijeka za interakciju	Ljekar	Zaštićeni naziv lijeka	Količina propisana	Količina izdata	Dijagnoza
03 MART	JZU Dom zdravlja Andrijevica	M01AB05	359840	Rapten forte tbl.sa mod.osl. 20 x 100 mg kol=1;	1	1	C07AB07	2564	Concor cor tabl. film 30 x 2.5 mg	1	1	HYPERTENSIO ARTERIALIS ESSENTIALIS (PRIMARIA)
			578723	Rapten duo tabl. 30 x 75 mg kol=1;	1	1	C07AB07	2564	Concor cor tabl. film 30 x 2.5 mg	1	1	THYREOIDITIS AUTOIMMUNIS
	JZU Dom zdravlja Bar	M01AB05	110060	Rapten duo tabl. 30 x 75 mg kol=1;	1	1	C07AB07	1975	Concor cor tabl. film 30 x 5 mg	1	1	HYPERTENSIO ARTERIALIS ESSENTIALIS (PRIMARIA)
			150734	Rapten duo tabl. 30 x 75 mg kol=2;	2	2	C07AB07	2503	Concor cor tabl. film 30 x 2.5 mg	1	1	HYPERTENSIO ARTERIALIS ESSENTIALIS (PRIMARIA)
			243310	Rapten duo tabl. 30 x 75 mg kol=1;	1	1	C07AB07	374	Concor cor tabl. film 30 x 2.5 mg	1	1	ANGINA PECTORIS
									Concor cor tabl. film 30 x 5 mg	1	1	ANGINA PECTORIS
			285821	Rapten duo tabl. 30 x 75 mg kol=1;	1	1	C07AB07	1398	Concor cor tabl. film 30 x 2.5 mg	1	1	MORBI THYREOIDEAE ALII
			558398	Rapten forte tbl.sa mod.osl. 20 x 100 mg kol=1; Diklofenak rastvor za inj. 5 x amp. 3 ml (75 mg / 3 ml) kol=1;	2	1	C07AB07	4556	Concor cor tabl. film 30 x 5 mg	1	1	MEDICINSKO POSMATRANJE I PRACENJE ZBOG SUMNJE NA NEKE BOLESTI ILI STANJA
			569749	Rapten duo tabl. 30 x 75 mg kol=1;	1	1	C07AB07	3469	Concor cor tabl. film 30 x 2.5 mg	1	1	INFECTIONES RESPIRATORIAE SUPERIORIS ACUTAE ALIAE, LOCORUMMULTIPLICIUM
			748163	Rapten duo tabl. 30 x 75 mg kol=4;	4	4	C07AB07	2503	Concor cor tabl. film 30 x 5 mg	4	2	LUPUS ERYTHEMATOSUS SYSTEMICUS, FORMAE ALIAE
	JZU Dom zdravlja Berane	M01AB05	295805	Diklofenak rastvor za inj. 5 x amp. 3 ml (75 mg / 3 ml) kol=3;	3	1	C07AB07	2186	Concor cor tabl. film 30 x 2.5 mg	1	1	HYPERTENSIO ARTERIALIS ESSENTIALIS (PRIMARIA)

During the whole period of monitoring it was noticed that diclofenac had often been prescribed as concomitant with a large number of other medicines. Prescribing of diclofenac concomitantly with the medicines whose Summary of Product Characteristics contains information on significant interactions was analysed with special attention.

2.5 Analysis of reasons behind the prescription

Anamnestic data were analised in specific situations regarding diagnosis and medicines prescribed. These data could be used as additional information on prescribing practise. It was noticed that these data are not available for all patients and episodes.



3. Conclusion

BI tools provide large amount of data for analysis. It is possible to explore prescribing practise od diclofenac in PHC regarding all important characteristics of the medicines and patients. Visual representation of the data is also available which makes the results of analysis easier to interpret. In the monitored time period diclofenac was prescribed with an extremely high number of diagnoses to the patients of both genders, in all PHC units. As for the diagnoses, it was noticed that diclofenac was predominantly prescribed for the therapy of inflammatory and painful conditions in line with the indications approved. However, prescription of diclofenac related to various other diagnoses, some of which related to the increased risk of the occurrence of adverse effects of diclofenac, was also observed. When it comes to the patients' gender, diclofenac was predominantly prescribed to women. Most patients prescribed with diclofenac belong to

the group of 45 to 64 years of age, while the lowest number of patients belongs to the group younger than 17 years. Diclofenac was prescribed to women of reproductive age to a significant extent. Prescribers had a large number of medicines containing diclofenac as an active substance at their disposal, of various forms, strengths and trade names. Diclofenac was prescribed to patients with numerous comorbidities, with the large number of medicines used concomitantly. Diclofenac was prescribed to a significant extent in the same period as the medicines for which major interactions were identified: antihypertensives (e.g. beta-blockers), other nonsteroidal anti-inflammatory drugs (e.g. acetylsalicylic acid) and heart disease therapy medicines (e.g. digitalis glycosides). Detailed anamnestic data describing reason for diclofenac prescription are not always available.