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

WP5

The importance of Information Technologies (IT) and other possible collaboration between regulatory agencies for medicines and healthcare institutions in order to better implement regulatory recommendations for medicinal products in clinical practice

and

Possible application of information technologies in the implementation of risk minimization measures in clinical practice - past experiences and future perspective

Author:

Viola Macolić Šarinić

European Medicines Agency

Amsterdam, Netherlands

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

INTRODUCTION

The EU Pharmacovigilance legislation from 2010 which came into force in 2012 emphasises the importance of the communication of safety and all other regulatory information to the public regardless how the medicinal products are authorised – purely nationally, nationally through the Mutual recognition procedure (MRP), decentralised procedure (DCP) or via the European medicines agency's (EMA) centralised procedure (CAP). The decision made for the medicinal product (MP) and the outcome has to be fully transparent with the assessment repots available and with a clear information about the recommendations made how to use the medicine in clinical practice. To do so the Regulation (EC) No 726/2004 in its article 26 lays down that "The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a European medicines web-portal for the dissemination of information on medicinal products authorised in the Union" (1). The Directive 2001/83/EC in its article 106 under chapter 2 "Transparency and communications" says that "Each Member State shall set up and maintain a national medicine web-portal which shall be linked to the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004" (2).

As Montenegro as an EU accession candidate country aligns its regulatory system to the European one it is of importance to develop the national regulatory portal and information system together with the healthcare system in the country including HTA and payers.

This paper discusses the importance of Information Technologies (IT) and other possible collaboration between regulatory agencies for human medicines and healthcare institutions in order to better implement regulatory recommendations for medicinal products in clinical practice.

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

INFORMATION TECHNOLOGY AND THE IMPLEMENTATION OF REGULATORY INFORMATION IN CLINICAL PRACTICE

As per the Directive 2001/83/EC (2) the Members state (MS) has to ensure to make publicly available at least the following:

- Public assessment reports (PAR) for medicinal products together with a summary of the PAR,
- Summaries of product characteristics (SmPC) and package leaflets (PIL),
- Summaries of risk management plans (RMP) for medicinal products,
- The list of national and centralised authorised medicinal products (CAP),
- Information on the different ways of reporting suspected adverse reactions to medicinal products to national competent authorities by healthcare professionals and patients, including the web-based structured forms

The Regulation (EC) No 726/2004 (1) lays down the requirement for the EMA to ensure the transparent information on all outcomes of regulatory procedures and the information how to use the medicinal product in practice to ensure safe and effective therapy in clinical practice in the EU. This requirement should be fulfilled through the establishment of a European medicines web-portal for the dissemination of information on medicinal products authorised in the EU.

The Agency has to ensure to make public at least the following:

- The names of members of the EMA Scientific Committees the members of the HMA's coordination group (CMDh), together with their professional qualifications and with the declarations of interest,
- Agendas and minutes from each meeting of the EMA Scientific Committees referred and CMDh as regards pharmacovigilance activities,
- A summary of the RMPs for the medicinal products authorised in the EU,
- The list of medicinal products authorised via the centralised procedure in the EU,
- A list of the locations in the EU where pharmacovigilance system master files (PSMF) are kept and contact information for pharmacovigilance enquiries for all medicinal products authorised in the EU,
- Information about how to report to national competent authorities (NRA) suspected adverse reactions to medicinal products and publish the standard structured forms for reporting by patients and healthcare professionals, including links to national websites,

This project is co-funded by the European Union

The project is implemented by

- Union reference dates and frequency of submission of periodic safety update reports (PSUR) established in accordance with Article 107c of the Directive 2001/83/EC (EURD list),
- Protocols and public abstracts of results of the post-authorisation safety studies (PASS).
- The initiation of the procedure of safety referrals, the active substances or medicinal products concerned, and the issue being addressed, any public hearings pursuant to that procedure and information on how to submit information and to participate in public hearings
- Conclusions of assessments, recommendations, opinions, approvals, and decisions taken by the Scientific Committees (CHMP, PRAC) and CMDh, the national competent authorities (NCAs) and the European Commission (EC).

The Regulation also lays down that before the launch of this portal, and during subsequent reviews, the EMA (Agency) shall consult relevant stakeholders, including patient and consumer groups, healthcare professionals and industry representatives (1).

The European medicines web-portal is not yet functional but the EMA cooperative web site acts as the portal before it will become fully functional, and the web pages of the national regulatory agencies are updated in line with the Directive (2). The required information by the EU legislation are available but they are not easy to find as they are “hidden” under different links which are not intuitive to find, and important information could be missed by the healthcare professionals (HCPs) – prescribers and dispensers and the patients and wider public.

The most important information to the healthcare professionals are the list of medicinal products available in the country with the availability of safety information such as the Direct healthcare professional communication (DHPC letters) and educational materials together with the templates for ADR reporting.

One of the examples of an IT solution via the National regulator’s web page is the solution given by the Croatian medicinal agency HALMED where the information is available via the links to the national documents (SmPC, Public assessment, Educational material and also the availability of the medicinal product in the country).

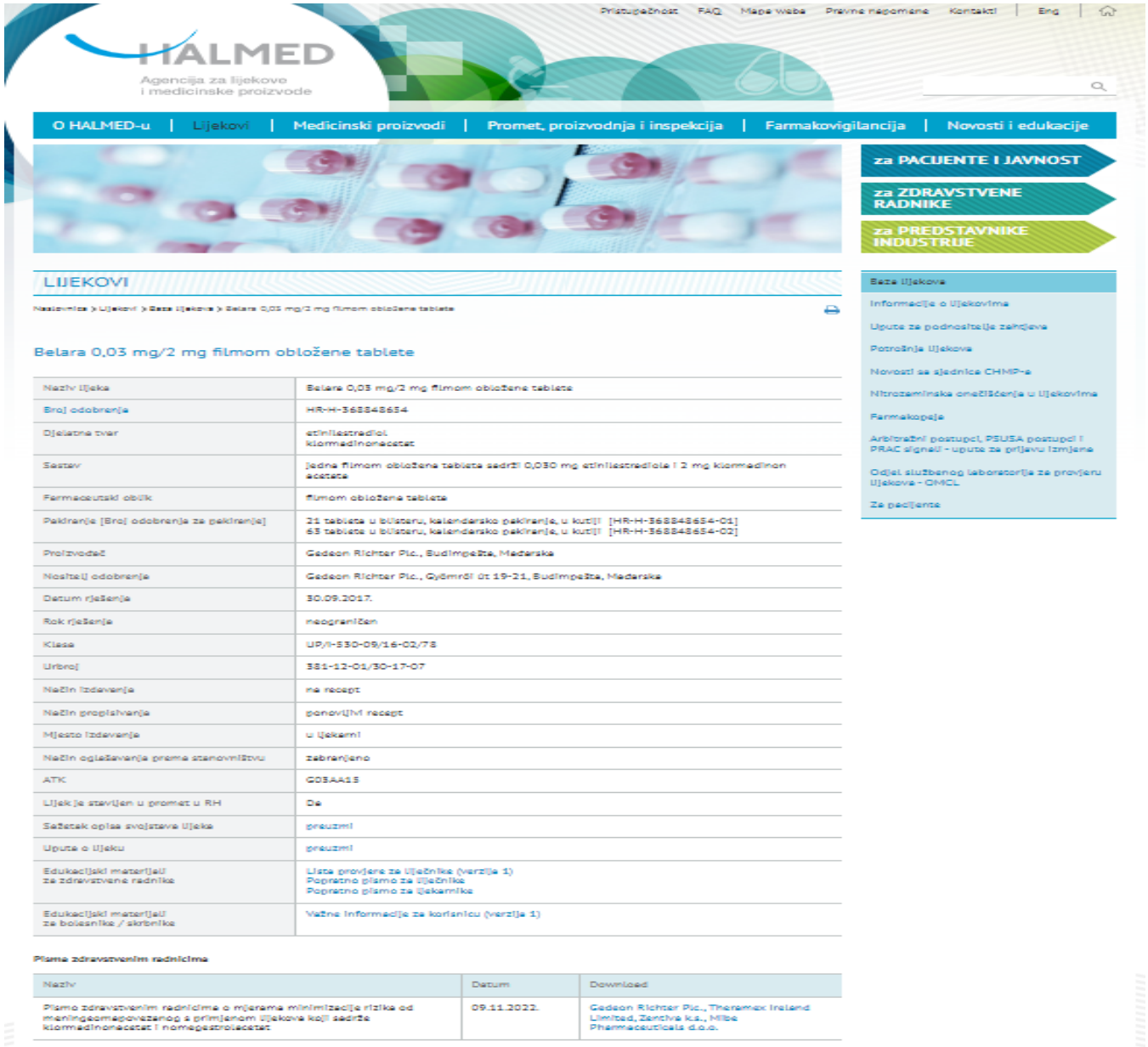
The implementation of the required information is shown for the medicinal product containing ethinylestradiol and chlormadinone. As an outcome of an Article 31 safety referral additional Risk minimisation measures (aRMM) are required:

- Prescribing check list
- Patient card

In addition to the Educational material 94 DHPC is issued to inform the HCPs on higher risk of meningioma in women with risk factors and longer term use of this combined oral contraceptive.

The available information which is showing after the online search in the national database (HALMED) for this COC is as follows:

Picture 1 – regulatory information on the medicinal product with the availability of the product with the SmPC, PIL and safety information (Educational material and DHP) (3)



HALMED
Agencija za lijekove i medicinske proizvode

Pristupačnost | FAQ | Mapa weba | Pravne napomene | Kontakt | Eng

O HALMED-u | Lijekovi | Medicinski proizvodi | Promet, proizvodnja i inspekcija | Farmakovigilancija | Novosti i edukacije

za PACIJENTE I JAVNOST
za ZDRAVSTVENE RADNIKE
za PREDSTAVNIKE INDUSTRIJE

LIJEKOVI

Naslovnica > Lijekovi > Baza lijekova > Belara 0,03 mg/2 mg filmom obložene tablete

Baza lijekova
Informacije o lijekovima
Upute za podnositelje zahtjeva
Potrošnja lijekova
Novosti sa sjednica CHMP-a
Nitrozaminska onečišćenja u lijekovima
Farmakopeja
Arbitražni postupci, PSUSA postupci i PRAC signali - upute za prijavu izmjena
Odjel službenog laboratorija za provjeru lijekova - OMCL
Za pacijente

Belara 0,03 mg/2 mg filmom obložene tablete

Naziv lijeka	Belara 0,03 mg/2 mg filmom obložene tablete
Broj odobrenja	HR-H-368848654
Djelatna tvar	etinilestradiol klormadinonacetat
Sastav	jedna filmom obložena tableta sadrži 0,030 mg etinilestradiola i 2 mg klormadinon acetata
Farmaceutski oblik	filmom obložena tableta
Pakiranje [Broj odobrenja za pakiranje]	21 tableta u blisteru, kalendarsko pakiranje, u kutiji [HR-H-368848654-01] 63 tablete u blisteru, kalendarsko pakiranje, u kutiji [HR-H-368848654-02]
Proizvođač	Gedeon Richter Plc., Budimpešta, Mađarska
Nositelj odobrenja	Gedeon Richter Plc., Gyömrői út 19-21, Budimpešta, Mađarska
Datum rješenja	30.09.2017.
Rok rješenja	neograničen
Klasa	UP/I-530-09/16-02/78
Urbroj	381-12-01/30-17-07
Način izdavanja	na recept
Način propisivanja	ponovljivi recept
Mjesto izdavanja	u ljekarni
Način oglašavanja prema stanovništvu	zabranjeno
ATK	G03AA15
Lijek je stavljen u promet u RH	Da
Sažetak opisa svojstava lijeka	preuzmi
Upute o lijeku	preuzmi
Edukacijski materijali za zdravstvene radnike	Lista provjere za ljječnike (verzija 1) Popratno pismo za ljječnike Popratno pismo za ljekarnike
Edukacijski materijali za bolesnike / skrbnike	Važne informacije za korisnicu (verzija 1)

Pisma zdravstvenim radnicima

Naziv	Datum	Download
Pismo zdravstvenim radnicima o mjerama minimizacije rizika od meningeomapovezanog s primjenom lijekova koji sadrže klormadinonacetat i nomegestrolacetat	09.11.2022.	Gedeon Richter Plc., Theramex Ireland Limited, Zentiva k.s., Milpe Pharmaceuticals d.o.o.

Picture 2 – Checklist for the prescriber (4)

LISTA PROVJERE ZA PROPISIVAČA – KOMBINIRANI HORMONSKI KONTRACEPTIVI

Molimo Vas koristite ovu listu za provjeru uz Sažetak opisa svojstava lijeka prilikom svake konzultacije o kombiniranim hormonskim kontraceptivima (KHK).

- Tromboembolija (npr. duboka venska tromboza, plućna embolija, srčani udar i moždani udar) je rijedak, ali važan rizik povezan s korištenjem KHK.
- Ukupan rizik ovisit će također o osnovnom riziku od tromboembolije koji svaka žena ima. Pri odluci o korištenju KHK moraju se, dakle, uzeti u obzir kontraindikacije i prisustvo čimbenika rizika pojedinačno kod svake žene, pogotovo onih za tromboemboliju – vidjeti donje tablice i Sažetak opisa svojstava lijeka.
- Pri korištenju KHK rizik o tromboembolije viši je:
  - U prvoj godini primjene
  - Pri ponovnom započinjanju s primjenom nakon stanke od 4 ili više tjedana
- Za KHK koji sadrže etinilestradiol u kombinaciji s levonorgestrelom, norgestimatom ili noretisteronom smatra se da nose najniži rizik od venske tromboembolije (VTE).
- Odluku o korištenju bilo kojeg drugog KHK osim onih koji nose najniži rizik mora se donijeti tek nakon razgovora s pacijenticom, kako bi se osiguralo da ona razumije:
  - Učinak intrinzičnih čimbenika rizika na njezin rizik od tromboze
  - Rizik od tromboembolije povezan s njezinim KHK
  - Kako mora budno pratiti na eventualnu pojavu znakova i simptoma tromboze

	Ako označite ijednu od kućica u ovom dijelu, nemojte propisati KHK. Ima li pacijentica:
☐	Tromboembolijski događaj u osobnoj povijesti bolesti npr. duboka venska tromboza, plućna embolija, srčani udar, moždani udar, tranzitorna ishemijska ataka, angina pektoris?
☐	Poremećaj zgrušavanja krvi?
☐	Migrenu sa žarišnim neurološkim simptomima u povijesti bolesti?
☐	Diabetes mellitus s vaskularnm komplikacijama?
☐	Vrlo visoki krvni tlak npr. sistolički ≥160 ili dijastolički ≥100 mmHg?
☐	Vrlo visoke vrijednosti lipida u krvi?
☐	Nadolazeći veliki kirurški zahvat ili period produljene imobilizacije? Ako da, prekinite korištenje i savjetujte ne-hormonsku metodu kontracepcije najmanje 4 tjedna prije i 2 tjedna nakon potpune remobilizacije.

	Ako označite ijednu kućicu u ovom dijelu, razgovarajte s pacijenticom o prikladnosti KHK:
☐	Ako je njezin indeks tjelesne mase preko 30 kg/m²?
☐	Ako je starija od 35 godina?
☐	Ako puši? Ako puši i starija je od 35 godina mora joj se strogo savjetovati da prestane pušiti ili da koristi ne-hormonsku metodu kontracepcije.
☐	Ako ima visoki krvni tlak npr. sistolički 140-159 ili dijastolički 90-99 mmHg?
☐	Ako je netko od članova njene uže obitelji (npr. roditelj ili brat/sestra) imao tromboembolijski događaj (vidjeti listu gore) u mlađoj dobi (npr. mlađi od 50 godina)?
☐	Ako ona ili netko u njezinoj užoj obitelji ima povišene vrijednosti lipida u krvi?
☐	Ako ima migrene?
☐	Ako ima kardiovaskularno stanje poput fibrilacije atrija, artimije, koronarne bolesti srca, bolesti srčanih zalistaka?
☐	Ako ima šećernu bolest?
☐	Ako je rodila u posljednjih nekoliko tjedana?
☐	Ako planira dugotrajni let avionom (>4 sata) ili putuje dulje od 4 sata dnevno?
☐	Ako ima neko drugo medicinsko stanje koje može povisiti rizik od tromboze (npr. karcinom, sistemski lupus eritematodes, anemija srpastih stanica, Chronova bolest, ulcerozni colitis, hemolitičko-uremijski sindrom)?
☐	Ako uzima neke druge lijekove koji mogu povisiti rizik od tromboze (npr. kortikosteroide, neuroleptike, antipsihotike, antidepresive, kemoterapiju itd.)?

Prisustvo više od jednog čimbenika rizika može značiti da se ne smije koristiti KHK.
Ne zaboravite, individulani rizici pacijentice mogu se s vremenom promijeniti te ih se mora ponovno procijenjivati u redovitim intervalima.

Molimo Vas, osigurajte da Vaša pacijentica razumije kako je potrebno da obavijesti zdravstvenog radnika o činjenici da koristi kombinirani kontraceptiv ako joj je:

- potrebna operacija
- potreban period produljene imobilizacije (npr. zbog bolesti ili ozljede ili ako joj je noga u gipsu)

◇ U tim slučajevima najbolje bi bilo razgovarati o korištenju ne-hormonske kontracepcije dok se rizik ne vrati u normalu.

Molimo Vas, obavijestite Vašu pacijenticu da se rizik od krvnog ugruška povećava:

- Na dugim putovanjima (npr. dugotrajni let avionom)
- Razvojem jednog ili više gore navednih čimbenika rizika za kombinirane kontraceeptive
- Ako je rodila unutar zadnjih nekoliko tjedana

◇ U tim slučajevima Vaša pacijentica mora posebno budno paziti na znakove i simptome tromboembolije.

Molim Vas **savjetujte Vašoj pacijentici** da Vas obavijesti ako se bilo koje od gore navednih stanja promijeni ili pogorša.

Molimo Vas da snažno potaknete pacijentice da pročitaju Uputu o lijeku priloženu u svakom pakiranju KHK. To uključuje i simptome krvnih ugrušaka na koje mora paziti.

Svaku sumnju na nuspojavu uzrokovanu kombiniranim kontraceptivom prijavite na kontakt podatke nositelja odobrenja ili Agenciji za lijekove i medicinske proizvode (HALMED)

(ustanova - liječnik)

(ime i prezime bolesnika)

20 _____

Rp./

(potpis - pečat)

Verzija 1, 01.10.2014.

VAŽNE INFORMACIJE O LIJEKU I RIZIKU OD KRVNIH UGRUŠAKA

Svi kombinirani hormonski kontraceptivi (KHK) povisuju rizik od nastanka krvnog ugruška. Ukupan rizik od nastanka krvnog ugruška je nizak, ali ugrušci mogu biti ozbiljni te mogu u rijetkim slučajevima imati smrtni ishod.

Vrlo je važno prepoznati stanja kad imate viši rizik od nastanka krvnog ugruška, znati na koje znakove i simptome morate paziti te što morate poduzeti.

U kojim slučajevima je rizik od nastanka krvnih ugrušaka najviši?

- U prvoj godini primjene KHK (ili kad se ponovno počinje s primjenom nakon stanke od 4 ili više tjedana)
- Ako ste vrlo pretili
- Ako ste stariji od 35 godina
- Ako je netko od članova Vaše uže obitelji imao krvni ugrušak u mlađoj dobi (npr. mlađi od 50 godina)
- Ako ste rodili u prethodnih nekoliko tjedana

Ako pušite i stariji ste od 35 godina, strogo Vam se savjetuje da prestane te pušiti ili da koristite ne-hormonsku metodu kontracepcije

Hitno potražite liječničku pomoć ako primjetite bilo koji od sljedećih simptoma:

- Jaku bol ili oticanje jedne noge koja može biti popraćena osjetljivošću, povećanom toplinom ili promjenama boje kože, npr. ako pobljedi, pocrveni ili poplavi. Moguće da imate **duboku vensku trombozu.**
- Iznenadni neobjašnjivi nedostatak zraka ili ubrzano disanje; oštra bol u prsištu koja se može pojačati kod dubokog disanja; iznenadni kašalj bez očitog uzroka (uz moguće iskašljavanje krvi). Moguće da imate ozbiljnu komplikaciju duboke venske troboze koju zovemo **plućna embolija**. Do nje dolazi ako krvni ugrušak dospije iz noge u pluća.
- Bol u prsištu, često akutna, ali ponekad samo nelagoda, pritisak, težina, nelagoda u gornjem dijelu tijela koja se širi u leđa, čeljust, grlo, ruku popraćena osjećajem punoće povezanxim s probavnim tegobama ili gušenjem, znojenjem, mučninom, povraćanjem ili omaglicom. Moguće je da imate **srčani udar.**
- Slabost ili utrnulost lica, ruke ili noge, osobito na jednoj strani tijela; otežan govor i razumijevanje; iznenadna smetenost; iznenadni gubitak vida ili zamućen vid; jaka glavobolja/migrena (jača od uobičajene). Moguće da imate **moždani udar.**

Pripazite na simptome krvnog ugruška, pogotovo ako:

- Ste vrlo nedavno imali operacijski zahvat
- Dugo mirujete (npr. zbog ozljede ili bolesti ili imate nogu u gipsu)
- Dugo putujete (više od 4 sata)

Obavijestite svog liječnika, medicinsku sestru ili kirurga da koristite KHK ako:

- Trebate ići na operaciju
- Vas zdravstveni radnik pita uzimate li neke lijekove

Za više informacija pročitajte priloženu Uputu o lijeku
Ako sumnjate da imate nuspojavu povezanu s uzimanjem KHK obavijestite o tome vašeg liječnika ili ljekarnika, a možete prijaviti izravno Agenciji za lijekove i medicinske proizvode (HALMED), Odsjek za farmakovigilanciju, Roberta Frangeša Mihanovića 9, 10 000 Zagreb, Republika Hrvatska, fax: +385 (0)1 488 117, website: www.halmed.hr, e-mail: nuspojave@halmed.hr

Verzija 1, 01.10.2014.

This project is co-funded by the European Union

The project is implemented by

Picture 3 – Letter for prescribers and dispensers (5, 6)

Zagreb, dd. mm. gggg.

Kombinirani hormonski kontraceptivi – edukacijski materijali za liječnike i pacijentice

Poštovani,

Bayer d.o.o., Farmal d.d., Merck Sharp & Dohme d.o.o., Sandoz d.o.o. i Johson&Johnson SE d.o.o., u suradnji s Agencijom za lijekove i medicinske proizvode (HALMED) žele Vas obavijestiti kako su razvijeni dokumenti u svrhu olakšanja konzultacija, uključujući popis za provjeru kojeg propisivači trebaju proći s pacijenticom da bi se osiguralo da je kombinirani hormonski kontraceptiv (KHK) primjeren. Također je razvijena kartica za pacijentice u kojoj će biti navedeni važni znakovi venske (VTE) i arterijske (ATE) tromboembolije kojih pacijentica treba biti svjesna.

Ocjena sigurnosti primjene KHK provedene u Europi potvrđuje prethodne stavove prema kojima je razina rizika od VTE (venske tromboembolije) niska za sve KHK niske doze (etinilestradiol <50 µg). Postoje valjani dokazi za razlike u riziku za vensku tromboemboliju (VTE) između KHK, ovisno o vrsti progestagena kojeg sadrže. Prilikom propisivanja KHK, obavezno je pažljivo uzeti u obzir prisutnost čimbenika rizika pojedinačno kod svake žene, osobito onih za VTE, kao i razliku u riziku za VTE između lijekova. Sada je fokus na naglašavanju važnosti prisutnosti čimbenika rizika pojedinačno kod svake žene i potrebe za redovitom ponovnom procjenom rizika, te na podizanju svijesti o znakovima i simptomima VTE i ATE, koje ženama treba opisati prilikom propisivanja KHK. Uvijek uzmite u obzir mogućnost tromboembolije povezane s primjenom KHK kod žena koje imaju simptome tromboembolije.

Edukacijski materijali sastoje se od:

- Liste provjere za propisivača
- Kartice s informacijama za korisnicu

Molimo Vas koristite ovu listu za provjeru uz Sažetak opisa svojstava lijeka prilikom svake konzultacije o kombiniranim hormonskim kontraceptivima (KHK). Lista provjere osmišljena je da olakša proces konzultacije s pacijenticom na način da navodi kontraindikacije i mjere opreza kroz koje bi liječnik trebao proći zajedno s pacijenticom prije propisivanja KHK, te sadrži osnovne podatke o tromboemboliji.

Prilikom propisivanja KHK svakoj pacijentici mora biti uručena Kartica za korisnicun od strane liječnika. Recept koji liječnik uručuje pacijentici na poleđini ima otisnutu Karticu s informacijama za korisnicu.

U prilogu Vam dostavljamo bilježnicu s listovima koji na svojoj lijevoj strani sadrže otisnutu Listu provjere koju Vas molimo da prođete s pacijenticom. Desna strane lista može se otkinuti, a sadrži privatni recept koji trebate uručiti pacijentici, a na čijoj poleđini se nalazi Kartica s informacijama za korisnicu. Dodatne količine listova možete preuzeti na internetskoj stranici Agencije za lijekove i medicinske proizvode www.halmed.hr u rubrici Farmakovigilancija - edukacijski materijali.

This project is co-funded by the European Union

The project is implemented by

Ovi edukacijski materijali odnose se na sljedeće lijekove sljedećih nositelja odobrenja:

Bayer d.o.o., Radnička cesta 80, 10000 Zagreb, tel.: 01/6599900, faks: 01/6599952, www.bayer.hr, e-mail: pv.croatia@bayer.com

Logest 0,02 mg/0,075 mg obložene tablete (gestoden, etinilestradiol)
Qlaira filmom obložene tablete (estradiol, dienogest)
Yasmin 0,03 mg/3 mg filmom obložene tablete (etinilestradiol, drospirenon)
Yaz 0,02 mg/3 mg filmom obložene tablete (etinilestradiol, drospirenon)

Farmal d.d., Zavrtnica 17, 10000 Zagreb, telefon: (01) 6061-137, faks: (01) 6040-166, e-mail: mario.roubin@farmal.hr

Adexa 0,03 mg + 0,15 mg filmom obložene tablete (etinilestradiol, levonorgestrel)
Estal 0,03 mg + 2 mg filmom obložene tablete (etinilestradiol, klormadinon)

Johnson & Johnson S.E. d.o.o., Janssen Medicinski odjel, Oreškovićeva 6h, 10010 Zagreb, Hrvatska, Tel: + 385 1 6610 750, Faks: + 385 1 6610 751, e-mail: JJSAFETY@jnjcr.jnj.com

Evra 203 mikrograma/24 sata + 33,9 mikrograma/24 sata transdermalni flaster (norelgestromin etinilestradiol)

Merck Sharp & Dohme d.o.o., Heinzelova 62a, 10000 Zagreb, tel.:01/6611333, faks: 01/6611351, www.msd.hr, e-mail: mailbox-croatia.pharmacovigilance@merck.com

NuvaRing 11,7mg+2,7mg intravaginalni prsten (etonogestrel, etinilestradiol)

Sandoz d.o.o., Maksimirska 120, 10000 Zagreb, telefon: (01) 2353-111, faks: (01) 2337-785, web stranica: www.sandoz.hr

Belara 0,03 mg/2 mg filmom obložene tablete (etinilestradiol, klormadinon)
Lindynette 0,075 mg + 0,02 mg obložene tablete (gestoden, etinilestradiol)
Lindynette 0,075 mg + 0,03 mg obložene tablete (gestoden, etinilestradiol)
Novynette 0,020 mg + 0,150 mg filmom obložene tablete (etinilestradiol, dezogestrel)

S poštovanjem,

Bojan Gnjatović, mag.pharm. (Bayer d.o.o.)

Jelena Bošković, mag.pharm. (Merck Sharp&Dohme d.o.o.)

Mario Roubin, mag.pharm. (Farmal d.d.)

Miro Papić, dr. med. (Sandoz d.o.o.)

Alden Dalagija, dr. med. (Johson&Johnson SE d.o.o.)

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

Zagreb, dd. mm. gggg.

Kombinirani hormonski kontraceptivi – edukacijski materijali za liječnike i pacijentice

Poštovani,

Bayer d.o.o., Farmal d.d., Merck Sharp & Dohme d.o.o., Sandoz d.o.o. i Johson&Johnson SE d.o.o., u suradnji s Agencijom za lijekove i medicinske proizvode (HALMED) žele Vas obavijestiti kako su razvijeni dokumenti u svrhu olakšanja konzultacija, uključujući popis za provjeru kojeg propisivači trebaju proći s pacijenticom da bi se osiguralo da je kombinirani hormonski kontraceptiv (KHK) primjeren. Također je razvijena kartica za pacijentice u kojoj će biti navedeni važni znakovi venske (VTE) i arterijske (ATE) tromboembolije kojih pacijentica treba biti svjesna.

Ocjena sigurnosti primjene KHK provedene u Europi potvrđuje prethodne stavove prema kojima je razina rizika od VTE (venske tromboembolije) niska za sve KHK niske doze (etinilestradiol <50 µg). Postoje valjani dokazi za razlike u riziku za vensku tromboemboliju (VTE) između KHK, ovisno o vrsti progestagena kojeg sadrže. Prilikom propisivanja KHK, obavezno je pažljivo uzeti u obzir prisutnost čimbenika rizika pojedinačno kod svake žene, osobito onih za VTE, kao i razliku u riziku za VTE između lijekova. Sada je fokus na naglašavanju važnosti prisutnosti čimbenika rizika pojedinačno kod svake žene i potrebe za redovitom ponovnom procjenom rizika, te na podizanju svijesti o znakovima i simptomima VTE i ATE, koje ženama treba opisati prilikom propisivanja KHK. Uvijek uzmite u obzir mogućnost tromboembolije povezane s primjenom KHK kod žena koje imaju simptome tromboembolije.

Edukacijski materijali sastoje se od:

- Liste provjere za propisivača
- Kartice s informacijama za korisnicu

Svakoj pacijentici kojoj se propiše KHK mora biti uručena Kartica za korisnicu od strane liječnika. Recept koji liječnik uručuje pacijentici na poleđini ima otisnutu Karticu s informacijama za korisnicu.

Važno je da svaka korisnica dobije informacije o svojoj terapiji, dio izdavanja lijeka je također važno mjesto na kojem pacijentica dobija informacije o svojoj terapiji. Pacijentice bi trebale dolaziti po svoj lijek s receptom koji na poleđini sadrži Karticu za korisnicu. Ako pacijentica nema takav recept ili nema karticu za korisnicu ljekarnik joj treba uručiti karticu za korisnicu prije izdavanja lijeka.

U prilogu Vam dostavljamo Kartice s informacijama za korisnicu. Dodatne količine Kartica s informacijama za korisnicu možete preuzeti na internetskoj stranici Agencije za lijekove i medicinske proizvode www.halmed.hr u rubrici Farmakovigilancija – edukacijski materijali.

This project is co-funded by
the European Union

The project is implemented by
MG SOFT engineering-software

Ovi edukacijski materijali odnose se na sljedeće lijekove sljedećih nositelja odobrenja:

Bayer d.o.o., Radnička cesta 80, 10000 Zagreb, tel.: 01/6599900, faks: 01/6599952, www.bayer.hr, e-mail: pv.croatia@bayer.com

Logest 0,02 mg/0,075 mg obložene tablete (gestoden, etinilestradiol)
Qlaira filmom obložene tablete (estradiol, dienogest)
Yasmin 0,03 mg/3 mg filmom obložene tablete (etinilestradiol, drospirenon)
Yaz 0,02 mg/3 mg filmom obložene tablete (etinilestradiol, drospirenon)

Farmal d.d., Zavrtnica 17, 10000 Zagreb, telefon: (01) 6061-137, faks: (01) 6040-166, e-mail: mario.roubin@farmal.hr

Adexa 0,03 mg + 0,15 mg filmom obložene tablete (etinilestradiol, levonorgestrel)
Estal 0,03 mg + 2 mg filmom obložene tablete (etinilestradiol, klormadinon)

Johnson & Johnson S.E. d.o.o., Janssen Medicinski odjel, Oreškovićeva 6h, 10010 Zagreb, Hrvatska, Tel: + 385 1 6610 750, Faks: + 385 1 6610 751, e-mail: JJSAFETY@jnjcr.jnj.com

Evra 203 mikrograma/24 sata + 33,9 mikrograma/24 sata transdermalni flaster (norelgestromin etinilestradiol)

Merck Sharp & Dohme d.o.o., Heinzelova 62a, 10000 Zagreb, tel.:01/6611333, faks: 01/6611351, www.msd.hr, e-mail: mailbox-croatia.pharmacovigilance@merck.com

NuvaRing 11,7mg+2,7mg intravaginalni prsten (etonogestrel, etinilestradiol)

Sandoz d.o.o., Maksimirska 120, 10000 Zagreb, telefon: (01) 2353-111, faks: (01) 2337-785, web stranica: www.sandoz.hr

Belara 0,03 mg/2 mg filmom obložene tablete (etinilestradiol, klormadinon)
Lindynette 0,075 mg + 0,02 mg obložene tablete (gestoden, etinilestradiol)
Lindynette 0,075 mg + 0,03 mg obložene tablete (gestoden, etinilestradiol)
Novynette 0,020 mg + 0,150 mg filmom obložene tablete (etinilestradiol, dezogestrel)

S poštovanjem,

Bojan Gnjatović, mag.pharm. (Bayer d.o.o.)

Jelena Bošković, mag.pharm. (Merck Sharp&Dohme d.o.o.)

Mario Roubin, mag.pharm. (Farmal d.d.)

Miro Papić, dr. med. (Sandoz d.o.o.)

Alden Dalagija, dr. med. (Johson&Johnson SE d.o.o.)

Picture 4 – Patient information (7)

VAŽNE INFORMACIJE O LIJEKU I RIZIKU OD KRVNIH UGRUŠAKA

Svi kombinirani hormonski kontraceptivi (KHK) povisuju rizik od nastanka krvnog ugruška. Ukupan rizik od nastanka krvnog ugruška je nizak, ali ugrušci mogu biti ozbiljni te mogu u rijetkim slučajevima imati smrtni ishod.

Vrlo je važno prepoznati stanja kad imate viši rizik od nastanka krvnog ugruška, znati na koje znakove i simptome morate paziti te što morate poduzeti.

U kojim slučajevima je rizik od nastanka krvnih ugrušaka najviši?

- U prvoj godini primjene KHK (ili kad se ponovno počinje s primjenom nakon stanke od 4 ili više tjedana)
- Ako ste vrlo pretili
- Ako ste stariji od 35 godina
- Ako je netko od članova Vaše uže obitelji imao krvni ugrušak u mlađoj dobi (npr. mlađi od 50 godina)
- Ako ste rodili u prethodnih nekoliko tjedana

Ako pušite i stariji ste od 35 godina, strogo Vam se savjetuje da prestane te pušiti ili da koristite ne-hormonsku metodu kontracepcije

Hitno potražite liječničku pomoć ako primjetite bilo koji od sljedećih simptoma:

- Jaku bol ili oticanje jedne noge koja može biti popraćena osjetljivošću, povećanom toplinom ili promjenama boje kože, npr. ako poblijedi, pocrveni ili poplavi. Moguće da imate **duboku vensku trombozu.**
- Iznenadni neobjašnjivi nedostatak zraka ili ubrzano disanje; oštra bol u prsištu koja se može pojačati kod dubokog disanja; iznenadni kašalj bez očitog uzroka (uz moguće iskašljavanje krvi). Moguće da imate ozbiljnu komplikaciju duboke venske troboze koju zovemo **plućna embolija**. Do nje dolazi ako krvni ugrušak dospije iz noge u pluća.
- Bol u prsištu, često akutna, ali ponekad samo nelagoda, pritisak, težina, nelagoda u gornjem dijelu tijela koja se širi u leđa, čeljust, grlo, ruku popraćena osjećajem punoće povezanim s probavnim tegobama ili gušenjem, znojenjem, mučninom, povraćanjem ili omaglicom. Moguće je da imate **srčani udar.**
- Slabost ili utrnulost lica, ruke ili noge, osobito na jednoj strani tijela; otežan govor i razumijevanje; iznenadna smetenost; iznenadni gubitak vida ili zamućen vid; jaka glavobolja/migrena (jača od uobičajene). Moguće da imate **moždani udar**.

Pripazite na simptome krvnog ugruška, pogotovo ako:

- Ste vrlo nedavno imali operacijski zahvat
- Dugo mirujete (npr. zbog ozljede ili bolesti ili imate nogu u gipsu)
- Dugo putujete (više od 4 sata)

Obavijestite svog liječnika, medicinsku sestru ili kirurga da koristite KHK ako:

- Trebate ići na operaciju
- Vas zdravstveni radnik pita uzimate li neke lijekove

Za više informacija pročitajte priloženu Uputu o lijeku
Ako sumnjate da imate nuspojavu povezanu s uzimanjem KHK obavijestite o tome vašeg liječnika ili ljekarnika, a možete prijaviti izravno Agenciji za lijekove i medicinske proizvode (HALMED), Odsjek za farmakovigilanciju, Roberta Frangeša Mihanovića 9, 10 000 Zagreb, Republika Hrvatska, fax: +385 (0)1 488 117, website: www.halmed.hr, e-mail: nuspojave@halmed.hr

Verzija 1, 01.10.2014.

This project is co-funded by the European Union

The project is implemented by

Picture 5 – Direct health care communication (DHPC) (8)

09. studenog 2022.

Pismo zdravstvenim radnicima o mjerama minimizacije rizika od meningeoma povezanog s primjenom lijekova koji sadrže klormadinonacetat i nomegestrolacetat

Poštovani,

u suradnji s Agencijom za lijekove i medicinske proizvode (HALMED) i Europskom agencijom za lijekove (EMA), nositelji odobrenja za stavljanje u promet lijekova koji sadrže klormadinonacetat i nomegestrolacetat, tvrtke Gedeon Richter Plc, Theramex Ireland Limited te Mibe Pharmaceuticals d.o.o. žele Vas informirati o sljedećem:

Sažetak

- **Lijekovi koji sadrže klormadinonacetat (5 - 10 mg po tableti) ili nomegestrolacetat (3,75 - 5 mg po tableti) indicirani su samo kada druge terapijske mogućnosti nisu primjenjive. Liječenje treba biti ograničeno na najnižu učinkovitu dozu i najkraće moguće trajanje.**
- **Postoji povećani rizik od razvoja meningeoma (pojedinačnog ili višestrukog) nakon upotrebe klormadinonacetata ili nomegesterolacetata, prvenstveno pri visokim dozama uz dugotrajnu primjenu. Rizik se povećava uz porast kumulativnih doza.**
- **Lijekovi koji sadrže klormadinonacetat ili nomegestrolacetat kontraindicirani su u bolesnika s meningeomom ili anamnezom meningeoma.**
- **U bolesnika se trebaju pratiti znakovi i simptomi meningeoma, u skladu s kliničkom praksom.**
- **Ako je bolesniku liječenom klormadinonacetatom ili nomegestrolacetatom dijagnosticiran meningeom, liječenje ovim lijekovima treba se trajno prekinuti.**

Dodatne informacije

Nacionalno odobreni lijekovi i odobrene indikacije razlikuju se između država članica Europske unije.

U Republici Hrvatskoj nisu odobreni lijekovi s navedenim visokim dozama klormadinonacetata (5 – 10 mg) ili nomegestrolacetata (3,75 – 5 mg).

Lijekovi koji sadrže niske doze klormadinonacetata (2 mg - Belara i Estal) ili nomegestrolacetata (2,5 mg - Zoely) u kombinaciji s estrogenom odobreni su u Republici Hrvatskoj te su indicirani za hormonsku kontracepciju.

Meningeom je rijedak, najčešće dobroćudni tumor moždane ovojnice. Klinički znakovi i simptomi meningeoma mogu biti nespecifični i mogu uključivati promjene vida, gubitak sluha ili zvonjenje u ušima, gubitak njuha, glavobolje koje se pogoršavaju s vremenom, gubitak pamćenja, napadaje ili slabost u ekstremitetima.

Nedavno su rezultati dvaju francuskih epidemioloških kohortnih ispitivanja pokazali kumulativnu povezanost ovisnu o dozi između klormadinonacetata ili nomegestrolacetata i meningeoma.[1;2] Ova ispitivanja temeljena su na podacima francuskog zdravstvenog osiguranja koji su uključivali 828.499

the European Union

he project is implemented by

bolesnica koje su primale klormadinonacetat i 1.060.779 bolesnica koje su primale nomegestrolacetat. Učestalost meningeoma liječenih operativnim zahvatom ili radioterapijom bila je uspoređena između žena izloženih visokoj dozi klormadinonacetata (kumulativna doza > 360 mg) ili visokoj dozi nomegestrolacetata (kumulativna doza > 150 mg) i žena koje su bile blago izložene klormadinonacetatu (kumulativna doza ≤ 360 mg) ili nomegestrolacetatu (kumulativna doza ≤ 150 mg).

Rezultati za klormadinonacetat:

Kumulativna doza klormadinonacetata	**Stopa učestalosti (u bolesnik-godina)**	**HRadj (95% CI)[a]**
Blaga izloženost (≤ 0,36 g)	**6,8/100 000**	**Ref.**
Izloženost > 0,36	**18,5/100 000**	**4,4 [3,4-5,8]**
1,44 to 2,88 g	**11,3/100 000**	**2,6 [1,4-4,7]**
2,88 to 5,76 g	**12,4/100 000**	**2,5 [1,5-4,2]**
5,76 to 8,64 g	**23,9/100 000**	**3,8 [2,3-6,2]**
Više od 8,64 g	**47,0/100 000**	**6,6 [4,8-9,2]**

[a] Prilagođeni omjer rizika (engl. *adjusted hazard ratio*, HRadj) s obzirom na dob; kumulativna doza i dob kao vremenski ovisne varijable.

Primjerice, kumulativna doza od 1,44 g može odgovarati 5-mjesečnom liječenju dnevnom dozom od 10 mg.

Rezultati za nomegestrolacetat:

Kumulativna doza nomegestrolacetata	**Stopa učestalosti (u bolesnik-godina)**	**HRadj (95% CI)[a]**
Blaga izloženost (≤0,15 g)	**7,0/100 000**	**Ref.**
Izloženost > 0,15	**19,3/100 000**	**4,5 [3,5-5,7]**
1,2 to 3,6 g	**17,5/100 000**	**2,6 [1,8-3,8]**
3,6 to 6 g	**27,6/100 000**	**4,2 [2,7-6,6]**
More than 6 g	**91,5/100 000**	**12,0 [8,8-16,5]**

[a] Prilagođeni omjer rizika (engl. *adjusted hazard ratio*, HRadj) s obzirom na dob; kumulativna doza i dob kao vremenski ovisne varijable.

Primjerice, kumulativna doza od 1,2 g može odgovarati 18-mjesečnom liječenju dnevnom dozom od 5 mg tijekom 14 dana svakog mjeseca.

S obzirom na navedene podatke, liječenje visokom dozom klormadinonacetata ili visokom dozom nomegestrolacetata treba biti ograničeno na situacije kada druge terapijske mogućnosti nisu primjenjive.

Nije identificiran novi sigurnosni rizik za pojavu meningeoma povezanog s upotrebom lijekova koji sadrže nisku dozu (2 mg) klormadinonacetata ili lijekova koji sadrže nisku dozu (2,5 mg) nomegestrolacetata. Međutim, kako se rizik od meningeoma povećava s povećanjem kumulativne doze lijekova koji sadrže klormadinonacetat ili nomegestrolacetat, lijekovi s niskom dozom ovih djelatnih tvari kontraindicirani su u bolesnika kod kojih je već prisutan meningeom ili s meningeomom u povijesti bolesti te bi liječenje trebalo trajno prekinuti u slučaju znakova i simptoma meningeoma.

Poziv na prijavljivanje nuspojava

Sve sumnje na nuspojave potrebno je prijaviti Agenciji za lijekove i medicinske proizvode (HALMED). HALMED poziva zdravstvene radnike da prijave sumnje na nuspojave putem informacijskog sustava OPeN koji je dostupan na internetskim stranicama HALMED-a (https://open.halmed.hr).

Prijave poslane ovim putem jednako se boduju od strane Hrvatske liječničke komore i Hrvatske ljekarničke komore kao i prijave putem obrasca poslanog elektroničkom poštom, poštom ili telefaksom.

Za lijekove Estal 0,03 mg + 2 mg filmom obložene tablete i Belara 0,03 mg/2 mg filmom obložene tablete:

▼Ovi su lijekovi pod dodatnim praćenjem. Time se omogućuje brzo otkrivanje novih sigurnosnih informacija. Od zdravstvenih radnika se traži da prijave svaku sumnju na nuspojavu za ove lijekove.

Kontakt podaci predstavnika nositelja odobrenja u RH

Nositelj odobrenja/ predstavnik nositelja odobrenja u RH	**Naziv lijeka**	**E-mail**	**Telefon/fax**
Zentiva, k.s. ZENTIVA	Zoely 2,5 mg/1,5 mg filmom obložene tablete	PV-Croatia@zentiva.com	Tel.: +385 1 6641 830
Mibe Pharmaceuticals d.o.o. mibe pharmaceuticals	▼ Estal 0,03 mg + 2 mg filmom obložene tablete	pharmacovigilance.hr@dermapharm.com	Tel.: +385 1 6061 137
Gedeon Richter Croatia d.o.o.	▼ Belara 0,03 mg/2 mg filmom obložene tablete	drugsafety.hr@gedeonrichter.eu medinfo.hr@gedeonrichter.eu	Tel. +385 1 5625 712

Popis literature:

1) Nguyen P et al. (2021) - EPI-PHARE - Groupement d'intérêt scientifique (GIS) ANSM-CNAM "Utilisation prolongée de l'acétate de chlormadinone et risque de méningiome intracrânien : une étude de cohorte à partir des données du SND". Dostupno putem poveznice: https://www.epi-phare.fr/app/uploads/2021/04/epi-phare_rapport_acetate_chlormadinone_avril-2021-1.pdf

2) Nguyen P et al. (2021) - EPI-PHARE - Groupement d'intérêt scientifique (GIS) ANSM-CNAM "Utilisation prolongée de l'acétate de nomégestrol et risque de méningiome intracrânien : une étude de cohorte à partir des données du SNDS". Dostupno putem poveznice: https://www.epi-phare.fr/app/uploads/2021/04/epi-phare_rapport_acetate_nomegetrol_avril-2021.pdf

S poštovanjem,

mr. sc. Ivana Stojčević, dr. dent. med.
Lokalna odgovorna osoba za farmakovigilanciju za Zentiva, k.s.

Filip Kozlina, mag. pharm.
Lokalna odgovorna osoba za farmakovigilanciju za Mibe Pharmaceuticals d.o.o.

Maja Brozović, mag. pharm.
Zamjenik lokalno odgovorne osobe za farmakovigilanciju za Gedeon Richter Croatia d.o.o.

The information which is available through the NCA websites should be consulted by the HCPs – the prescribing physicians and pharmacists and they should ideally have the information also in writing in a paper format which had to be distributed by the Marketing authorisation holder (MAH) as this is the obligation of the MAHs by the EU regulation and directive in dispensing the information (1,2).

A few studies were conducted so fare in the European Union (EU) to understand the impact this regulatory action. The results of a Danish study from 2021 (9) indicates that certain DHPCs may be disregarded because of the motivations that prescribers attribute to the DHPC senders. The interviewed Danish General Practitioners (GPs) disregard regulatory drug safety advisories primarily because they have negative pre-existing expectations and associations to them. They expect advisories to have limited clinical utility, they are concerned that they are commercially biased, and they infer that advisory are detached from clinical practice, associating it with placing blame, "defensive medicine" and the reallocation of responsibility onto physicians. The study suggests that the limited adoption is less due to the risk information presented in the letter and more due to the external governance of emergent drug risks. The novelty of these results demonstrates the value and importance of conducting formative user-centered evaluation focused on the content, form, and delivery of to target audience in addition to process- and outcome-oriented evaluation. Another study conducted in the Netherlands within hospital settings (hospital pharmacists and specialists) in 2022 (10) indicates that inn general, drug safety information was used at the individual

level or in specific hospital committees when evaluating new treatments, for updates of treatment protocols and in response to patients presenting with adverse events. In Dutch hospitals, there seem to be no hospital-wide procedures on how to handle drug safety information or DHPCs. The assessment of whether other actions are required following a DHPC was mostly an individual task for prescribers in hospitals.

These findings indicates that the DHPC messages are failing the audience to even read and then react upon as they are perceived as biased because disseminated by the MAHs (pharmaceutical industry). There is a low understanding that these measures are imposed by the regulatory authorities to implement additional risk minimisation and other regulatory measures for a safe and efficacy use of the medicine by the patient. This brings up the need that this information has to be integrated in the healthcare information system in the individual member state to build trust on the level the healthcare professionals and that it can be acted upon for generally and not only on the individual HCP level.

The safety/regulatory information disseminated by the regulatory authority should not only be sent out by the pharmaceutical company and published on the NCA's web page but has to be integrated in healthcare system to be easily available by the HCPs. Indeed, this is recognised by the EU regulatory network and an overall discussion is launched to bring the key recommendation through the further revision and update of the GVP module XVI on RMM (11). The discussion opens the door to the use digital tools in the integration of RMM in clinical practice, but the discussion is just staring on the level of the network. Different MSs are starting to implement the safety information for the prescribers with educational materials and prescribing check lists in their e-prescription databases but with no official studies on their impact in the safe and rational prescribing so far. Some MSs have unofficially communicated that they have opposite outcomes to what was expected as the prescribers have seen the information as burdensome (not believe in clinical relevance of the measures) and ignore the information during the prescription of the medicines. This has to be further investigated as this is crucial on how to design and implement the information to the e-prescription and healthcare databases.

These preliminary findings from these official studies and informal communication in the EU also show that the education of the HCPs on what the risk minimisation measures are about and which relevance they have to the positive benefit/risk balance of the authorized products is needed in parallel with the introduction of these materials in e-prescription and other healthcare databases. The prescribers have to be informed also on the role and obligation of the MAHs, and the MAHs have to be supervised by the regulatory authorities (GVP inspections) that they perform the safety information dissemination in an unbiased way. The DHPC and the educational materials have to free from any marketing biased information (see also Pictures 2-7).

There are only few articles published on the impact of the safety information available in e-prescription databases and there are exclusively from the US. Porterfield A, and al. (12) conclude in their overview of published e-prescription outcomes that in regard safety information E-prescribing has eliminated some of the possibilities for mistakes and can potentially that e-prescribing helps to prevent more than 2 million ADEs a year, 130,000 of which are life threatening in the US. It also has been shown to reduce medication errors in the ambulatory setting by as

much as sevenfold. E-prescribing removes mistakes due to illegibility and helps providers make better informed decisions about what medications to prescribe on the basis of patient histories and allergy data, all of which are available in systems that are integrated with e-prescribing databases. The systems alert prescribers when an allergy or interaction with other medications or health conditions is detected. A problem with these alerts is that in some cases alerts pop up when there is minimal risk or when there is not a true complication. Prescribers may be overloaded with alerts and click through them rather than read each one, potentially missing an important interaction.

Metadata list – describing real world data

The EMA together with the HMA is conducting the Big data project where member state databases with real world data are brought together as a source for conducting RWE studies. These studies are particularly relevant in the research of the impact of safety minimisation measures in the post-authorisation period. The project which brings these databases together is cold the DARWIN project (13). To be able to conduct the studies the data have to be harmonized and the List of metadata for real World data catalogue is out for public consultation (14).

As the DARWIN project goes beyond the European Union healthcare/e-prescription databases Montenegro can already now adapt its e-prescription database to the metadata requirements and can be listed as one of the databases to generate RWE for PASS.

The list of the metadata which the document defines are as follow (14):

Data source metadata

I. Data source – Administrative details

II. Data source – Data elements collected

III. Data source - Quantitative descriptions

IV. Data source – Data flows and management

V. Data source - Vocabularies

Study metadata

I. Study – Administrative details

II. Study – methodological aspects

III. Study – Data management

Institution metadata

Network metadata

KEY FINDINGS

Key Findings #1

The EU legislation on human medicines lay down the minimum information which has to be communicated by the EMA and national regulatory agencies on safety and other regulatory information for the authorized medicinal products in the EU. The information is disseminated through the EMA corporate web site for CAPs, and NCA corporative websites for NAPs with link to the EMA web sites for CAPs.

Key Findings #2

HCPs do not read the information provided by the regulatory authorities – especially the DCPC is regarded as biased as they are sent out by the MAHs. Also, if read, the action is on the individual HCP (prescriber) and not a general one.

Key Findings #3

To overcome these barriers the safety and other regulatory information should be integrated in e-prescription databases if available. US data on this integration of data show that medication error have substantially declined, but there are limitations regarding safety information as they sometimes are not validated, and clinically irrelevant information is popping up (for example in drug-drug interaction) which is then skipped and with that relevant information could be missed. The implementation of RMM prescriber check lists in the e-prescriber databases is not assessed sufficiently, and no data exist in this regard (higher use of the checklist versus the printed version of it, etc.)

Key Findings #4

To gain confidence by the HCP to the risk minimisation measures in parallel to the implementation of the RMM in the e-prescription database trainings and workshops organised by the regulatory authority supported by the individual MS healthcare system. These trainings have to teach on the regulatory requirements of the regulator and MAHs as they by law have to disseminate the safety information to clinicians. The MAHs must not disseminate any safety information without the endorsement of the regulatory authority.

Key Findings #5

Safety information which has to be implemented in the e-prescription database should follow the additional RMM published by the regulatory authority. See the example above. Prescription check lists should be incorporated in the way that the prescription process cannot be concluded before this prescription check list has to be fulfilled. If the checklist indicates that the product cannot be prescribed for that individual patient this has to be saved in the database with the alert why the medicinal product couldn't be prescribed. For other safety pop-ups as for example drug-drug interactions only the clinically relevant ones for the relevant age group should be integrated in the

database. A validation of the safety information has to be made by regulatory/healthcare authorities and has to be prospectively followed up.

Key Findings #6

To be able to integrate regulatory measures in the e-prescription database a close collaboration with the healthcare provider has to be established. It has to be avoided that only medicinal products which are listed at the positive reimbursement list are listed in the e-prescription database, as many of the prescription only medicines (POM) will be missed for example the above mentioned COC. It is of highest importance that all prescription only medicines authorized in the member state are covered in the e-prescription database and linked to the additional RMMs regardless of if the prescription is covered by the paying institution or the patient pays by himself (so called "private" prescription).

Key Finding #7

The e-prescription database has to serve also as the database from which annual surveys on the efficacy of safety measures for medicinal products can be measured. These surveys have to performed in regard to the planned PASS – performed by the MAH or the regulatory authority together with the healthcare provider who is the owner of the e-prescription database. It is important to regulate the use of the database from the side of the MAH who could use this source as a secondary data source for its obligation to conduct RMM effectiveness measures for the medicinal product they own.

Key Findings #8

The Montenegro's E-prescription database can apply to be part of the wide Europe DARWIN project for generation of RWE and a database to be used in post-authorisation RWE PASS studies conducted by the regulatory agencies. To be compliant with other databases the List of metadata for Real world Data catalogues has to be considered.

CONCLUSION

Data from the US indicates that the implementation of the safety data in the e-prescription database leads to safe use of the medicinal product but has also some limitations such as the overload of information for the prescriber. This has to be carefully thought about and guidance which information fulfil the criteria to be integrated in the e-prescription database should be developed and carefully followed up with impact research of these integrated measures and how they are used by HCPs.

So far not much published data exists on how the integrated safety information impacts the safe and rational prescription of medicines in the EU MSs. These kinds of studies are yet had to come, as the implementation of e-prescription databases on the level of the EU is in early stage.

It is essential to build a collaboration between the regulatory authority of the country with the healthcare system and the healthcare provider to link the regulatory and safety information into clinical practice. No guidance on this is yet existing on the level of the EU, but it is recognised as an important and key element to implement the safety guidelines to the clinical practice to get the HCPs to act upon. For now, the regulatory and safety information are not seen as reliable by the HCPs but "biased" as MAHs are involved in the dissemination of the safety and other regulatory information in the EU. Training of the HCPs are essential in this regard to understand the regulatory framework of medicines in the EU so they can implement it in clinical practice.

The E-prescription database could join in the near future the EU RWE DARWIN project as it has the potential to serve as a RWE database for Drug Utilisation Studies and other PASS measuring the impact of risk minimisation measures imposed for medicinal products authorized in the EU.

REFERENCES

1. Regulation (EC) No 726/2004: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02004R0726-20190128&from=EN

2. Directive 2001/83/EC: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02001L0083-20190726&from=EN

3. Regulatory information for the medicinal product Belara: Belara 0,03 mg/2 mg filmom obložene tablete - Baza lijekova | Lijekovi .: HALMED

4. Checklist for prescribers: Lista_Provjere_za_lijecnike-(3)-635-1304.pdf

5. Letter for physicians: CHC-EM_cover_hr_lijecnici_FINAL-1305.pdf

6. Letter for pharmacists: CHC-EM_cover_hr_ljekarnci_FINAL-1306.pdf

7. Patient information: Logest-Vazne_informacije_za_korisnicu-636-1307.pdf

8. DHPC: DHCP-nomegestrolacetat-i-klormadinonacetat.pdf

9. Møllebæk M, Kaae S. Why do general practitioners disregard direct to healthcare professional communication? A user-oriented evaluation to improve drug safety communication. Basic Clin Pharmacol Toxicol (2021); 128:463–471. https://doi.org/10.1111/bcpt.13516

10. de Vries E, Bakker E, Francisca RDG, Croonen S, Denig P, Mol PGM. Handling of New Drug Safety Information in the Dutch Hospital Setting: A Mixed Methods Approach; Drug Safety (2022); 45:369–378. https://doi.org/10.1007/s40264-022-01149-4

11. GVP Module XVI guideline on Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3): https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-xvi-risk-minimisation-measures-selection-tools_en.pdf

12. Amber Porterfield, Kate Engelbert, and Alberto Coustasse. Electronic Prescribing: Improving the Efficiency and Accuracy of Prescribing in the Ambulatory Care Setting. Perspectives in Health Information Management, Spring 2014. Standards for the Content of the (nih.gov)

13. Big data project – DARWIN - Big data | European Medicines Agency (europa.eu)

14. List of metadata World data catalogue: EMA final list of metadata for RWD catalogues (europa.eu)

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

This project is co-funded by
the European Union

The project is implemented by

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

WP5

Interactions of diclofenac

- An analysis of simultaneous prescription of diclofenac and aspirin at primary healthcare level in Montenegro -

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

Drug interactions are defined as a modification of the pharmacodynamic and/or pharmacokinetic properties of one drug due to previous or simultaneous administration of another drug, i.e. as a quantitative or qualitative change in the action of one drug under the action of another drug that can clinically manifest as synergism, antagonism or idiosyncrasy. Drug interactions do not only refer to the consequences of the interaction of two or more drugs, but also include changes in the effect or properties of the drug caused by food, alcohol, endogenous substances, tobacco smoke, herbal drugs and various environmental factors (eg. industrial chemicals, pesticides,...). However, the largest number of drug interactions refer to those of the drug-drug type.

Although the term 'drug interaction' usually refers to an outcome with an unwanted effect, it should be emphasized that certain drug interactions are beneficial, which is why, quite often, certain drugs are combined with the aim of achieving better therapeutic effects (for example, combinations of certain antihypertensives or analgesics with the achievement of a stronger effect and the possibility of reducing the dose of an individual drug, which ensures their better tolerability) (Bexter, 2010; BNF, 2021).

It is known that the manifestation of adverse drug reactions is positively correlated with the number of drugs taken at the same time (about 10% in the case of simultaneous administration of two drugs up to 88% in the case of administration of eight or more drugs), which is why the interactions between them are considered one of the the main causes of side effects of the drug, and even hospitalization as a result (Dechanont et al, 2014). That is why nowadays drug interactions are given great attention, and knowledge of them and regular monitoring of news in that area is one of the basic postulates of modern, rational pharmacotherapy.

2. Interaction of non-steroidal anti-inflammatory drugs (NSAIDs) including diclofenac

There are 392 drugs known to interact with diclofenac, along with 13 disease interactions, and 3 alcohol/food interactions. Of the total drug interactions, 92 are major, 282 are moderate, and 18 are minor (Anonymous, 2022).

The most important drug-drug interactions (DDIs) of diclofenac and other NSAIDs are listed below (BNF, 2021; Voltarol Rapid 50 mg tablets, 2021).

***Lithium*:** If used concomitantly, diclofenac may increase plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

***Digoxin*:** If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

***Diuretics and antihypertensive agents*:** Like other NSAIDs, concomitant use of diclofenac with diuretics and antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis.

Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity.

Drugs known to cause hyperkalemia: Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently

***Anticoagulants and anti-platelet agents*:** Caution is recommended since concomitant administration could increase the risk of bleeding. Although clinical investigations do not appear to indicate that diclofenac has an influence on the effect of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulant concomitantly. Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other nonsteroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.

***Other NSAIDs including cyclooxygenase-2 selective inhibitors and corticosteroids*:** Co-administration of diclofenac with other systemic NSAIDs or corticosteroids may increase the risk of gastrointestinal bleeding or ulceration. Avoid concomitant use of two or more NSAIDs.

***Selective serotonin reuptake inhibitors (SSRIs)*:** Concomitant administration of SSRI's may increase the risk of gastrointestinal bleeding.

***Antidiabetics*:** Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

***Methotrexate*:** Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increase. Cases of serious toxicity have been reported when methotrexate and NSAIDs, including diclofenac are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID.

***Ciclosporin*:** Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.

***Tacrolimus*:** Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. This might be mediated through renal antiprostagladin effects of both NSAID and calcineurin inhibitor.

***Quinolone antibacterials*:** Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.
***Phenytoin*:** When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.

Colestipol and cholestyramine: These agents can induce a delay or decrease in absorption of diclofenac. Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/ cholestyramine.

***Cardiac glycosides*:** Concomitant use of cardiac glycosides and NSAIDs in patients may exacerbate cardiac failure, reduce glomerular filtration rate (GFR) and increase plasma glycoside levels.

***Mifepristone*:** NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

***Potent CYP2C9 inhibitors*:** Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.

***CYP2C9 inducers*:** Caution is recommended when co-prescribing diclofenac with CYP2C9 inducers (such as rifampicin), which could result in a significant decrease in plasma concentration and exposure to diclofenac.

Among adverse effects of NSAIDs, gastrointestinal (GI) complications are well-recognized risks of their use as a class and vary by the respective NSAID used as well as by dose (ie, higher doses = more GI risk) (Henry et al, 1996; Schoenfeld et al, 1999; Henry and McGettigan, 2003). In terms of nonselective NSAIDs, a meta-analysis of data from three retrospective case-control studies found that ibuprofen had the lowest odds ratio (OR) for development of GI bleeding versus diclofenac, naproxen, piroxicam, and indomethacin, but that the OR increases with dose level for each agent (Figure 1) (Lewis et al, 2002).

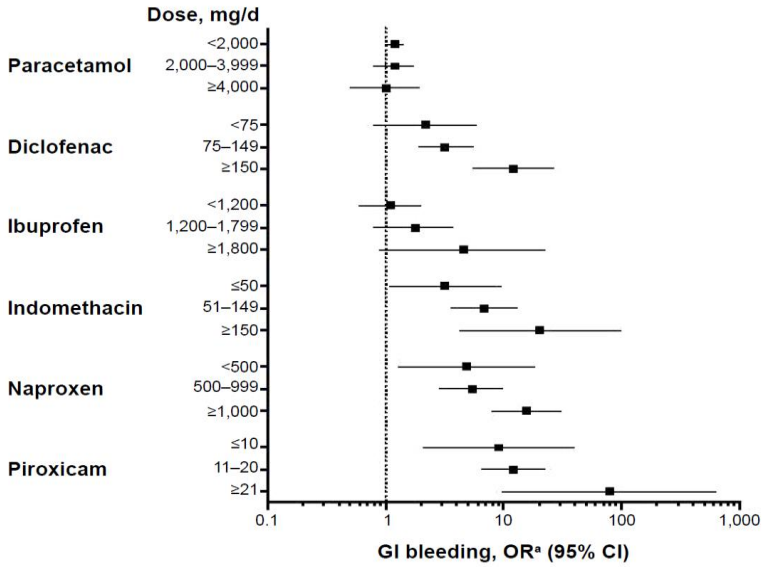


Figure 1. Effect of dose on odds ratio of uppoer gastrointestinal bleeding: meta-analysis of here case-control studies (Lewis et al, 2002)

Aspirin increases bleeding risk, even at low cardioprotective doses (eg, 75–300 mg) (Weil et al, 1995; Derry and Loke, 2000).

Bearing in mind that diclofenac alone, used in usual doses, can cause bleeding in the stomach, and that aspirin even in low, so-called cardioprotective doses increases risk of serious gastrointestinal complications, such a combination should be avoided and used only under special circumstances (Anonymous, 2022). Unfortunately, in everyday clinical practice, the simultaneous use of diclofenac and aspirin is very common, especially in older people who, in addition to rheumatic complaints for which diclofenac is indicated, also have cardiovascular diseases for which the use of aspirin in cardioprotective doses is indicated. In these patients diclofenac should be avoided in any case due to its unwanted cardiovascular effects, but, despite the regulatory measures taken, it has been shown that it is still prescribed to patients with or at increased risk of cardiovascular diseases (see Report 4: Prescribing and consumption of diclofenac in patients with or at high risk of cardiovascular diseases after new recommendations related to its cardiovascular adverse effects, October 2022).

Therefore, it is of interest to establish the extent to which diclofenac and aspirin are still prescribed simultaneously.

3. Simultaneous prescription of diclofenac and aspirin at the primary healthcare level in Montenegro

Data on the simultaneous prescription of diclofenac and aspirin were taken from the integrated information system that was implemented in all healthcare centers on the territory of Montenegro (in total 18). The year 2021 was analyzed.

The results showed that during the year 2021, each month, an average of 180-210 patients were simultaneously prescribed diclofenac (most often in solid oral forms in a dose of 75 mg) and aspirin (mostly in tablets of 100 mg). These drugs were most often prescribed to patients who had hypertension (25%), followed by ischemic heart disease (about 22%), and significantly less to patients with other cardiovascular diseases that are contraindicated (peripheral arterial disease, cerebrovascular diseases) or require increased caution when using diclofenac (diabetes, hyperlipoproteinemia), a total of about 10%. Other patients, who were prescribed these two drugs at the same time, mostly had Covid-19. In any case, almost 70% of patients with or at increased risk of cardiovascular diseases in whom the use of diclofenac is contraindicated or requires increased precautions received this drug together with aspirin putting them at increased risk of GI bleeding.
This result is worrying and once again shows that in practice the current recommendations contained in the Summary of Product Characteristics are not respected.

4. Conclusion and recommendation

Like other NSAIDs, diclofenac may interact with many drugs. Some of these interactions can have very serious consequences. Among them is the interaction of diclofenac with antiplatelet drugs such as aspirin that can result in gastrointestinal bleeding. It has been shown that at the level of primary healthcare in Montenegro, the combination of these two drugs is often prescribed to patients with or at increased risk of cardiovascular diseases, in whom the use of diclofenac is contraindicated or requires increased caution.

Therefore, it is still necessary to strengthen the measures of supervision over the prescription of drugs in primary healthcare, strengthen educational measures among health workers, and continue to improve the electronic prescribing of drugs by installing certain tools that will help the prescribing doctor to choose the most optimal therapy for a specific patient.

5. References

Anonymous (2022). Diclofenac Interactions. Available at: **https://www.drugs.com/drug-interactions/diclofenac.html.**

Baxter K, ed. (2010). Stockley's Drug interactions pocket companion 2010. London: Pharmaceutical Press.

BNF 81 (2021). British National Formulary – BNF 81 (March – September 2021). London:BMJ Group and Pharmaceutical Press.

Dechanont S, et al. (2014). Hospital admission/visits associated with drug-drug interactions: a systematic review and meta-analysis. Pharmacoepidemiol Drug Saf; 23(5): 489-97.

Derry S, Loke YK (2000). Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. BMJ; 321(7270):1183–7.

Henry D, et al. (1996). Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. BMJ; 312(7046):1563–6.

Henry D, McGettigan P (2003). Epidemiology overview of gastrointestinal and renal toxicity of NSAIDs. Int J Clin Pract Suppl; 135:43–9.

Lewis SC et al. (2002). Dose-response relationships between individual nonaspirin nonsteroidal anti-inflammatory drugs (NANSAIDs) and serious upper gastrointestinal bleeding: a meta-analysis based on individual patient data. Br J Clin Pharmacol;54(3):320–6.

Schoenfeld P, et al. (1999). Review article: nonsteroidal anti-inflammatory drug-associated gastrointestinal complications – guidelines for prevention and treatment. Aliment Pharmacol Ther;13(10):1273–85.

Voltarol Rapid 50 mg tablets (2021). Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/4333/smpc#gref

Weil J, et al (1995). Prophylactic aspirin and risk of peptic ulcer bleeding. BMJ;310(6983):827–30.

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

.

This project is co-funded by
the European Union

The project is implemented by